



**ENVIRONMENTAL LEAD AND CHILDREN'S  
INTELLIGENCE AT AGES 11-13 YEARS  
- THE PORT PIRIE COHORT STUDY**

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## SUMMARY

The relationship between low-level exposure to environmental lead and childhood development is an important scientific and public health issue. The accumulated epidemiological evidence indicates a moderate, inverse relation between lead exposure and the cognitive performance of young children. Although environmental exposure to lead may impair cognitive development in early childhood, the implications of such effects for later childhood development are uncertain.

To pursue this important issue, 375 children living in and around the lead smelter town - Port Pirie, South Australia - were followed from birth to ages 11-13 years. Children's intelligence at ages 11-13 years was assessed using the revised version of the Wechsler Intelligence Scale for Children (WISC-R) , and their exposure status was estimated by serial blood lead concentrations measured from before birth to ages 11-13 years. A large number of socio-environmental, familial, and biomedical factors which might confound the relationship between lead exposure and child development were also measured.

The geometric mean blood lead concentrations at various ages varied between 7.9 (at ages 11-13 years) and 21.4 ug/dl (2 years). Intercorrelations of blood lead concentrations at different ages ranged from 0.41 to 0.84. The mean scores for verbal, performance, and full-scale IQ were 97.6 (95% confidence interval [CI]: 96.6 to 98.7), 103.0 (95% CI: 101.6 to 104.4), and 100 (95% CI: 98.8 to 101.2), respectively.

An inverse and statistically significant association between both prenatal and postnatal exposure to lead and children's IQ at ages 11-13 years was apparent in the simple analyses. After adjustment by multiple regression for a wide range of confounding factors, the association of early postnatal exposure to lead with children's IQ remained evident. A dose-effect relationship between early postnatal blood lead concentrations and children's IQ was demonstrated in the results of both simple and multivariable analyses. These findings support the suggestion that exposure to low levels of lead may adversely affect children's IQ. Further, they provide new evidence that the adverse effect of lead exposure on early cognitive development persists into middle childhood even though their mean blood lead levels declined by 63 percent from 21.4 (at age 2 years) to 7.9 ug/dl (at ages 11-13 years). The lead effect observed in this study, however, was not large, viz., an estimated 3 points (95% confidence interval: 0.2 to 5.8) deficit in IQ for an increase in lifetime average blood lead concentration from 10 to 20 ug/dl.

The magnitudes of the deficit in cognitive development at various ages were found to be quite similar. This finding provides support for the constant decrement model, i.e., the

cognitive deficits attributable to early exposure to environmental lead seem to remain constant over the time. Within the range of blood lead concentration encountered in this study, there is little evidence that a threshold of lead exposure exists, since both the plots of IQ versus the current or lifetime average blood lead concentrations offer little support for the existence of a threshold. However, because there are few data available at lower levels of exposure (e.g., lifetime average blood lead concentration < 10 ug/dl), the power to detect a threshold is limited.

Children's full-scale IQ was found to be inversely and significantly associated with most of the postnatal blood lead measures and with lifetime average blood lead concentration. Some aspects of intellectual development appear more sensitive to the effects of low-level lead exposure than others. For example, among the WISC-R subscales, Information, Arithmetic, Block design, and Maze were the most sensitive to the effects of lead. Some fundamental underlying functions, such as concentration, attention, visual-motor coordination, and memory are considered to be important components of these performances. These results suggest that chronic exposure to low levels of lead may affect cognitive development through various mechanisms.

Nevertheless, because of the modest size of the apparent effect of lead upon childhood cognitive development, and therefore the plausibility of alternative explanations for all or some of this effect (e.g., residual confounding), additional research to explore and corroborate further aspects of this relationship is desirable. Epidemiological findings need also to be evaluated in light of the accruing evidence from animal experimental studies.



## DECLARATION

I certify that this thesis contains no material which has been accepted for the award of any other degree or diploma in any university or other tertiary institution; and that to the best of my knowledge and belief it contains no material previously published or written by another person except where due reference is made in the text of the thesis.

I consent to this thesis, if accepted for the award of the degree, being made available for photocopying and loan.

SHILU TONG 

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## ABBREVIATIONS

AAS	Australian Academy of Science
BAS	British Ability Scales
BIB	Bayley Infant Behaviour
BOTMP	Bruininks-Oseretsky Test of Motor Proficiency
BSID	Bayley Scales of Infant Development
G/RBE	Graham/Rosenblith Behavioural Examination
HOME	Home Observation for Measurement of Environment
IQ	Intelligence Quotient
K-ABC	Kaufman Assessment Battery for Children
KID	Kent Infant Development
K-TEA	Kaufman Test of Education Achievement
MSCA	McCarthy Scales of Children's Abilities
NBAS	Neonatal Behavioural Assessment
NHMRC	National Health and Medical Research Council
PbB	Blood lead concentration
PbD	Lead concentration in dentine
PbT	Lead concentration in whole tooth
S-B	Stanford-Binet Intelligence Scale
SCAN	Screening Test for Auditory Processing Disorders
TTQ	Toddler Temperament Questionnaire
US ATSDR	United States Agency for Toxic Substances and Disease Registry
US CDC	United States Center for Disease Control
US EPA	United States Environmental Protection Agency
WISC-R	Wechsler Intelligence Scale for Children-Revised
WPPSI	Wechsler Preschool and Primary Scale of Intelligence



## PREFACE

Lead (Pb: atomic number 82) is the most abundant of the natural heavy metals on the earth, and its average crustal abundance is 7 to 20 parts per million (Zimdahl, 1979). The use of lead since prehistoric times, and its mobilization into the environment, has resulted in increased exposure to, and uptake of, this inessential element by humans.

The first description of acute lead poisoning from an occupational exposure was reported as early as 370 BC (Kazantzis, 1989). Over the ensuing centuries, various adverse effects of lead exposure on human health have been recognized (Smith, 1986). It has been well known that exposure to high levels of lead may cause encephalopathy and death, and survivors of acute lead poisoning may suffer permanent disabilities, such as mental retardation and seizures (Hunter, 1978; Winder, 1984; Kazantzis, 1989). However, lead poisoning in children, through contact with leaded house-paint, was only described in Queensland, Australia, early this century (Gibson, 1904). In 1943, in the USA, a follow-up study of 20 school children who had acute lead poisoning in infancy or early childhood found that exposure to environmental lead insufficient to produce clinical encephalopathy was associated with long-term deficits in neuropsychological development (Byers & Lord, 1943).

Because of substantial scientific evidence showing a wide variety of adverse effects of lead exposure on human health, the permissible exposure level in the working environment has progressively declined since the late last century (Hunter, 1978; Winder, 1984). However, the advent of motor vehicles this century has increased the lead contamination in environment, through the use of lead in both petrol and batteries. Until recent decades, lead was also increasingly used in

house paint and in solder in food cans. As a result, while frank occupational lead poisoning in developed countries has largely disappeared, community exposure to environmental lead has increased throughout much of this century. The entry of lead into the ambient environment in most developed countries has decreased in recent years, reflecting the reduced commercial usage of lead - particularly, lead in petrol (US CDC, 1991; Edwards-Bert et al., 1994). Average blood lead concentrations have also declined (Rabinowitz & Needleman, 1982; Anness, 1983; Edwards-Bert et al., 1994).

While the problems of frank lead poisoning have thus receded in developed countries, chronic exposure to low levels of lead is still a major public health issue. Moreover, both occupational and environmental exposures have remained a serious problem in many of developing and industrialising countries (US EPA, 1986; Grant & Davis, 1989). This situation has been drawing recent attention on possible adverse effects of chronic exposure to "low-level"\* lead on childhood neuropsychological development.

\* The term "low level" refers to exposure that is below that at which clinical signs of lead poisoning are apparent (Needleman & Bellinger, 1991). Although different studies have examined effects at different exposure levels, blood lead concentrations of up to 25 ug/dl are currently considered as an index of low level exposure (US ATSDR, 1988).

Since the early 1970s, various epidemiological studies have examined the relationship between body lead burden and childhood development. Before the mid-1980s, most such studies were of limited scope and duration (US EPA, 1986; Smith, 1989). In 1979, however, a pioneering study by Needleman and colleagues found that the elevated dentine lead levels were significantly associated with cognitive deficits and behavioural problems in children (Needleman et al., 1979). A number of well-designed cross-sectional studies were conducted over the past decade, and most of them found a significant association of body lead burden with childhood development (US ATSDR, 1988; Needleman & Gatsonis, 1990).

Since cross-sectional studies are unable to provide the ancillary information required to infer a causal relationship and/or to estimate a complete profile of past exposure, prospective studies have been carried out in several countries. These studies have sought prospective evidence of the relationship between low-level lead exposure in early life and subsequent childhood development. Although there have been some inconsistencies among the prospective studies, the prevailing view is that early exposure to low levels of lead is associated with deficits in childhood neuropsychological development, particularly in cognitive performance (US EPA, 1990; Thacker et al., 1992).

To date, the accumulated epidemiological evidence, from both cross-sectional and prospective studies, suggests a moderate, inverse relation between exposure to low levels of lead and the cognitive performance of young children (Davis & Svendsgaard, 1987; US ATSDR, 1988; US EPA, 1990; Davis, 1990; Lee & Moore, 1990; Needleman & Gatsonis, 1990; Mushak, 1992; Commonwealth Department of Human Services and Health, 1994). The emergence of this scientific evidence has prompted public health authorities in many countries during the past two decades to lower progressively the blood lead levels deemed to warrant environmental intervention and medical evaluation. For instance, in the United

States, the Centers for Disease Control, in 1985, reduced its definition of an elevated blood lead level from 30 ug/dl to 25 ug/dl (US CDC, 1985). In the subsequent decade, the CDC responded to further epidemiological, clinical and toxicological studies demonstrating adverse health effects at blood lead levels as low as 10 ug/dl by recommending in October 1991 that community-wide childhood lead poisoning prevention activities be initiated when a large proportion of children in a community have blood lead levels in the range of 10-14 ug/dl (US CDC, 1991).

The potentially adverse effects of lead exposure on neuropsychological development constitute an important scientific and public health issue for the following reasons.

First, uptake of lead by children is a widespread problem in both industrial societies and some developing countries where lead is entering the environment from a variety of industrial, transport, commercial and domestic sources. For example, the US Agency for Toxic Substances and Disease Registry (1988), using data from the 1976-1980 National Health and Nutrition Examination Survey, estimated that, among the base population of 13.8 million children aged six months to five years, 2.4 million (17.2%) children had blood lead levels above 15 ug/dl, and that 715,500 (5.2%) and 199,700 (1.4%) children had levels above 20 ug/dl and 25 ug/dl respectively. In Australia, there were approximately 1.2 million children 0-4 years of age in 1986, and it was estimated that there were up to 264,000 (22%), 90,000 (7.5%) and 38,000 (3.2%) children 0-4 years with blood lead levels over 15, 20 and 25 ug/dl, respectively (Burt-Edwards et al., 1993).

Second, as already mentioned, modern epidemiological and toxicological research methods have made it possible to detect a range of subtle effects of exposure to low levels of lead upon childhood development. The results from the studies using these methods suggest that the social and educational significance of even small

neuropsychological effects of exposure to lead, when applied to a total population, may be substantial. For example, in a hypothetical population of 100 million, 2.3 million would have an IQ above 130, based on the population mean of 100 and standard deviation of 15. If, due to the effects of lead exposure, the population mean IQ was shifted to 95, the number of individuals scoring above 130 in a total population of 100 million would drop by 57 percent from 2.3 to 1.0 million (Weiss, 1988). In the meantime, the number of individuals with IQ below 70 (i.e., mental retardation) would correspondingly increase from 2.3 to 3.6 million. Such a difference in mean IQ might well occur between hypothetical populations with average blood lead levels of 10 and 30 ug/dl in early childhood (Baghurst et al., 1992a).

While low-level lead exposure may impair neuropsychological development, other alternative explanations need considering: are the published studies representative; is there inadequate allowance for confounders; are there selection biases in recruiting and following children; and do children with neuropsychological deficits (e.g., lower intelligence) adopt behaviour which makes them more prone to lead uptake (reverse causality)? (Pocock et al., 1994)

If there is an effect of exposure to low levels of lead on neuropsychological development, there are still some unresolved scientific issues which include:

1. Does early low-level exposure to lead have long-term effects on neuropsychological development that are evident in late childhood?
2. How much of the variation in measures of children's neuropsychological development (e.g., IQ) is attributable to lead exposure, compared with the variation due to other factors? That is, how well does exposure to lead predict children's intelligence?

3. Is there a safe threshold exposure for the effects of lead upon development, i.e., an exposure level below which changes in lead exposure have no effect on even the most sensitive measure of child development?

This thesis aims to explore these issues, and is presented in six chapters. The first three chapters provide an introduction to the general topic of lead as an environmental contaminant and a critical review of epidemiological evidence of lead exposure and neuropsychological (particularly, cognitive) development, a description of the research design and methods, and an evaluation of the validity and precision of the study (including a discussion of the potential effects of bias and confounding and a review of the quality control procedures used in the study). The final three chapters present results, discussion, and conclusions and recommendations.

## CHAPTER 1. INTRODUCTION

### Summary

*This chapter contains three sections. The first section reviews briefly the use of lead through the ages, lead contamination of the global environment, and the adverse effects of lead exposure on human health. The second section assesses the sources, pathways and uptake of lead in children, lead metabolism, and the epidemiology of exposure to low levels of lead and neuropsychological development in early childhood. Included is an overview of the literature on previous studies of the relationship between exposure to low levels of lead and child development, and a closer examination of methodological issues which might affect an interpretation of studies regarding the relation of low-level lead exposure with neuropsychological functioning. The third section describes the rationale and objectives of the present study.*

### 1.1. LEAD IN HISTORY

#### 1.1.1. THE USE OF LEAD THROUGH AGES

Lead may have been the first metal to have been smelted by human beings. Lead beads have been found, together with gold and copper ornaments, in Anatolia dating from 7000 to 6500 BC. Lead has been found in a sixth millennium BC setting at Yarum Tepe in Iraq, at the fifth millennium BC site of Arpachiyeh in Iraq and at the fourth millennium BC sites of Anau I in Turkestan, Hissar III in Iraq, and Naqada in Egypt (Winder, 1984; Smith, 1986; Kazantzis, 1989).

These findings suggest that lead smelting, albeit on a small scale, began as early as 8-9 thousand years ago (Winder, 1984; Smith, 1986). References to lead in the Old Testament of the Christian Bible include the use of lead in the construction of the Hanging Gardens of Babylon, and lead mining by the Phoenicians in Spain from about 2000 BC (Smith, 1986; Kazantzis, 1989). In China, lead metal, pigments, and lead glass were known at least as early as the Chou Dynasty (5th century BC) (Rabinowitz, 1995).

The elemental symbol for lead, Pb, is from the latin "plumbum" from which the word "plumber" is derived - a reference to the importance of lead in plumbing practice (until very recently). The alchemical symbol for lead was Saturn, because the mediaeval alchemists considered lead to be the father of metals due to the ease with which the nobler metals, such as silver and gold, dissolved in molten lead (Winder, 1984). Plumbism and Saturnism are both old medical names used for clinical lead poisoning.

Galena or lead sulphide (PbS), the principal ore of lead, is found in many parts of the world, especially Australia, USA, Spain and Mexico. Other common ores of lead are cerussite (PbCO<sub>3</sub>) and anglesite (PbSO<sub>4</sub>). Lead ores were mined in ancient times, in large part for their silver content (Hunter, 1978; Winder, 1984).

The useful physical properties of elemental lead - i.e., its malleability, ductility, corrosion resistance and poor conductance - have resulted in a multiplicity of uses of the metal for over thousand years. The ancient civilizations of Phoenicia, Egypt, Greece, India and China are known to have smelted and used lead for vessels, roofs, water ducts, utensils, ornaments and weights. The Romans used lead throughout their empire for the construction of aqueducts and cisterns. In Roman times, cooking utensils were made of lead and copper, and pewter was made of a lead-tin alloy (Nriagu, 1983; Winder, 1984). Although its importance



initially lay in its close association with silver, lead emerged from the background and assumed a dominant role in the technology of the developing Roman Empire. One reason for the Roman invasion of Britain in the first century was to exploit the mines of lead (and other minerals) in England in order to satisfy the Roman enthusiasm for sanitation and bathing (Nriagu, 1983; Smith, 1986).

Following the fall of the Roman Empire in the fourth century, the use of lead diminished considerably and was mainly confined to products such as sheeting, tubing, vessels, glazes, pigments and alloys until the Industrial Revolution (Ratcliffe, 1981; Kazantzis, 1989).

There was a great upsurge in the use of lead during the period of the Industrial Revolution. Women and children were employed indiscriminately in all lead-associated industries, including the smelting of lead ores, manufacture of lead paints and pottery glazing. The advent of mass industrialization and, in particular, the motor vehicle, brought about dramatic increases in lead usage: as a component of the lead-acid storage battery and (from about 1923) as the 'anti-knock' additive (tetraethyl- and tetra-methyl lead) in petroleum (Hunter 1978; Ratcliffe, 1981; Kazantzis, 1989).

Even today, lead is still the most widely used nonferrous metal. For example, over the past decade, over 2.5 million metric tonnes of lead were mined annually world-wide. The lead-acid battery accounts for over half of this total. Other major uses of lead are in the manufacture of petrol additives, cable sheathing, lead sheet and pipes, pigments, bearings, solders, printing, and shielding for ionizing radiation (Hernberg, 1975; Kazantzis, 1989).

### 1.1.2. LEAD CONTAMINATION OF THE GLOBAL ENVIRONMENT

Exposure of human populations to lead has increased with the emergence of the industrial age and large-scale mining. The magnitude of lead contamination in the environment is high relative to that of any other trace elements (Flegal & Smith, 1992a). On a global scale, the extensive processing of lead ores is estimated to have released about 300 million metric tonnes of lead into the environment over the past five millennia, the vast bulk being released within the past 500 years [Figure 1.1]. The greatly increased circulation of lead through soil, water and air as a result of human activities remains an important environmental issue which may entail unknown health risks for future generations (Nriagu & Pacyna, 1988).

The natural (preindustrial) blood lead concentration of humans is estimated to be about 0.016 ug/dl which is 50- to 200-fold lower than the lowest reported blood lead levels of contemporary humans in remote regions of the southern (0.78 ug/dl) and northern (3.20 ug/dl) hemispheres (Flegal & Smith, 1992b). It is more than 600-fold lower than the current level of concern (i.e., 10 ug/dl) proposed by the Center for Disease Control and Prevention of the United States (1991). This estimate of "natural" blood lead concentration was obtained by application of the results of regressing bone lead on blood lead concentrations in humans and laboratory animals to the skeletal lead levels of preindustrial humans. Lead concentrations in human skeletal remains indicate that the body lead burden in contemporary populations is 500- to 1000-fold greater than in their preindustrial counterparts (Ericson et al., 1979; Patterson et al., 1991).

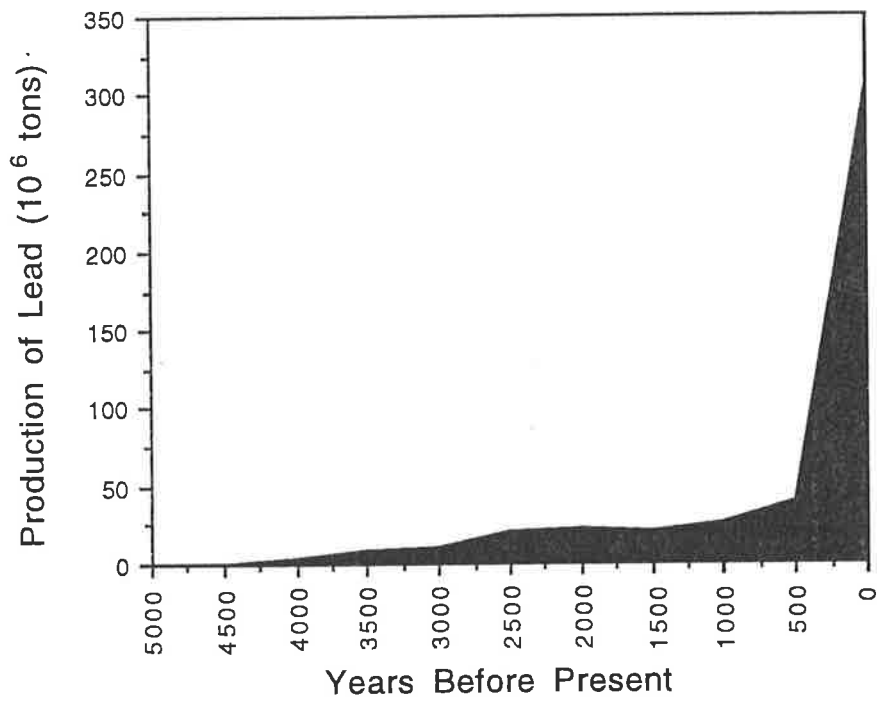


Figure 1.1. Estimated cumulative release of anthropogenic lead to the environment over the past five millennia (reproduced with permission from Flegal & Smith, 1992a).

### 1.1.3. ADVERSE HEALTH EFFECTS OF LEAD

Since lead has been used so widely for such a long time, the history of lead poisoning is an extensive one. The many symptoms of plumbism were noted long before they were ascribed to the action of lead. The earliest clinical description of acute lead poisoning has been attributed to Hippocrates, who in 370 BC described a severe attack of colic and constipation in a worker who extracted metals, although lead was not specifically identified (Hernberg, 1975; Kazantzis, 1989). In the second century BC, the Greek physician, Nikander was able to associate constipation, colic, pallor, paralysis of limbs and ocular disturbance with exposure to lead (Major, 1948). In the first century AD, Pliny described lead workers tying up their faces in loose bags to 'avoid inhaling pernicious dusts', which meant that lead poisoning through exposure to lead in dusts was known in his day; Dioscorides reported that ingestion of lead compounds caused colic, paralysis and delirium (Hunter, 1978).

However, lead poisoning was more than an occupational disease in Roman times. An epidemic of lead colic which, 'took its origin from regions in Italy, moreover in many other places in Roman territory, when it spread like the contagion of a pestilential plague', was described by Paul of Aegina, a Greek physician of the seventh century, but he did not recognise the cause of this epidemic (Major, 1945). Indeed, Gilfillan (1965) and Nriagu (1983) put forward the theory that lead poisoning resulted in a deteriorating health status, low birth rate and high infant mortality among the aristocracy, and was a significant factor in the decline and fall of the Roman Empire. It has been argued, however, that the role of lead is likely to have been overestimated by these authors. In fact, the 'fall' of Rome was a very gradual process, and while lead may have been one negative influence, it was certainly not the only one (Waldron, 1973; Simms, 1984; Smith, 1986).

Since Paul of Aegina described an epidemic of lead poisoning occurring in the seventh century, there have been several other descriptions of similar epidemics; mainly as the result of using lead-lined vessels for the fermentation of alcoholic beverages. The 'colic of Poitou' in France in the 17th century, 'Devonshire colic' in England in the 18th century, and 'dry belly-ache' in the West Indies in America in the 18th century were just a few examples of epidemics of lead poisoning occurring in medieval times (Major, 1948; Smith, 1986).

The huge increase in demand for lead and other minerals caused by the Industrial Revolution brought with it the problem of occupational diseases, of which lead poisoning was only one. During the Industrial Revolution, with more people employed in factories and the increased use of lead in industrial processes, lead poisoning from occupational exposure increased. In 1767 Franklin obtained a listing of all the patients in La Charité Hospital in Paris who had been hospitalised for symptoms which although not recognised then, would now be diagnosed as lead poisoning. He showed that all the patients were involved in occupations which exposed them to lead. In 1839, Tanquerel des Planches published his classic description of acute lead poisoning based on 1213 admissions to the same hospital in the years 1830-38. It is noteworthy that his study was so complete that little has subsequently been added to the clinical knowledge of symptoms and signs of acute lead poisoning in adults (Hunter 1978; Smith, 1986; Kazantzis, 1989).

In Britain in the mid-nineteenth century, occupational lead poisoning was a common disorder. Until 1882 following several deaths of employees in the lead industry, a Parliamentary Enquiry was initiated into work conditions in lead factories. This resulted in the 1883 Factory and Workshop Act (Prevention of Lead Poisoning), which required lead factories to conform to certain minimum standards (e.g., ventilation and protective clothing, etc.). It is notable for being the first Act of Parliament to be directed at a specific occupational disease. Following

the legislation, a gratifying fall occurred in both the incidence and severity of lead poisoning. The success of this legislation was even more remarkable, given that consumption of lead increased steadily during this period (Hunter, 1978; Winder, 1984; Smith, 1986). The legislation was followed some time later by a more thorough enquiry into the lead industry by a Home Office committee, which revealed that miscarriage, stillbirth, and premature delivery were markedly elevated in female lead workers. As a result, young women in England have been prohibited from working in the lead industry since 1896 (Winder, 1984; Smith, 1986).

While frank occupational lead poisoning has largely been controlled due to much improved work conditions, concern over the possible adverse effects of exposure to low levels of environmental lead has grown. In particular, lead poisoning in children experiencing non-occupational exposure has been the focus of attention (Rutter, 1983; Smith, 1989; Needleman & Bellinger 1991).

Childhood lead poisoning was first described by Gibson and colleagues in Brisbane, Australia, a century ago. Ten cases of lead colic in children were reported as early as 1892, and lead paint in the children's homes was identified as the environmental cause of the poisoning twelve years later (Gibson et al., 1892; Gibson, 1904). It has been found that many children who recovered from encephalopathy were left with permanent neurological sequelae (Ratcliffe, 1981; Rutter, 1983). In 1943, the first report that there could be persistent neurotoxic impairment following milder episodes of lead poisoning was reported (Byers & Lord, 1943). This finding was confirmed later by several other studies (Smith et al., 1955; Perlstein & Attala, 1966). However, until the 1970s there was a general assumption that increased lead levels were of little clinical and biological importance if blood lead levels were below 60 ug/dl (Rutter, 1983).

Over the past two decades, there has been increasing concern over the possible adverse effects of lead exposure at levels hitherto regarded as safe or acceptable. The major focus of recent public health debate has been whether exposure of young children to environmental lead, associated with blood lead concentrations of 10-30 ug/dl, adversely affects their development.

## 1.2. LEAD AND CHILDREN

### 1.2.1. SOURCES, PATHWAYS AND UPTAKE OF LEAD IN CHILDREN

Lead is present in food, air, water, dust, and household paint, all of which act as exposure routes for the human population. Because of the hand-to-mouth activities of early childhood, some of these routes (e.g., dusts/soils and paint pigment) are particularly important for young children.

Lead is a natural constituent of soil and dust (Zimdahl et al., 1979). However, urban soil and dust may be contaminated by a variety of atmospheric and non-atmospheric sources. These include leaded paint, gasoline, consumer products, lead smelter effluent, and other sources (e.g., coal combustion). As might be expected, lead levels in soil decrease with distance from point sources of lead (e.g., smelters) and with depth of soil. Concentrations of lead in "uncontaminated" soil (e.g., remote areas) range from 2 to 200 ppm, with most samples being in the range 5 to 25 ppm, but levels as high as 60,000 ppm have been measured in the soil near lead smelters (Zimdahl et al., 1979; Harrison et al., 1981). Lead in dust may exceed that in soil because the smaller soil particles that become part of the dust mixture tend to have higher concentrations of lead. Lead in dust and soil is a major contributor to lead exposure in young children because of the large amount of "hand-to-mouth activity" exhibited by this age group (US EPA, 1986; Baghurst et al., 1992b).

House paint can be a major source of exposure for children. It is estimated that there are 5 million tonnes of lead in household paint in the US (US ATSDR, 1988). Although, in each State of Australia, the lead content of paint has been regulated by legislation at different times (Edwards-Bert et al., 1993), lead paint still exists in old houses. For example, in a recent cross-sectional community



based survey in Sydney, Australia, the mean lead level in exterior paint around the houses investigated was 13,000 ppm (Fett et al., 1992). Young children - particularly those who exhibit the behaviour of "pica" - may chew and ingest sweet-tasting flakes of leaded household paint. A common source of lead exposure is from the improper removal of leaded paint from older houses during renovation (Alperstein et al., 1991). The removal of paint by sanding, sandblasting, scraping or burning can raise dust lead levels into the hazardous range.

Airborne lead is derived predominantly from combustion of leaded petrol and from industrial sources. With the phasing out of leaded gasoline, the overall mean blood lead concentrations in the United States population dropped from 14.6 ug/dl to 9.2 ug/dl between 1976 and 1980 (Mahaffey et al., 1982). There was a strong correlation in the time trends in leaded gasoline usage and in mean blood lead levels. However, because of changes in food canning techniques, the use of lead solder in food cans dropped simultaneously, and dietary intakes of lead fell by nearly an order of magnitude. Corresponding reductions in lead levels were reported in the umbilical cord blood samples of newborns (Rabinowitz et al., 1982). In Sydney, a similar trend has recently been observed in young children during the phasing out of leaded gasoline (Fett et al., 1992). Although the direct inhalation of airborne lead is a minor exposure pathway, particles containing lead which are deposited in soil from the air can be responsible for high lead levels in dust around children's living space (Alperstein et al., 1991).

A major source of lead in drinking water is lead-lined tanks (as water storage reservoirs), lead piping, and lead soldered joints. The problem is exacerbated by low or high pH (beyond pH6 to pH8) water which encourages the dissolving of lead in water (Moore, 1973). Water may be the main source of lead for young infants fed substitute milk formula (Shannon et al., 1992).

Food is also a significant source of lead in children. In the United States, background lead levels in the early 1980s were 0.02-0.06 ppm for meats, 0.003-0.037 ppm for grains and 0.002-0.045 ppm for vegetables (Penumarthy et al., 1980; US EPA, 1986). In Australia, the Market Basket Survey (NH&MRC, 1990) showed that mean lead levels were 0.01-0.037 ppm for meats and eggs, 0.01-0.11 ppm for fruits and 0.01-0.06 ppm for grains and vegetables. Some bone meals and soup bones sold in supermarkets and health food stores for calcium replenishment have much higher concentrations of lead. Lead contamination of food is quite common, and most contamination occurs during processing. Food from soldered cans has much higher levels of lead than most unprocessed food and food from seamless, aluminium cans or welded steel cans (Needleman & Bellinger, 1991). The lead concentration in breast milk from women living in highly polluted areas may be considerably elevated (Namihira et al., 1993).

Finally, uncommon sources of lead include folk remedies (e.g., some herb medicines), cosmetics, soldered domestic vessels and utensils, lead glazed ceramics, and some hobby activities (e.g., pottery glazing and soldering) (AAS, 1981; Needleman & Bellinger, 1991). Petrol sniffing is also an important source of lead exposure among Aboriginal youth in Australia (Alperstein et al., 1991).

### 1.2.2. LEAD METABOLISM

The biokinetic behaviour of lead is determined by the dynamic balance between the processes relating to the absorption, distribution, retention and excretion of lead (US ATSDR, 1988).

Lead absorption is influenced not only by levels of the element in a given medium, but also by various physical and chemical parameters as well as host factors, such as age and nutritional status. Generally, young children absorb more lead than adults through the gastrointestinal and respiratory routes. For example, children absorb approximately 50% of ingested lead as compared with 10-15% in adults (US EPA, 1986). Respiratory uptake of lead also appears to be comparatively greater in children than in adults. It is estimated that children have a deposition rate which is 1.6- to 2.7-fold higher than that for adults on a body-weight basis. (James, 1978). Percutaneous transmission plays only a minor role in the absorption of inorganic lead, but organic tetra-ethyl lead enters the body much more readily by this route (AAS, 1981; US EPA, 1986). Transplacental transfer is another important route of lead uptake. In several prospective studies, cord blood lead levels have been found to correlate strongly with maternal blood lead levels (Dietrich et al., 1991; Baghurst et al., 1992a).

Lead, once absorbed, is distributed among the three major "compartments", blood, soft tissue, and mineralizing tissue (Rabinowitz et al., 1976). Lead in the blood is the most exchangeable; lead in soft tissue is exchanged more slowly; and lead in bone accumulates steadily in several subcompartments, which differ in their exchangeability with blood (US ATSDR, 1988). After being absorbed, lead enters the bloodstream where, under steady exposure conditions, 99.3% is

bound within the erythrocytes (DeSilva, 1981). In short-term experimental studies with adults, whole blood lead, in equilibrium with other compartments, has a mean-life\* of about 36 days (Rabinowitz et al., 1976). Variations in blood lead concentration depend largely on the magnitude and direction of recent changes in exposure. However, changes in blood lead of children may occur over a slower time frame, since the biological half-life of blood lead in 2-year-old children has been reported to be about 10 months (Succop et al., 1987).

Lead uptake in soft tissue is mainly determined by specific tissue kinetics and the lead levels in circulating blood. The structural and functional integrity of some tissues is particularly vulnerable to lead. For example, the lead content in human brain tissue with severe acute and chronic neurotoxic damage is, in many cases, only 1 to 2 ppm or even less (US ATSDR, 1988). This level of lead content, however, causes little apparent damage in other tissues.

Biopsy and autopsy data have shown that 95-99 percent of lead in adults is lodged in mineral tissues, i.e., bones and teeth (Barry, 1975; Rabinowitz et al., 1976). However, the overall percentage of lead burden in mineral tissues is less (about 72%) in children (Barry, 1975). The concentration of lead in the bones of children increases far more rapidly than does their soft tissue mass (Barry, 1975; 1981). While lead in bone used to be considered metabolically inert, it is now recognised that this component of body lead is readily exchangeable, and may be available to other critical soft tissue sites, particularly during childhood and lactation (Rosen, 1985; Mushak, 1989).

\* Half-life = (mean-life x ln(2)) or (mean-life x 0.693) (US EPA, 1986).

For adults, about 10-15 percent of ingested lead is absorbed, and the rest passes out unabsorbed in the feces. Of the lead absorbed, nearly 75% is rapidly excreted in the urine. Some is excreted through endogenous faecal excretion (from the bile and pancreatic secretions, etc) and via other routes (sweat, hair, and nails). The remainder accumulateds in deeper body pools, mostly the skeleton (Rabinowitz et al., 1973; Rabinowitz et al., 1976; US EPA, 1986). For children, lead retention is considerably higher (Ziegler et al., 1978).

### 1.2.3. ASSESSMENT OF LEAD EXPOSURE

To assess the effects of lead on children's development accurately, valid and precise assessment of lead exposure is extremely important. Assessment of the exposure of children is approached either directly through biological monitoring, or indirectly through environmental monitoring (US EPA, 1986; Mushak et al., 1989). In the former approach, lead is measured directly in some biological medium or indirectly through some early biochemical change. As an integrated measure of lead exposure from all environmental sources, biologically-based measurement is more commonly used in epidemiological and clinical studies of lead exposure and toxicity. In environmental monitoring, lead is measured in media that typically act as routes of exposure, e.g., air and water. This is a relatively inaccurate method of estimating an individual's exposure, unless there is some dominant (e.g., occupational) source with readily assessable categories of exposure. (Mushak et al., 1989; Mushak, 1989).

The concentrations of lead in whole blood (PbB), dentine (PbD) or whole tooth (PbT) are the most commonly used indices of exposure to lead in children. PbB is the best measure of recent exposure (US EPA, 1986; Mushak, 1989) while PbD and PbT are generally used as indices of past or cumulative exposure. A major advantage of using blood and tooth lead as indices of exposure is their capacity to provide quantitative information about exposure, which can then be used to study the dose-effect relationship. At present, no other biological measure of lead, e.g., hair lead, plasma lead, lead in urine, can be used in this way (US EPA, 1986; Mushak, 1989; Smith, 1989).

Both blood and tooth lead concentrations, however, have limitations as measures of exposure to environmental lead. For example, the tooth contains several distinct compartments (i.e. enamel, primary and secondary dentine),

each of which accumulates lead at a different rate and time during development (US EPA, 1986; Smith, 1989; Mushak, 1989). As a result, PbD and PbT may vary as a function of location and type of the tooth within the mouth. There are also few quality control programs for the measurement of PbD/PbT. As a result, it is difficult to compare results from different studies. PbB most accurately reflects recent exposure (about one month), and is largely determined by variations in the magnitude and direction of recent exposure (US EPA, 1986; US ATSDR, 1988). Also, at low PbB (e.g., < 10 ug/dl), it is difficult to obtain accurate measurements because of the risk of contamination during sample collection, processing and analysis (Flegal & Smith, 1992a). Furthermore, since little is known about the biokinetics of transfer of lead from blood to brain, the relationship between PbB and brain lead concentration is still poorly understood.

Despite its limitations, PbB is regarded as the most useful and practical biological exposure index because of the following reasons (US ATSDR, 1988):

- (1) PbB is a valid measure of lead exposure;
- (2) blood samples can be obtained readily;
- (3) the analytic method for PbB determinations has been standardised.

In the future, *in vivo* X-ray fluorescence (XRF) appears to be a promising new technique for the assessment of chronic lead accumulation in skeletal tissues. When fully developed, this noninvasive dosimetric technology may enable reconstruction of past exposure histories on an individual basis and facilitate accurate description of dose-response/effect relationships for chronic lead intoxication (Todd et al., 1992; Landrigan et al., 1992).

## 1.2.4. LEAD EXPOSURE AND NEUROPSYCHOLOGICAL DEVELOPMENT

### 1.2.4.1. GENERAL CONSIDERATIONS

There is substantial scientific evidence, predominantly epidemiologic, of adverse effects of exposure to environmental lead on children and other high-risk subsets of the general population (US EPA, 1986; Davis et al., 1987; US ATSDR, 1988; Needleman et al., 1990; Davis, 1990; Lee et al., 1990; US CDC, 1991). Lead may cause encephalopathy and death at blood levels as low as 70 ug/dl. Survivors of the acute phase may suffer long-term disabilities, such as seizures and mental retardation. Lead toxicity affects almost every organ system, most importantly, the central and peripheral nervous systems, kidneys, and blood. Lead has also been suggested to be a potential carcinogen, although there is no evidence for carcinogenicity in children exposed to environmental lead (US EPA, 1986). The effects of lead are multifarious. For example, it is well known that impairment of haem synthesis by lead can, on its own, result in the disruption of a wide variety of important physiological processes [Figure 1.2].

Although the health effects of exposure to high levels of lead are well known, it is still debated whether there is any adverse effect of low level lead exposure on human health, in particular, on children's neuropsychological development. The potential for adverse effects on neuropsychological development in children is enhanced by four factors:

- (1) At any given level of environmental exposure, the intake of lead on a unit body weight basis is higher for children than for adults (US EPA, 1986).



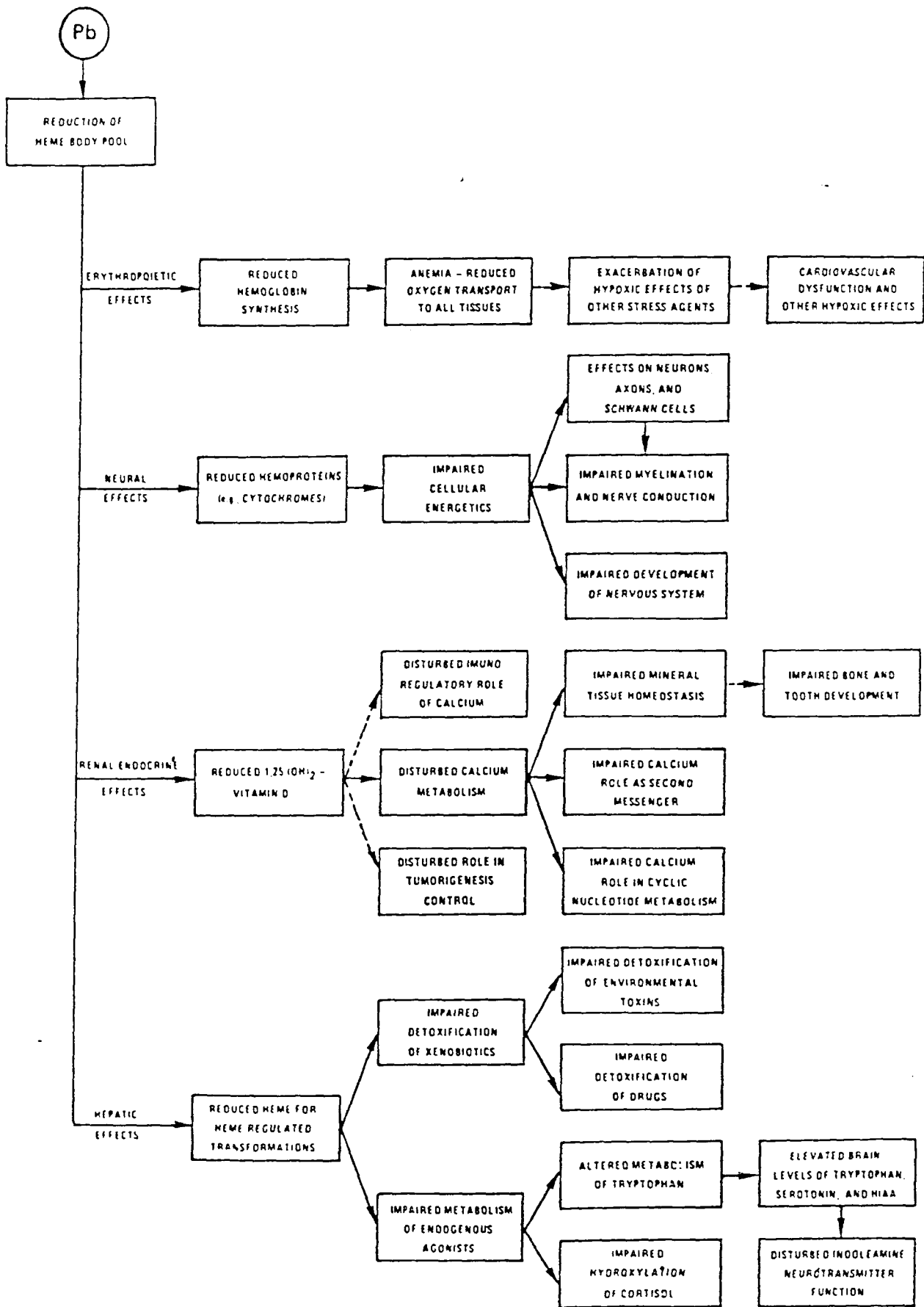


Figure 1.2. Multi-organ impact of reductions of haem body pool by lead (US EPA, 1986).

(2) Young children often relate to their environment through oral exploration, i.e., mouthing activity with ingestion of dust and soil, so that much higher lead intake occurs in children than in adults in environments where the dust or soil is contaminated with lead (US ATSDR, 1988).

(3) The physiological uptake rates of lead in children are higher than those for adults (James, 1978; US EPA, 1986).

(4) Young children are undergoing rapid development and as a result they are more vulnerable to lead effects than adults, especially in relation to the developing central nervous system (US EPA, 1986; US ATSDR, 1988; Mushak, 1992).

Epidemiological studies, using both cross-sectional and longitudinal study designs, have been the principle means of identifying and quantifying the effects of lead exposure on neuropsychological development in children (Smith, 1989; Grant & Davis, 1989; Needleman & Gatsonis, 1990; Schwartz, 1994). Over the past two decades, most studies have reported an inverse association between low-level exposure to lead and childhood neuropsychological development. However, the nature and extent of this association after adjustment for the confounding effects of socioeconomic, environmental and biomedical covariates has been heavily debated.

Methodological considerations in the epidemiological studies of low-level exposure to lead and neuropsychological development include (Needleman & Gatsonis, 1990; Thacker et al, 1992; McMichael et al., 1992):

(1) the adequacy of markers of exposure;

(2) the appropriateness of measures of developmental outcome;

(3) the control of factors that might confound the estimation of an association between lead exposure and child development;

(4) the avoidance of biases in sample selection, conduct of measurement, and the follow-up of study subjects;

(5) a sample size sufficient to provide adequate statistical power;

(6) the use of appropriate statistical methods for the analysis of data, and the avoidance of three types of errors (i.e., false positive, false negative and inappropriate modelling);

(7) the identification and quantification of the interactive effects of lead and other factors on child development.

Since the late 1970s a large number of epidemiological studies, using either cross-sectional or prospective designs, have been conducted. The advantages and disadvantages of these two different research designs are compared in Table 1.1. In brief, a cross-sectional study is able to provide information indicative of an association between exposure to lead and child development, but unable to provide the ancillary information required to infer a causal relation since it cannot determine the temporal relationships between exposure, outcomes and covariates which vary with time. Prospective studies are potentially capable of providing more information on exposure-outcome relationships (e.g., the time sequence, and temporal changes in exposure and outcomes, etc.), but they may be vulnerable to bias due to losses to follow-up.

Table 1.1. Comparison of cross-sectional and prospective studies in relation to studying the health effects of exposure to environmental lead

Advantages	Disadvantages
<p>Cross-sectional studies:</p> <ol style="list-style-type: none"> <li>1. Provide information indicative of an association between lead exposure and child development, thereby generating hypotheses.</li> <li>2. Quick, requiring only an "once-off" examination of both exposure and outcome.</li> <li>3. Relatively cheap.</li> </ol>	<ol style="list-style-type: none"> <li>1. Cannot determine the temporal changes of exposure, outcomes, and covariates over time.</li> <li>2. Cannot provide a complete profile of past exposure.</li> <li>3. Unable to provide, therefore, the ancillary information required to infer a causal relationship from observational data.</li> <li>4. Vulnerable to selection bias.</li> </ol>
<p>Prospective studies:</p> <ol style="list-style-type: none"> <li>1. Potentially capable of providing more information about lead-outcome relationship because of the time sequence of the study.</li> <li>2. Can measure temporal changes in outcome over time in relation to prior levels of exposure.</li> <li>3. Provide a more complete and precise profile of exposure history.</li> <li>4. Permit a more thorough consideration of covariates, and minimise recall bias and other types of information bias.</li> <li>5. Can estimate the direction and magnitude of potential selection bias.</li> </ol>	<ol style="list-style-type: none"> <li>1. Longer time required.</li> <li>2. Relatively expensive.</li> <li>3. Some participants leave the geographic area of the study and cannot be traced; some lose interest in participating; and some are inevitably lost to follow-up, despite intensive efforts to track them. This may introduce bias.</li> </ol>

#### 1.2.4.2. EPIDEMIOLOGICAL STUDIES OF NEUROPSYCHOLOGICAL EFFECTS OF LOW LEVEL LEAD EXPOSURE

**Cross-sectional studies.** In 1979, Needleman and colleagues reported results from a study of 2,335 children who were attending first or second grade at schools in Massachusetts, USA (Needleman et al., 1979). Of the 2,335 children, 270 with dentine lead levels in the highest and lowest deciles were examined using a range of measures to assess intelligence, speech and language ability, attention span, and classroom behaviour. After adjustment for confounders, the high lead level group (> 20 ppm) scored significantly lower than the low lead level group (< 10 ppm) on IQ, speech and language processing measures. Children with higher PbD also had a significantly poorer attention span, and more problems with classroom behaviour.

Smith et al. (1983) examined the association between lead levels in teeth (adjusted mean PbT = 5.8 ppm) and measures of intelligence and behaviour in 403 6-year-old children in London, England. After correcting for confounding factors, no statistically significant association was found. However, reanalysis of these data by Pocock et al., (1987) using regression techniques with an interaction term between lead and gender, did show a significant inverse association between PbT and IQ in boys. The possible explanations as to why a different pattern of results was found in their study include:

(1) The actual concentrations of lead in each child's tooth were used in the reanalysis (rather than simply classifying children into high, medium and low lead groups). This enabled a more powerful assessment of the association between IQ and body lead burden.

(2) The methods of multiple regression, including an 'optimal' selection strategy, were more fully exploited in the reanalysis.

(3) The possibility of interactions between lead and confounders was explored in the reanalysis (Smith et al., 1983; Pocock et al., 1987).

Blood lead concentrations and neuropsychological development were measured for 187 children at age 2.5 years in Birmingham, United Kingdom (mean PbB: 15.6 ug/dl). The strength of the relationship between PbB and intelligence was small and statistically non-significant after adjustment for confounding factors (Harvey et al., 1984). However, statistical power was a serious problem in this study, since only 48 subjects with complete data were included in the regression analysis, which adjusted for 16 covariates. This analytical approach reduced the statistical power of the study and hence there was a strong possibility of a type II error (i.e., false negative) resulting from the analysis.

Fulton and colleagues (1987) studied 501 children in Edinburgh, Scotland, and found a strong relationship between PbB (geometric mean = 11.5 ug/dl) and the scores on the British Ability Scales (BAS), with no evidence of a threshold within the range of exposure studied. An important issue addressed in this study was the existence of a threshold in the lead-related health risk.

Fergusson et al. (1988) studied 724 children in Christchurch, New Zealand, and found that dentine lead levels (mean PbD = 6.2 ppm) were significantly inversely related to reading, spelling, handwriting and mathematics scores. There was an inverse association between PbD and IQ, but this was not statistically significant when confounding factors were taken into account. Therefore, the results of their study seemed to be inconsistent with those found in the Massachusetts study (Needleman et al., 1979). One of the explanations offered was that the level of exposure in the Christchurch sample was much lower than in Massachusetts.

A pooled analysis of cross-sectional data from the European Multicenter Study on lead neurotoxicity in children showed that PbB was significantly and consistently associated with outcome measures on the Bender Gestalt test and with serial choice reaction performance. Moreover, there was a borderline significant association between PbB and children's intelligence, although the results between individual studies were not highly consistent (Winneke et al., 1990).

Recently, the PbT and IQ of 764 children were assessed in Taiwan. The study reported that intelligence scores from Raven's Colored Progressive Matrices Test were inversely correlated with PbT, especially among girls and among children whose parents had less education. This investigation of possible lead effects in a non-western culture is the first step toward an assessment of the generalisability of lead's putative toxic properties (Rabinowitz et al., 1991; 1992).

Other cross-sectional studies have provided supporting evidence that elevated lead exposure is associated with deficits in cognitive and behavioural development. For instance, Hansen et al. (1989) studied 162 children in Aarhus, Denmark, and found that dentine lead was significantly associated with IQ and scores on the Bender-Gestalt test. Studies by Schroeder et al. (1985) in North Carolina, USA, Bergomi et al. (1989) in Sassuolo, Italy, and Hatzakis et al. (1989) in Lavrion, Greece also showed a significant association between lead exposure and childhood development.

Although there have been some inconsistencies among the cross-sectional studies (see more discussions in Chapter 1.2.4.5), most of them have indicated a significant and inverse association between exposure to low levels of lead and childhood neuropsychological development (Needleman & Gatsonis, 1990; Pocock et al, 1994).

Cross-sectional studies, nevertheless, cannot identify the relationship between past exposure and later neuropsychological development since they measure exposure and outcome at only one instant in time. Although measurement of lead in teeth provides some kind of integrated measure of past exposure, its exact relation with body burden has been unclear, and furthermore, the use of PbT/PbD cannot define the period of maximum sensitivity of lead exposure (if it exists) during childhood.

In an attempt to overcome these methodologic difficulties, cohort studies were commenced in several locations in the late 1970s. These investigations sought more definitive, prospective evidence of the relationship between exposure to lead early in life and subsequent neuropsychological consequences.



**Prospective studies.** To date, seven major prospective studies of early childhood exposure to lead and its neuropsychological consequences have provided data which can be critically examined. This inventory of studies - in Boston, Cincinnati, and Cleveland in the United States, in Port Pirie and Sydney in Australia, in Glasgow, Scotland, and in Kosovska Mitrovica, Yugoslavia - was identified from MEDLINE searches spanning the time period between January 1983 and December 1992, and from adjunct searching methods (e.g., hand searching of key journals, review of the bibliographies of reports known to be relevant, consulting with experts, and use of Science Citation Index). Since, in each of these studies, the history of lead exposure has been determined by repeatedly measuring PbB from birth (or even in the mother antenatally), and neuropsychological development has been assessed by generally consistent use of similar outcome measures, the results of these studies can be compared, albeit with some caution [Table 1.2].

(1) **Boston:** The first prospective study to report effects of prenatal lead exposure on early neuropsychological development was conducted in Boston by Bellinger and colleagues (Bellinger et al., 1987; 1990; 1991; 1992). Cord blood samples were obtained from 11,837 infants born from April 1979 to April 1981 in the Boston urban and suburban area. This sample represents 97 percent of the live births in these areas during that time period (Rabinowitz et al., 1982). Although the sampling method is not entirely clear in publications, it appears that 249 infants, from the low ( $< 3$  ug/dl), middle (6-7 ug/dl), and high ( $\geq 10$  ug/dl) cord blood lead categories, were selected for neuropsychological assessment. Reasons for exclusion included birth complications, the family being non-English-speaking, lack of parental consent, difficult accessibility, or failure to locate. PbB and developmental status of the children were measured at ages 6, 12, 18, 24 and 57 months, and 10 years (Table 1.2).

Table 1.2. Characteristics of seven prospective studies concerning lead exposure and child development\*

Location (N†)	Age of blood sampling	Neuropsychological outcomes	Key confounders considered	Comment	
Boston (249)	Cord	At 6, 12, 18 & 24 months	Alcohol use	Major source of exposure: lead in general environment;	
	6 months	BSID	HOME scores**		
	12 months		Maternal IQ	Middle & upper-middle	
	18 months		Maternal age	class children;	
	24 months		Smoking	Correlation between	
	57 months		Social class	capillary & venous PbB	
	10 years			was unknown	
			At 57 months	HOME scores	
			MSCA	Maternal IQ	
				Preschool use	
			Social class		
		At 10 years	Child stress		
		WISC-R	HOME scores		
		K-TEA	Maternal IQ		
			Social class		

Table 1.2. Characteristics of seven prospective studies concerning lead exposure and child development (Continued)

Location (N)	Age of blood sampling	Neuropsychological outcomes	Key confounders considered	Comment
Cincinnati (305)	Maternal first visit Cord 10 days 3 months 6 months Every three months up to five years old 66 months .72 months	At 3, 6, 12 & 24 months  BSID     At 4 years  K-ABC    At 5 years  K-ABC  SCAN   At 6 years  BOTMP	Birth weight  Gestation  Maternal age  Race and sex  Social class  Maternal IQ  Birth weight  HOME scores  Social class  Maternal cigarette use   Head circumference & length at birth  HOME scores  Maternal IQ  Social class   HOME subscales  Maternal IQ  Social class  Race and gender	Major source of exposure: lead in paint, dust & exterior soil; Low-class children; Community-based sample; No evaluation of intra- observer variations.

Table 1.2. Characteristics of seven prospective studies concerning lead exposure and child development (Continued)

Location (N)	Age of blood sampling	Neuropsychological outcomes	Key confounders considered	Comment
Cleveland (359)	Maternal At delivery or next day Cord 6 months 2 years 3 years	Infants NBAS G/RBE  At 6, 12 & 24 months BSID  At age 58 months WPPSI	Alcohol use Gestational age Maternal age Race and gender Age at testing Birth order Birth weight HOME scores Maternal IQ Race and gender HOME scores Maternal IQ Parent education Race	Primary objective: to examine the impact of maternal lifestyle factors (esp. alcoholism) on childhood development; Major source of lead exposure: unclear; Low-class children; Lead-outcome relation can be diminished by the impacts of exposure to alcohol.

Table 1.2. Characteristics of seven prospective studies concerning lead exposure and child development (Continued)

Location (N)	Age of blood sampling	Neuropsychological outcomes	Key confounders considered	Comment
Port Pirie (723)	Maternal (venous) 20 & 32 weeks At delivery Cord Children (capillary) 6 months 15 months 2 years 3 years 4 years 5 years 6 years 7 years	At age 2 years BSID       At 4 years MSCA       At 7 years WISC-R	Birth order Gestational age HOME scores Maternal IQ Maternal age Parent education Parental relation  Birth order Birth weight HOME scores Maternal IQ Social class  Birth order Birth weight HOME scores Maternal IQ Social class Parental smoking	Major source of exposure: lead in dust/soil; Middle-lower class children; Community-based sample; No formal evaluation of intra-observer variations

Table 1.2. Characteristics of seven prospective studies concerning lead exposure and child development (Continued)

Location (N)	Age of blood sampling	Neuropsychological outcomes	Key confounders considered	Comment
Sydney (318)	Maternal Cord 6 months 12 months 18 months 24 months 30 months 36 months 42 months 60 months	At 6, 12 & 24 mos BSID BIB TTQ At 3 & 4 years MSCA	Father's job Gestational age HOME scores Parental edu. Father's job Gestational age HOME scores Maternal verbal IQ	Major source of exposure: lead in general environment; Middle-class children; Correlation between capillary & venous PbB was unknown.
Glasgow (151)	Maternal 1 years 2 years	At 1 & 2 years BSID	Birth weight HOME scores Social class	Small power & under-adjustment for confounding, e.g., maternal IQ

Table 1.2. Characteristics of seven prospective studies concerning lead exposure and child development (Continued)

Location (N)	Age of blood sampling	Neuropsychological outcomes	Key confounders considered	Comment
Kosovo (541)	Maternal Cord 6 months 12 months 18 months 24 months	At 6, 12, 18 & 24 months BSID	Birth order Birth weight HOME scores Maternal age Maternal IQ Race and gender Years of maternal education	Major source of exposure: airborne lead; Social class: unclear; Community-based sample; Under-adjustment for socioeconomic status.

\* BIB: Bayley Infant Behaviour; BOTMP: Bruininks-Oseretsky Test of Motor Proficiency; BSID: Bayley Scales of Infant Development; G/RBE: Graham/Rosenblith Behavioral Examination; K-ABC: Kaufman Assessment Battery for Children; K-TEA: Kaufman Test of Educational Achievement; MSCA: McCarthy Scales of Children's Abilities; NBAS: Neonatal Behavioural Assessment; SCAN: Screening Test for Auditory Processing Disorders; TTQ: Toddler Temperament Questionnaire; WISC-R: Wechsler Intelligence Scale for Children-Revised; WPPSI: Wechsler Preschool and Primary Scale of Intelligence.

\*\* HOME: The Home Observation for Measurement of Environment (HOME) inventory.

† Number of the children in the initial cohort.

In the follow-up of this cohort, performance on the Bayley Mental Developmental Index (MDI) at ages 6, 12, 18 and 24 months was found to be inversely associated with cord PbB (Bellinger et al., 1987). The developmental deficit in the MDI in the high cord PbB group was approximately 4-8 points relative to the low PbB group. At age 57 months, a significant inverse association was found between PbB at age 24 months and the McCarthy scores, after adjustment for covariates (Bellinger et al., 1991). However, no significant association was found between cord PbB and developmental outcomes at age 57 months. The change in cognitive performance between 24 and 57 months of age was examined in relation to pre- and postnatal lead exposure and various sociodemographic factors (Bellinger et al., 1990). Among children with high prenatal lead exposure, greater recovery of function was associated with having a lower PbB at 57 months, higher socioeconomic status, higher HOME scores, higher maternal IQ, and female gender. At age 10 years, an increase of 10 ug/dl in 24 month PbB was associated with a 6.0 point decline in Wechsler's Full-Scale IQ ( $p=0.006$ ) and an 8.8 point decrement in Kaufman's Composite score ( $p=.0005$ ) (Bellinger et al., 1992).

(2) **Cincinnati**: Dietrich and colleagues conducted a prospective study of 305 children, recruited from consecutive births between 1979 and 1984 in a geographical area within Cincinnati, Ohio, where there has been an historically high incidence of childhood lead poisoning (Dietrich et al., 1987; 1990; 1991; 1992). Lead in paint, dust and exterior soils has been demonstrated to be a major source of exposure for children residing in this area. Exclusion criteria employed in the Cincinnati study included having a mother known to be addicted to drugs (including alcohol), or who suffered from diabetes, neurologic disorders, psychoses, or mental retardation; premature birth (i.e., infants of less than 35 weeks' gestation), low birthweight (i.e., <1,500 gm) and/or an Apgar score of 6 or less at five minutes after birth.



Blood samples were obtained from mothers antenatally, and from each child at birth (cord blood), 10 days, and every three months thereafter. The developmental status of the children was evaluated at ages 3, 6, 12 and 24 months, 4, 5 and 6 years (Table 1.2).

The mean maternal and cord PbB were 8.0 and 6.3 ug/dl, respectively. The mean neonatal and postnatal PbB ranged from 4.6 ug/dl at 10 days of age to 17 ug/dl at 2 years. A statistically significant inverse association was found between both prenatal and neonatal PbB and performance on the Bayley MDI at ages 3 and 6 months (Dietrich et al., 1987). However, no significant association was observed between either prenatal or postnatal blood lead concentrations and the Bayley MDI scores at the age of two years (Dietrich et al., 1990). This was attributed to “neurobehavioural catch-up growth” for infants whose central nervous system may have been compromised by lead or other factors that influence prenatal growth and maturation. At age 4, neonatal PbB was inversely associated with performance on the Kaufman Assessment Battery for Children (K-ABC), but the association was limited to children from disadvantaged families. A modest inverse relationship was observed between postnatal PbB and performance on the K-ABC subscale which assesses visual-spatial and visual-motor integration skills (Dietrich et al., 1991). Both prenatal and postnatal PbB were inversely associated with central auditory processing abilities. Higher postnatal PbB was associated with poorer performance on all cognitive developmental subscales of the K-ABC at age 5 years. However, following full covariate adjustment, few associations were still statistically significant (Dietrich et al., 1992). It was postulated that cognitive and academic outcomes are likely to be confounded with sociohereditary factors in low socioeconomic status populations. However, this postulate is not supported by other studies (Pocock et al., 1987; Bellinger et al., 1989; McMichael et al., 1992). At six years of age, after adjustment for covariates, neonatal PbB was associated with poorer

performance on a measure of upper-limb speed and dexterity and the fine motor composite (indexed by the subtests of Response Speed, Visual-Motor Control, and Upper-Limb Speed and Dexterity). Postnatal PbB was inversely associated with scores obtained from measures of bilateral coordination, visual-motor control, upper-limb speed and dexterity, and the fine-motor composite. The results showed that low to moderate lead exposure is associated with moderate deficits in gross and especially fine-motor developmental status (Dietrich et al., 1993). These findings suggest that measures of motor development may be more sensitive markers of the effects of lead exposure than cognitive and academic measures.

(3) **Cleveland:** A prospective study was conducted in Cleveland, Ohio by Ernhart and colleagues (Ernhart et al., 1986; 1987; 1988; 1989a). The study included a total of 359 socially disadvantaged urban neonates. Maternal blood samples were collected during labor or on the first day postpartum, and children's blood samples were obtained at birth (cord blood), and at ages 6, 24 and 36 months. The children's developmental status was assessed at ages 6 months, 1, 2, 3 and 5 years (Table 1.2).

The mean PbB for mothers, and for the children at birth and at ages 6 months, 2 and 3 years were 6.5, 6.0, 10.1, 16.7 and 17.0 ug/dl, respectively. The scores on the Abnormal Reflexes, Graham/Rosenblith (G/R) Neurological Soft Signs and Muscle Tonus scales were significantly related to either maternal or cord PbB. However, when the analyses were restricted to 132 pairs of complete mother-infant data, only the G/R Neurological Soft Signs of infants were significantly related to the cord PbB (Ernhart et al., 1986). The maternal PbB accounted for a significant proportion of the variation in 6-month scores on the Bayley MDI, Physical Developmental Index (PDI), and Kent Infant Development Scale (KID) (3.0, 2.9 and 7.8 percent, respectively), but did not relate to the measures of later development (Ernhart et al., 1987; 1988). At age 5 years, these children were

assessed with the Wechsler Preschool and Primary Scale of Intelligence (WPPSI). Although there was a significant and inverse correlation between most of the PbB measurements and IQ, none of the blood lead measures accounted for a statistically significant proportion of the variance, after adjustment for the effects of confounding factors (Ernhart et al., 1989a). Most of the analyses, however, were based on data from less than 150 children, and therefore, the statistical power for detecting a moderate association of the lead exposure with child development was limited. Moreover, since alcohol use in pregnancy was reported by over half of the women in the cohort, and early alcohol-related developmental deficits were present in the study population (Ernhart et al., 1985), the presence of a significant effect of prenatal alcohol exposure on the outcome under consideration might have made it more difficult to detect any effect of lead.

(4) **Port Pirie:** In Australia, a relatively large prospective study of the effects of lead exposure on childhood development has been carried out in and around the lead smelter town of Port Pirie, South Australia (Wigg et al., 1988; McMichael et al., 1988; Baghurst et al., 1992a). This study included 723 single live-births representing approximately 90% of all babies born in the community from May of 1979 to May of 1982.

Blood samples were taken from the pregnant women at specified times (including 14-20 weeks gestation, early in the third trimester, and at delivery); from the umbilical cord at delivery and the children themselves at ages 6, 15, 24 months and annually thereafter up to age 7 years. The developmental status of each child was assessed at ages 2, 4 and 7 years (Table 1.2).

The geometric means of maternal PbB and cord PbB were 9.1 and 8.3 ug/dl, respectively. Geometric mean values in the children increased from 14.4 ug/dl at age 6 months to 21.2 ug/dl at age 2 years, and then decreased to 11.6 ug/dl at

the age of seven years. Although no significant association was found between *prenatal* PbB and neuropsychological development after adjustment for socio-environmental, hereditary and biomedical factors, *early postnatal* PbB was inversely related to cognitive development at ages 2, 4 and 7 years. There are two possible explanations for these results. First, since average postnatal PbB in the Port Pirie cohort is higher than that in children in most other cohort studies, any adverse effects of prenatal elevations in PbB may have been overwhelmed by the much higher postnatal PbB. Second, the measures of cognitive development may not be sufficiently sensitive to detect subtle effects of prenatal exposure to lead. From this study, it has been estimated that, relative to a child with PbB of 10 ug/dl, a child with PbB of 30 ug/dl will have a deficit of 3.3 points on the Bayley MDI at age 2 years, 7.2 points on the McCarthy General Cognitive Index at age 4 years, and 5.3 points on the WISC-R IQ at the age of seven years. (Note: This thesis reports the results of the latest assessment of this cohort.)

(5) **Sydney**: This study comprised a cohort of 318 children born in three Sydney hospitals between April 1982 and March 1983 (Cooney et al., 1989a; Cooney et al., 1989b). PbB was measured at the time of birth, then at 6 monthly intervals to 4 years, and again at 5 years. The children's neuropsychological development was assessed at ages 6, and 12 months, 2, 3, and 4 years (Table 1.2).

The geometric means of maternal and cord PbB were 9.1 and 8.1 ug/dl, respectively. Postnatal PbB increased from 15.0 ug/dl at 6 months to a peak level of 16.4 ug/dl at 18 months and then declined to 10.1 ug/dl at 4 years. The correlations between PbB and developmental outcomes at various ages were generally small, mixed in sign, and statistically nonsignificant. After adjustment for covariates, only the association between cord PbB and PDI accounted for a marginally significant variance in the regression model ( $p=0.08$ ), but the direction of the association was positive. At age 4 years, analyses of both PbB at particular ages and composite measures of PbB (pairs of adjacent PbB averaged to

represent exposure level over a 12-month period) found no significant correlation, except for one positive association between first year PbB and McCarthy GCI performance. Regression analyses using either a weighted combination of previous PbB or current PbB as the independent variable also failed to yield a significant relationship. However, the possibility of lead contamination in the blood sampling and analysis cannot be fully excluded (Cooney et al., 1989a; Schwartz, 1994), hence, the misclassification bias may have made it difficult to detect any effect of lead exposure.

(6) **Glasgow**: This study included 151 subjects drawn from an initial selection of 885 families in Glasgow, Scotland (the sampling method was not available from publications) (Moore et al., 1982, 1989). On the basis of maternal PbB during pregnancy, three groups, matched for social class, were identified with high (> 30 ug/dl), medium (15-25 ug/dl), and low (< 10 ug/dl) PbB. The water supply constituted the major exposure vector for lead in this population. However, following a reduction in the acidity of drinking water by treatment with lime, the average PbB in this population fell dramatically. In simple analyses, Bayley MDI and PDI at ages 1 and 2 years generally decreased with increasing maternal PbB, and the individual scores at ages 1 and 2 years were significantly correlated ( $r=0.39$ ). However, stepwise linear regression analyses showed that the quality of the home environment, social class, and birth weight accounted for a much greater proportion of the variance in the Bayley scores than the measures of lead exposure (maternal PbB, water lead levels, and pica at ages 1 and 2 years). Since birthweight may be an intermediate variable in an assessment of the relationship between antenatal lead exposure and child development, it was excluded from the further stepwise regression model, but the explanatory power of the lead measures was not significantly improved. Once again, the sample size in the Glasgow study may have been insufficient to detect a moderate effect of low-level lead exposure (US EPA, 1990).

(7) **Kosovo**: Recently, results from another prospective study involving two communities in the province of Kosovo, Yugoslavia - Kosovska Mitrovica (K. Mitrovica; previously Titova Mitrovica) and Pristina - have been reported (Factor-Litvak et al., 1991; Wasserman et al., 1992). This is the first prospective study conducted in a developing country. K. Mitrovica is an area of high industrial exposure to lead, due to the activities of a large lead smelter, refinery, and a battery plant. Pristina, 40 km to the south, has minimal lead exposure and serves as a relatively non-exposed control community. Apart from the degree of exposure to lead, the characteristics of these two communities were comparable.

The study sample was derived from 1502 pregnant women living in those towns. Exclusion criteria included those for whom complete delivery data were not available; infants with central nervous system defects, chromosomal abnormalities, multiple births, and residence more than approximately 10 km from the pediatric clinic in either town. A total of 706 infants were eligible to participate in the follow-up study, which involved assessments at 6, 12, 18, and 24 months of age. Of these, the parents of 541 infants consented and brought their infants to at least one visit. Of those who consented, 392 children were examined at age 2 years. Blood samples were obtained from the mothers at mid-pregnancy, and from the children at birth (umbilical cord), 6, 12, 18 and 24 months of age. The developmental status of children was evaluated with the Bayley MDI at ages 6, 12, 18 and 24 months. The geometric mean maternal PbB was 18.3 ug/dl in K. Mitrovica and 5.2 ug/dl in Pristina, respectively. The mean cord PbB was 20.8 and 4.9 ug/dl, respectively. The PbB of children in K. Mitrovica gradually rose from 20.8 ug/dl at birth to 35.4 ug/dl at age 2 years. In Pristina it rose steadily from 4.9 to 8.5 ug/dl. A significant inverse association was found between PbB and MDI at age 2 years, and statistically nonsignificant decrements were associated with PbB measured at birth and at 6, 12, and 18 months of age. It was estimated that a rise in PbB at age 2 years from 10 to 30 ug/dl was associated with a 2.5 point decrement in MDI.

Other prospective studies have used PbD as the sole index of exposure (Fergusson et al., 1988, 1993; Needleman et al., 1990) or have not yet reported sufficient exposure data (Winneke et al., 1989; Shucard et al., 1989a,b; Rothenberg et al., 1989a,b) to warrant a detailed evaluation in this thesis. In brief, except for a New York study in which outcomes have not yet been reported (Shucard et al., 1989a,b), all other studies have found an inverse association between body lead burden and at least some neuropsychological measures.

The major findings of prospective studies are summarised in Table 1.3. The weight of evidence obtained in these studies indicates a moderate, inverse association between lead exposure and neuropsychological development in early childhood.

Table 1.3. Major findings from prospective studies of lead exposure and child development

Study	Age at PbB Measurement	Mean blood lead (ug/dl)	Difference* between high and low PbB	Reference
Boston	Umbilical Cord	6.5	4-8 points (MDI at 6-24 mos)	Bellinger et al, 1987
	24 months	6.8	5.3 points (GCI at 57 mos)	Bellinger et al, 1991
	24 months	6.5	6.0 & 8.8 points (WISC-R IQ & K-TEA CS at 10 yrs)	Bellinger et al, 1992
Cincinnati	Umbilical Cord	6.3	6-7 points (MDI at 3 & 6 mos)	Dietrich et al, 1987
	Neonatal	4.6	6.3 points (MPC at 4 yrs)	Dietrich et al, 1991
	0-4 years	14.1	2.0 points (SIM at 5 yrs)	Dietrich et al, 1992
	Neonatal	4.8	1-5 points (BOTMP at 6 yrs)	Dietrich et al, 1993



Table 1.3. Major findings from prospective studies of lead exposure and child development (Continued)

Study	Age at PbB Measurement	Mean blood lead (ug/dl)	Difference between high and low PbB	Reference
Cleveland	Maternal	6.5	Neurological soft signs	Ernhart et al, 1985 -1989
	Umbilical Cord	5.9		
	Postnatal (0 to 3 years)	10.0-16.7		
Port Pirie	6 months	14.4	1.6 points (MDI at 2 yrs)	Wigg et al 1988
	0-4 years	19.1	3.5 points (GCI at 4 yrs)	McMichael et al, 1988
	0-4 years	19.0	2.6 points (IQ at 7 yrs)	Baghurst et al, 1992

Table 1.3. Major findings from prospective studies of lead exposure and child development (Continued)

Study	Age at PbB Measurement	Mean blood lead (ug/dl)	Difference between high and low PbB	Reference
Sydney	Maternal	9.7	No significant association	McBride et al, 1989
	Umbilical Cord	8.4		Cooney et al, 1989
	Postnatal (0 to 3 years)	13.8-18.0		
Glasgow	Maternal	Not reported	No significant association	Moore et al 1989
	1 & 2 years	Not reported		
Kosovo	2 years	35.4	1.6 points (MDI)	Wasserman et al 1992

\* Deficit per 10 ug/dl increment in blood lead concentration - except for differences between high- and low-exposure groups in Boston Study at various time up to 2 years.

#### 1.2.4.3. METHODOLOGIC CONSIDERATIONS

The results, and hence the interpretation, of studies of the neuropsychological effects of low-level lead exposure are likely to be affected by several methodologic issues:

**Comparability:** The seven major prospective studies reviewed above are comparable to the extent that they used similar research designs and implementation. However, it should be borne in mind that characteristics of the study populations, measures of exposure and outcomes, and methods of data analysis in these studies were not identical. For instance, the majority of these studies employed the same psychological test (i.e., BSID) to assess children's developmental status before and at age 2 years, but different neuropsychological tests were administered at later ages (Table 1.2). Moreover, some prospective studies (Needleman et al, 1990; Fergusson et al., 1993) have used PbD as the exposure index, while others have used serial PbB measurements as the indicator of lead exposure. Thus, despite their similar research designs, the measures of exposure and outcomes which have been used in these studies differ sufficiently to make the drawing of an overall conclusion a difficult task. Similar problems occur with the cross-sectional studies.

**Measures of exposure:** It is widely accepted that PbB is a valid measure of environmental exposure, but that it may only reflect recent exposure (approximately one month) (Rabinowitz et al., 1976). Although PbB could be an indicator of much longer exposure to lead in children (Succop et al., 1987), the dynamic pattern of lead metabolism in children remains unclear. Therefore, to obtain a more complete and definitive index of the overall lead burden experienced by each study subject, it is necessary to conduct studies which are longitudinal in design with serial PbB measurements. In the seven prospective

studies reviewed above, serial PbB measurements were generally employed in an assessment of the relationship between exposure to lead and child development. Some longitudinal data have shown the tendency of an individual to maintain the same relative ranking of exposure within the study cohort - the phenomenon of "tracking" (Dietrich et al., 1991; Baghurst et al., 1992a), and thus, if environmental sources of exposure remain relatively constant, a single PbB measure may provide more information about past exposure than was originally anticipated. Another important issue is the relative accuracy of PbB measurements made on capillary and venous blood samples. Since capillary fingerprick samples can be easily contaminated, PbB measurement in venous blood samples is generally considered more accurate than that in capillary samples. However, little has been done by way of assessing the relative accuracy of these two blood sampling methods (US EPA, 1990; Thacker et al., 1992). The validity of these measures of exposure, therefore, is difficult to assess. It is more difficult to compare the results of cross-sectional studies since the measures of exposure may have been PbB or PbD or PbT.

**Measures of outcomes:** Without prior knowledge of the nature and size of specific effects of lead on children's neuropsychological development, it is difficult to select the specific measures which will be sensitive to low-level lead exposure (Yule, 1986; Smith, 1989). Investigators have used global measures of general intelligence together with a pot-pourri of less well-validated measures of neuropsychological dysfunction. The most widely used and best validated individual tests of development and cognitive functioning include the Bayley Scales of Infant Development, the McCarthy Scales of Children's Abilities, the Kaufman Assessment Battery for Children, and the revised version of Wechsler Intelligence Scales for Children. These tests are sensitive to large cognitive deficits, but may be less sensitive to more subtle cerebral dysfunction, for which lead may or may not be responsible (Sattler, 1988; Butler & Copeland, 1993). Moreover, in some studies, only the results of the total scores have been

reported. Useful information may be lost if only the total scores are reported since some subscales of a neuropsychological test may be more sensitive to lead than others (Baghurst et al., 1992a).

**Validity of study:** The validity of any epidemiological study can be impaired by various types of biases and/or uncontrolled confounding (This is discussed in more detail in Chapter 3). The cross-sectional and longitudinal designs, however, differ in the types of potential problems they might be expected to encounter. For instance, prospective studies may face potential bias due to non-random loss to follow-up (via the influence of interactive effects), while cross-sectional studies would have poorer ascertainment of temporal changes in exposure, outcomes, and covariates.

Selection bias: Most prospective studies have examined the impact of the loss to follow-up, but it is difficult to quantify precisely the effects of potential bias due to loss to follow-up. Selection bias is more likely to occur in cross-sectional studies - where both the exposure and outcome are measured at the same time - than in prospective studies - where exposure is ascertained before the development of any outcome of interest.

Misclassification (i.e., information) bias: This arises when measurement of exposure, or outcomes is incorrect. The most important issue is whether the inaccuracies in classification of exposure or outcome are differential or random (Mertens, 1993). If differential, the misclassification could result in either an underestimate or overestimate of effect, depending on the direction of the error. Non-differential (i.e., random) misclassification causes underestimation of the true effects. Therefore, non-differential misclassification could be responsible, totally or in part, for a finding of no association between exposure and outcome. Most of the cross-sectional studies and all 7 prospective studies had laboratory quality control procedures, and used a "double blind" method of collecting data,

i.e., both observer(s) and study subjects were unaware of the histories of each subject's exposure and development. These approaches would have helped to reduce this bias. Some studies employed more than one observer, and efforts were made to reduce the *inter-observer* effect (Bellinger et al., 1987; Dietrich et al., 1987; Cooney et al., 1989; Wasserman et al., 1992). All these measures would have helped to reduce bias due to differential and non-differential misclassifications. Nevertheless, even for a single observer, the quality of soliciting, recording and interpreting information may vary with time. None of the studies reported a full assessment of potential misclassification due to *intra-observer* variation over the period of the study.

Confounding: This is a major concern in the assessment of any adverse effects of lead exposure. Most studies have attempted to measure and adjust for a range of putative confounders, but some have not. For example, socioeconomic status and obstetric conditions (e.g., asphyxia at birth) were not measured in the Kosovo study (Wasserman et al., 1992), while these factors were found to be important confounders in other studies of lead effects (Bellinger et al., 1987; Dietrich et al., 1987; McMichael et al., 1988).

Four studies were conducted in predominantly middle or lower-middle class white populations (i.e., Boston, Sydney, Port Pirie, and Glasgow); two were conducted in lower class populations (i.e., Cincinnati and Cleveland); and one was carried out in a developing country (i.e., Kosovo). Differences in socioeconomic profiles of populations - and their potential confounding characteristics - may therefore account for some of the inconsistencies between studies. It has been postulated that cognitive and academic outcomes are likely to be confounded with sociohereditary cofactors in lower class populations (Dietrich et al., 1992). The allowance for confounding factors can never be fully satisfactory since one can never hope to measure all the complex of parental,

social and environmental factors (other than lead) that influence a child's intellectual attainment (Pocock et al., 1994).

Misclassification error in the measurement of potential confounders reduces the capacity of any study to control for confounding. This remains a largely unassessed aspect of all studies of lead and child neuropsychological development.

Interaction: To date, there have been three prospective (Bellinger et al., 1989, 1990; Dietrich et al., 1987; McMichael et al., 1988, 1992) and four cross-sectional (Harvey et al., 1984; Lansdown et al., 1986; Pocock et al., 1987; Rabinowitz et al., 1991) studies which have explored interaction of social class and/or gender with lead. It is generally agreed that children in lower social class are more vulnerable to lead effects. However, there have been some inconsistencies with respect to the interaction between gender and lead. For instance, four studies have found that boys are more sensitive to the effect of lead than girls (Harvey et al., 1984; Lansdown et al., 1986; Dietrich et al., 1987; Pocock et al., 1987), but others have found the opposite effect (McMichael et al., 1988; Rabinowitz et al., 1991).

Study power: Another methodologic problem encountered in both the cross-sectional and prospective studies is statistical power. Prospective studies typically experience attrition and decreasing sample sizes during follow-up. The initial sizes of the cohorts recruited in the prospective studies varied from 151 (the Glasgow study) to 723 (the Port Pirie study), and the proportions lost to follow-up during the course of the study differed widely. The issue of statistical power is especially problematic in the interpretation of the studies in which no significant association was found between lead exposure and childhood development (US EPA, 1990; Needleman & Bellinger, 1991). For example, the average size of the effect of lead exposure on measures of cognitive ability at

age 4 years in the Boston, Cincinnati, and Port Pirie studies was a decrement of 2.9 points (on a scale with a mean of 100 and a standard deviation of 15) for a 10 ug/dl increment in PbB, and the power of the Cleveland and Sydney studies to detect an effect of this size was 44% and 52%, respectively. (The children in the Glasgow and Kosovo studies have not been followed to age 4 years.)



#### 1.2.4.4. POSSIBLE NON-CAUSAL EXPLANATIONS

The results of the studies reviewed suggest that low level exposure to lead is associated with deficits in cognitive functioning (Chapter 1.2.4.2). There are several possible non-causal explanations for this observed association (Smith, 1989; Good, 1991; Ernhart, 1992; Pocock et al., 1994). The explanations which have been suggested include: (i) the findings are due to chance (this is not supported by the overall inter-study evidence discussed in the literature review, and therefore, chance can be readily dismissed as an explanation); (ii) published studies are not representative of all studies done (this is unlikely to be true since all known ongoing prospective studies are represented in this review; even if one or two cross-sectional studies have been missed, this would not substantially affect the overall evidence of this review in which eleven cross-sectional studies of cognitive effects of exposure to environmental lead have been included); (iii) the findings can be attributed to differences in nutritional status between children with different exposure levels (unproven, and except for iron status, there is no evidence that, even if differences did exist, these would affect cognitive performance); and (iv) the association arises as a consequence of confounding by medical risk factors, such as obstetrical complications and neurological abnormalities (unlikely in view of both the toxicological and epidemiological evidence in which various species and human populations have been assessed).

A serious concern of the nature of the association of lead with cognitive development is the possibility of "reverse causality" (Smith, 1989; Ernhart, 1992; Pocock et al., 1994) - i.e., do children with cognitive deficits (e.g., lower IQ) tend to adopt behaviour patterns which might enhance their uptake of lead (e.g., greater probability of lead ingestion)? This possibility of reverse causation has clouded the assessment of lead-IQ relations for more than a decade. A lead-IQ

relation may be observed because children with lower IQ are more likely to have behaviours (e.g., playing in dirt, lack of handwashing, thumbsucking and other “mouthing” activities) which would result in increased lead intake (Smith, 1989; Ernhart, 1992; Pocock et al., 1994). The temporal sequences of the lead-IQ relation have been examined in the prospective studies (Bellinger et al., 1987, 1991, 1992; Dietrich et al., 1987, 1990, 1991, 1992, 1993; Ernhart et al., 1987, 1988, 1989a; Wigg et al., 1988; McMichael et al., 1988; Baghurst et al., 1992a; Cooney et al., 1989a, 1989b). Most of these studies have suggested that exposure to low levels of lead precedes any deficits in cognitive development, although the possibility of reverse causality has not been thoroughly examined.

Other plausible non-causal explanations include measurement bias (Fergusson et al., 1993; Greene & Ernhart, 1993), confounding by care-giving factors (Ernhart, 1992), and by exposure to other unmeasured environmental agents (Lewis et al., 1992).

As studies might differ in the differential and/or non-differential errors of measurements of exposure, outcomes, or covariates, measurement bias may be an important consideration. To explain the observed associations of lead exposure and child development, it is necessary to argue that some sort of measurement bias has always tended to cause overestimation of lead effects. Evidence against this explanation comes from studies in which both the subjects and observers were unaware of the study hypotheses and consistent dose-effect relationships were shown (US ATSDR, 1988; Needleman & Bellinger, 1991). Moreover, non-differential bias may lead to an underestimation of the association between lead exposure and child development.

There is considerable difficulty in separating the possible effects of the care-giving environment and exposure to lead on cognitive development. It is well known that the care-giving environment conveys important information about a

child's development, and that it may also correlate with a child's exposure status (Ernhart, 1992). Therefore, failure to control for the care-giving environment could produce a spurious association between lead exposure and child development.

On the other hand, a child who has a poor score in the care-giving environment is more likely to live in a neighbourhood with high soil lead level and in an older house that provides greater opportunities for exposure to deteriorating lead-based paint (Needleman & Bellinger, 1989). Moreover, the mother living in a poor home environment may herself have experienced undue lead exposure as a child, which could conceivably result in lowered intellectual development and impaired caretaking abilities (Dietrich et al., 1991). Thus, the care-giving environment might also convey some information about environmental lead contamination, and concurrently about a child's blood lead level. Controlling for this aspect of the care-giving environment would partition the variance of outcomes that lead and care-giving factors share, and thus produce an underestimate of the association between lead exposure and child development. A number of studies, however, have reported a significant and inverse association between exposure to lead and neuropsychological development even after adjustment for a wide range of confounding factors, including the care-giving environment (US EPA, 1986, 1990; Thacker et al, 1992).

Recently, Lewis and colleagues (1992) argued that, since past prospective research on lead exposure has not considered the possible confounding effects of other heavy metals, like cadmium and mercury, it cannot be concluded that the association between lead exposure and child development is causal in nature. However, because of the general agreement between studies across which the nature and exposure to other heavy metals present have varied widely, possible confounding effects of other environmental agents on the association studied are

likely to be of minor significance (Australian Commonwealth Department of Human Services and Health, 1994).

Although those implausible reasons discussed above can be readily dismissed as explanations, some factors need serious consideration, for instance, reverse causality, and residual confounding by measured and unmeasured covariates. It is difficult, however, to determine the relative importance of these explanations for the association between lead exposure and cognitive development.

#### 1.2.4.5. CRITERIA FOR A CAUSAL ASSOCIATION

A systematic approach to determining the nature of an association was used by the United States Public Health Service (1964) to establish that cigarette smoking caused lung cancer. This approach was further elaborated by Austin B. Hill (1965), who proposed nine criteria to judge the likely causality of a statistical association: (1) strength, (2) consistency, (3) specificity, (4) temporality, (5) biological gradient, (6) plausibility, (7) coherence, (8) experimental evidence, and (9) analogy. On the basis of these concepts, different sets of "guidelines for causation" have been proposed (Elwood, 1988; Beaglehole et al, 1993). Among these, the Hill criteria have been widely acknowledged, but with reservations. Before these criteria are applied, it is worth noting that, with the exception of the temporality of an association, none of the criteria is a necessary condition for a causal association. For instance, "consistency" may not always exist for a causal association, because different exposure levels and other conditions may reduce the impact of the causal determinant in certain studies. "Specificity of association" has been criticised as an illogical criterion because causes of a given effect cannot be expected to be without other effects. "Plausibility" is a conservative criterion since seemingly implausible associations may eventually be shown to be causal (Rothman, 1986; Beaglehole et al, 1993).

Despite their inadequacies and shortcomings, the Hill criteria do provide a framework within which to examine epidemiological evidence. Here the criteria are applied to evaluate the observational data for the nature of a relationship between exposure to low levels of lead and cognitive development during childhood.

## Strength of association

Since, in most studies of lead exposure and cognitive development, both exposure and outcomes are continuous variables, the ratio of incidence rates for cognitive deficits of lead exposure has rarely been reported. Recently, a systematic review of 26 epidemiological studies since 1979, including both cross-sectional and prospective designs, revealed that a typical doubling of body lead burden (from 10 to 20 ug/dl (0.48 to 0.97 umol/l) blood lead or from 5 to 10 ug/g tooth lead) is associated with a mean deficit in full scale IQ of around 1-2 IQ points (Pocock et al., 1994). The association between exposure to low levels of lead and cognitive development is obviously very modest after adjustment for the confounding factors.

## Consistency

Some inconsistencies among cross-sectional studies should be acknowledged although most studies have shown an inverse association between exposure to low levels of lead and neuropsychological development. These inconsistencies may be due to the following reasons:

- (1) the differences in methodological approaches (e.g., the Birmingham study lacks sufficient statistical power);
- (2) the different characteristics of study populations among various studies (it is possible that detection of lead effects would be more difficult in populations in which other health hazards are coexistent or overriding);
- (3) judgement of the results of studies only according to whether the relation achieves some arbitrary level of significance. For instance, the results from the

Edinburgh study in which a significant association between PbB and IQ was found after adjustment for potential confounders seem to contradict those from the London study in which there was no significant association between PbT and IQ after allowance for confounders (Smith et al., 1983; Fulton et al., 1987). However, both studies are consistent in pointing towards a weak inverse association between body-lead burden and IQ in young children (i.e., a 2.56- and 0.65-point deficit in IQ per doubling of body-lead burden, respectively, in the Edinburgh and London studies, and considerable overlap between the confidence intervals for these two studies) (Pocock & Smith, 1987). The interpretability of statistical significance is limited because of its dependence on the estimate of the magnitude of the association as well as the size of the sample. Thus, the use of a systematic overview or meta-analysis provides a quantitative method of obtaining an overall estimate of effect (Needleman & Gatsonis, 1990; Pocock et al, 1994).

Needleman and Gatsonis (1990) reported the results of a meta-analysis of 24 cross-sectional studies and calculated joint probabilities on the basis of weighted (weighting by subject number), and unweighted samples. Their analysis indicated a statistically significant and inverse relationship between lead burden (PbB or PbT) and child development. The joint P values for the blood lead studies were less than .0001 with and without weighting; for the tooth lead studies, the joint probabilities were .0005 and .004, respectively.

Other reviewers, although admitting there were some inconsistencies among the prospective studies of lead exposure and child development, have concluded that early exposure to lead is associated with poorer cognitive development (US EPA, 1986, 1990; Davis & Svendsgaard, 1987; US ATSDR, 1988; Davis, 1990; Lee & Moore, 1990; Needleman & Bellinger, 1991).

## Specificity

The association of low-level lead exposure and child development is not specific. For example, exposure to lead may result in a multi-organ impairment, such as effects on haem biosynthesis, renal function, and neurochemical system (US EPA, 1986; Goldstein, 1992; Staessen et al., 1992). However, exposure to low levels of lead has generally been found to be inversely associated with neuropsychological functioning among the various outcomes measured to date (US ATSDR, 1988; Davis et al., 1990). Among neuropsychological outcomes, cognitive development has mostly been found to be modestly associated with lead exposure (Davis & Svendsgaard, 1987; US EPA, 1990; Goldstein, 1992). Nevertheless, efforts to dissect the functional basis of effects of lead on cognitive performance have so far been unsuccessful (Davis et al., 1990; Cicuttini et al., 1994).



## Temporality

This is a fundamentally important criterion. Prospective studies have suggested that chronic exposure to low levels of lead precedes any impairment in cognitive development, although the possibility of reverse causality has not been thoroughly examined (Bellinger et al., 1987, 1991, 1992; Dietrich et al., 1987, 1990, 1991, 1992, 1993; Wigg et al., 1988; McMichael et al., 1988; Baghurst et al., 1992a). However, the question of which period in a child's growth is most sensitive to lead exposure has not been resolved. A major reason for this is the tendency for individual children to maintain the same relative ranking of exposure within the study cohort.

## Biological gradient

There are a number of studies, employing cross-sectional or prospective designs, showing a dose-outcome relationship between exposure to low levels of lead and neuropsychological development in early childhood (US EPA, 1986; Needleman & Bellinger, 1991). In these studies, either PbB or PbT was used as a continuous exposure variable. It may be worth noting that, in crude analyses, a monotonic dose-outcome relationship between low level lead exposure and neuropsychological development has been observed in almost every study, but the nature and extent of this relation after adjustment for confounders is still being debated (Pocock et al., 1994).

## Biological plausibility

There are several lines of evidence for the plausibility of a causal relation between exposure to low levels of lead and neuropsychological development.

Human studies: The adverse effects of lead exposure at high levels on central nervous systems are well known. It is generally recognised that lead is a neurotoxin, and even low-level exposure may affect neuropsychological development in early childhood (Mushak et al, 1989; US EPA, 1990).

Animal studies: The plausibility of an association between the low level lead exposure and neuropsychological development is supported by animal experiments which indicate an effect of exposure to low levels of lead on the central nervous system (Davis et al., 1990). The mechanisms of neurotoxic effects of lead exposure have been widely investigated. For example, the biological mechanisms by which lead may exert its effect on cognitive development include the following:

(1). GABA-ergic neurotoxicity: Low-level exposure to lead can reduce GABA-ergic function. The importance of GABA ( $\gamma$ -aminobutyric acid) as a regulator of overall brain activity and mood is well known, particularly in light of its major role in regulating cortical electrical activity and its intricate involvement with benzodiazepine-mediated pathways (Silbergeld, 1980; Winder, 1984).

(2). Interaction with other positively charged physiological ions or their carriers, in particular calcium: Lead alters calcium metabolism, cellular calcium homeostasis and calcium handling in presynaptic terminals, thus altering neurotransmitter release processes. In addition, lead interferes with the activation of specific calcium binding proteins such as calmodulin (US EPA, 1986; Rius, 1988).

(3). Effects on enzyme activity: It is well known that lead disturbs haem biosynthesis. Since haemoglobin plays a basic role (e.g., oxygen supply, and metabolite disposal) in all organ systems, including the central nervous system, lead exposure can have a multi-organ impact through reductions of the haem body pool. Lead also alters the activities of tyrosine hydroxylase,

phenylethanolamine-N-methyl transferase, and choline acetyltransferase which are important neurochemical enzymes. Picomolar concentrations of lead significantly activate protein kinase C which is critical in the control of cellular signal transduction (Markovac & Goldstein, 1988; McIntosh et al., 1989; Mushak et al., 1989).

(4). Other toxicities: Exposure to low levels of lead results in apparent central neurotransmitter receptor changes, and impairs astrocyte function, viz., regulation of the ionic and amino acid concentration in the extracellular micromilieu, brain energy metabolism, and cell volume (Rossouw et al., 1987; Ronnback & Hanson, 1992).

### Coherence

A cause-effect interpretation for the association between low-level exposure to lead and neuropsychological development in early childhood does not conflict with what is known of the natural history and biology of lead effects. The data from animal studies have provided some compelling support for this cause-effect interpretation (US EPA, 1986; Davis et al., 1990). Comparisons of human and animal findings reveal a number of similarities in apparent lead effects on relatively complex neuropsychological processes such as cognition and learning (Davis et al., 1990).

### Analogy

No other heavy-metal toxicant is comparable to lead in terms of its effects on neuropsychological development. Although some metals such as mercury have known effects on the human nervous system, studies of low-level chronic exposure are not available (Thacker et al., 1992).

## Experimental evidence

Since intentional exposure of children to environmental lead is unethical, no experimental evidence is available for testing the relationship between lead exposure and childhood development. However, there is a large amount of experimental evidence from *animal* studies which suggest a causal relationship between exposure to lead and cognitive development (Goldstein, 1988; Davis et al., 1990).

## Concluding remarks

Since, as discussed above, there are no completely reliable criteria for determining whether an association is causal or not, causal inference is usually tentative, and uncertainty always remains. It should be admitted that the case for a causal relationship between lead exposure and cognitive development is not strong. However, convergence of the epidemiological evidence is in favour of a causal explanation since the association of exposure to low levels of lead with cognitive development, has been found in most studies, using different research designs, in different locations and cultures, over a period of more than a decade (US EPA, 1986, 1990; Davis & Svendsgaard, 1987; Grant & Davis, 1989; US CDC, 1991).

On the basis of the anticipated temporal relationship (essential) and different types of evidence (including plausibility, biological gradient, consistency, and coherence), it could be argued that the association between exposure to low levels of lead and cognitive development is likely to be causal.

#### 1.2.4.6. PERSISTENCE OF AN ASSOCIATION BETWEEN LOW-LEVEL EXPOSURE TO LEAD AND IMPAIRED COGNITIVE DEVELOPMENT

Although exposure to low levels of lead may cause adverse effects on cognitive development during early childhood, it is unclear whether these apparent effects extend into later life or whether the affected individuals eventually "catch up" with their peers. Only a few studies have been conducted to determine whether cognitive effects of early lead exposure in children persist once their exposure levels are reduced.

Needleman and colleagues (1990) re-examined 132 subjects (mean age: 18.4 years) from their original sample of 270 children, and found that those cognitive deficits and behavioural problems associated with higher PbD in early childhood persisted in subjects followed up 11 years later. Results from the Christchurch study also suggest that mildly elevated PbD early in life is associated with relatively long-term deficits in cognitive ability and attentional behaviours (Fergusson et al., 1993). However, neither of these studies has measured PbB at the follow-up assessment. Therefore, it is difficult to judge if there has been any change in relative exposure status during the period between assessments. The Cincinnati and Boston prospective studies did not find a persistent effect of prenatal lead exposure on children's cognitive development, but the Cincinnati study did show an inverse association of exposure to lead (including neonatal and postnatal PbB) with motor development at age 6 years (Dietrich et al., 1993), and the Boston study found a persistent relation between PbB at age 2 years and cognitive performance at ages 57 months and 10 years (Bellinger et al., 1991; 1992). It should be stressed, however, that the association of postnatal PbB with neuropsychological development cannot be fully distinguished from the impacts of prenatal exposure if levels of pre- and postnatal exposure to lead are correlated.

Recently, a study was conducted to determine whether chelation therapy or biochemical changes during a lead-lowering intervention were associated with changes in cognitive functioning of children with moderately elevated PbB (Ruff et al., 1993). A total of 154 children aged 13 to 87 months took part in the study, with blood lead levels between 25 and 55 ug/dl (i.e., 1.21 and 2.66 umol/l) at the time of enrolment. The children were treated with calcium disodium ethylenediaminetetraacetic acid (EDTA) and/or with orally administered iron supplement if the child's iron status was deficient. Average PbB was reduced from 34.0 to 26.1 ug/dl in six months. The results showed that, although, in the short term (7 weeks), changes in PbB were not related to changes in cognitive scores, changes in cognitive performance were significantly related to changes in PbB in the long term (6 months), even after controlling for confounding factors. However, this study has been subject to considerable criticism for methodological problems, such as residual confounding by age, iron status and educational factors (Binder & Matte, 1993; Schindler et al., 1993; Ernhart, 1993; Cunningham, 1993). In the study conducted in Wulun, Keelung County, Taiwan, a decrease in blood lead was reported to be associated with an improvement in IQ (Rabinowitz et al., 1993). Nevertheless, since the size of the study was fairly small (only 28 children who were exposed to fugitive lead were re-examined at about 5 years), it is difficult to make any firm conclusions.

The question of the persistence of the effects of early lead exposure has been addressed in animal studies. In one study, monkeys were dosed for 200 days from birth with 0, 50, or 100 ug/kg/day of lead, and this regimen resulted in blood lead levels of 3, 15, and 25 ug/dl, respectively. After cessation of exposure, PbB declined over the next 100 to 150 days to steady-state concentrations of 3, 11, and 13.1 ug/dl, respectively. Low-level lead exposure produced neurobehavioural toxicity which persisted for up to 10 years (Gilbert et al., 1987; Rice et al., 1988; Rice, 1989). Alteration of the visual evoked potential and of the

electroretinogram was also observed in lead-treated monkeys at the age of approximately 8 years, after they had been pre- and postnatally exposed to lead as 0, 350, or 600 ppm lead acetate in their laboratory diet (Lilienthal et al., 1988).

In a study of adult rats following neonatal lead exposure (the concentration of lead in the blood of the high lead-exposed offspring at 20 days of age was approximately 6 times that of controls: 66 ug/dl vs 11 ug/dl), a significant deficit was found in the ability of the high lead-exposure group to complete a simultaneous visual discrimination task conducted in an operant chamber. However, no significant differences were observed in the ability of lead-exposed rats to complete either a successive visual discrimination task or a cued go/no-go discrimination test. These results suggest that some effects of early lead exposure may persist even after the rat has reached maturity (Hastings et al., 1979).

Follow-up studies of several groups of rhesus monkeys - in which lead treatment was limited to the first year of life with an additional high pulse given five to six weeks after birth (the average blood lead levels for the first year were 5 and 70 ug/dl for the control and exposed groups, respectively) - have shown deficits in performance of delayed spatial alternation and spatial discrimination tasks for up to 6-9 years. However, no detectable differences between lead-treated and control monkeys were obtained in two other sets of monkeys subjected to similar exposure, but without an early high lead pulse (Levin et al., 1986; Levin et al., 1987; Levin et al., 1989). Behavioural deficits in the offspring were observed at maternal monkey gestational blood lead levels within the range 30 ug/dl to 70 ug/dl at age 6-18 months, but no significant deficits were found at 19 to 26 months of age (Hopper et al., 1986).

From a review of both human and animal studies, it is still unclear whether apparent effects of lead remain once exposure is reduced, and whether early

exposure to lead has effects on neuropsychological development which continue into later life.

It might be worth noting that, in terms of causal inference, the likelihood of an association being causal is strengthened when the removal of a possible cause results in a reduced outcome (Beaglehole et al., 1993). Nevertheless, the possibility of persistent effects of exposure to lead - i.e., when the removal or reduction of exposure results in little improvement in neuropsychological development (e.g., cognitive performance) - does not contradict an interpretation of a causal relation between lead exposure and childhood development, because it could indicate a long-lasting or perhaps irreversible effect of lead.



#### 1.2.4.7. UNRESOLVED ISSUES

Although exposure to low levels of lead may affect children's cognitive functioning, there are some major issues which have not yet been resolved. Three issues that will be addressed in this thesis are:

1. Does the apparent "effect" of early exposure to low levels of lead on cognitive development persist into later life? Assessment of the persistence of the cognitive effects of lead is an important issue in the risk assessment of low-level lead exposure since the implications of the lead effects for regulatory public health policy depend not only on short-term effects but also, and in particular, on their persistence over time. Neither the human nor animal evidence available so far is adequate to conclude whether the apparent cognitive effects of early-life lead exposure persist.

2. What is the relative importance of the apparent "effect" of lead on cognitive development? Although most epidemiological studies have shown that the association between low-level lead exposure and cognitive development is small-to-moderate, little quantitative data are available so far on the relative importance of the "effect" of lead, compared with that of other socio-environmental factors in children's cognitive development.

3. Is there a level of exposure (a threshold) below which the toxic effects are non-existent? According to the available scientific data, lead exposure levels in preindustrial times were 2-3 orders of magnitude lower than current levels (Flegal & Smith, 1992b). There are two possibilities with respect to the threshold issue: (i) the ideal exposure level may in fact be zero and there may be no threshold of lead exposure in human beings (Certainly, no biological role for lead has ever been found); (ii) there may well be a threshold for lead-induced

effects at a much lower region of the exposure continuum, since lead does occur naturally. Thus, as population exposures to lead continue to decline in response to decontamination programs, the existence of a threshold for lead neurotoxicity may become more apparent.

### 1.3. STUDY AIM AND HYPOTHESES

This prospective study seeks to examine the relationship of life-long lead exposure to cognitive development beyond the age of 10 years. No other published cohort study to date has examined this long-term relationship.

The specific hypotheses to be tested in this study were:

- 1) the average PbB in early childhood is inversely related to child's IQ at ages 11-13 years.
- 2) there is a dose-effect relationship between lead exposure and IQ.
- 3) the proportion of variation in IQ attributable to lead is small compared with other social and environmental factors.

## CHAPTER 2. STUDY DESIGN AND METHODS

### Summary

*This chapter describes the research design and methods used in the study. It also describes details of the study population, data collection, and measurement of blood lead and cognitive development. The selection and measurement of covariates which might confound an assessment of the relationship between low-level lead exposure and cognitive development are also discussed. Finally, data management and analysis procedures are described.*

### 2.1. BACKGROUND

Port Pirie, site of the world's largest pyrometallurgical lead smelter, is located on the shore of Spencer Gulf, some 200 km north of Adelaide in South Australia (Figure 2.1.1). The city was developed during the 1880s with the establishment of a smelter for the rich lead-silver-zinc ore mined at Broken Hill in New South Wales. Concentrated lead sulphide ore is transported by rail 400 km from the Broken Hill Mines and smelted in Port Pirie to produce lead and other metals (Body et al., 1988).

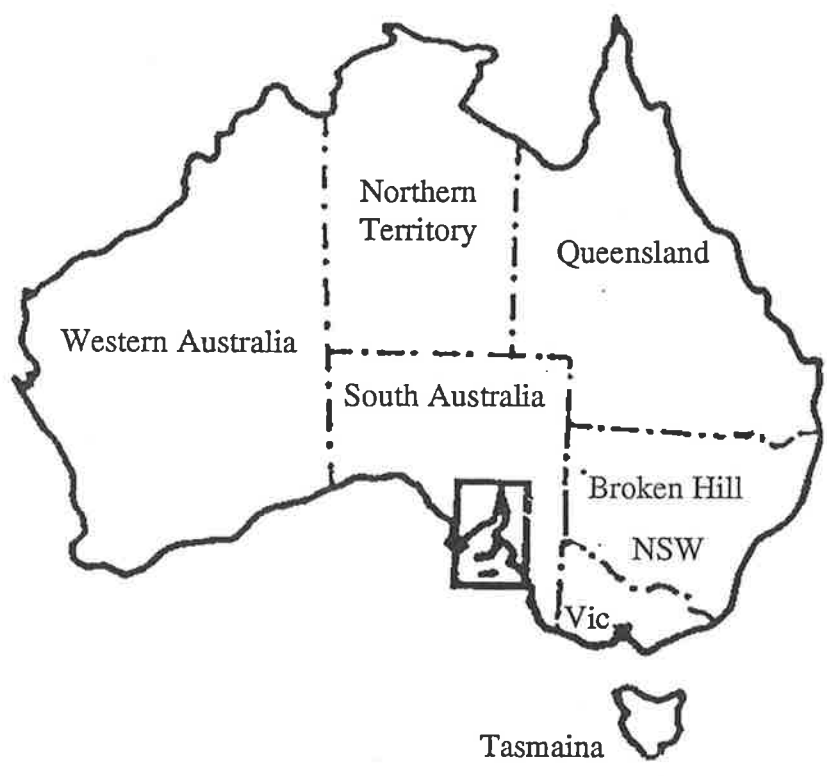
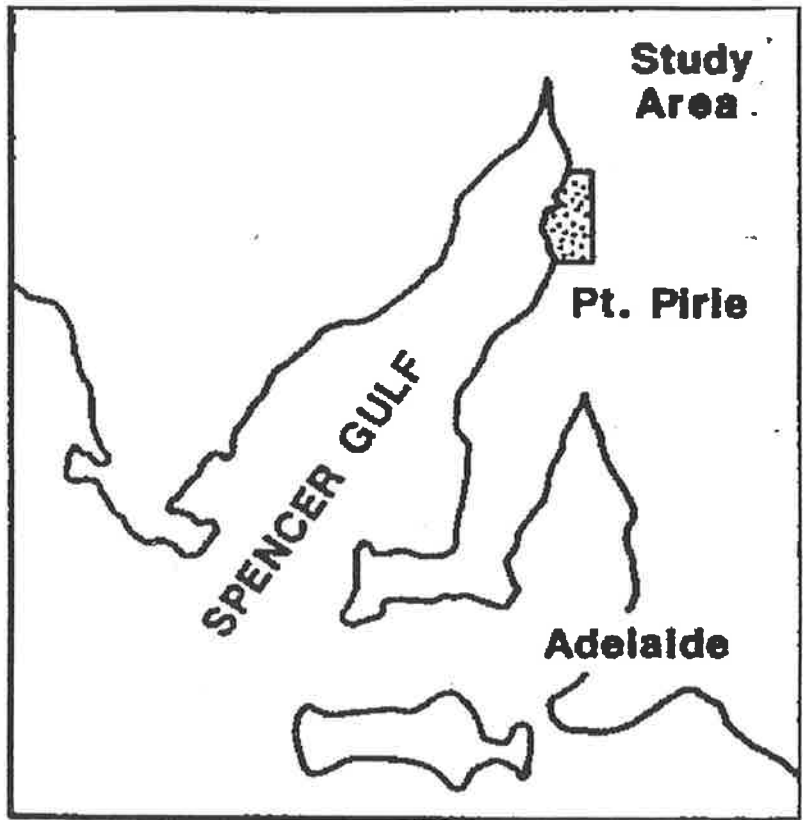


Figure 2.1.1. Location map of the study area.

The Port Pirie community, with a population of approximately 17,000 inhabitants living directly adjacent to the smelter, has been exposed to environmental lead as a consequence of operations of the lead smelter for more than 100 years.

Besides the pathways of exposure in general (see Chapter 1), children in Port Pirie are exposed to lead from several particular sources and by way of multiple environmental pathways (Figure 2.1.2) as follows:

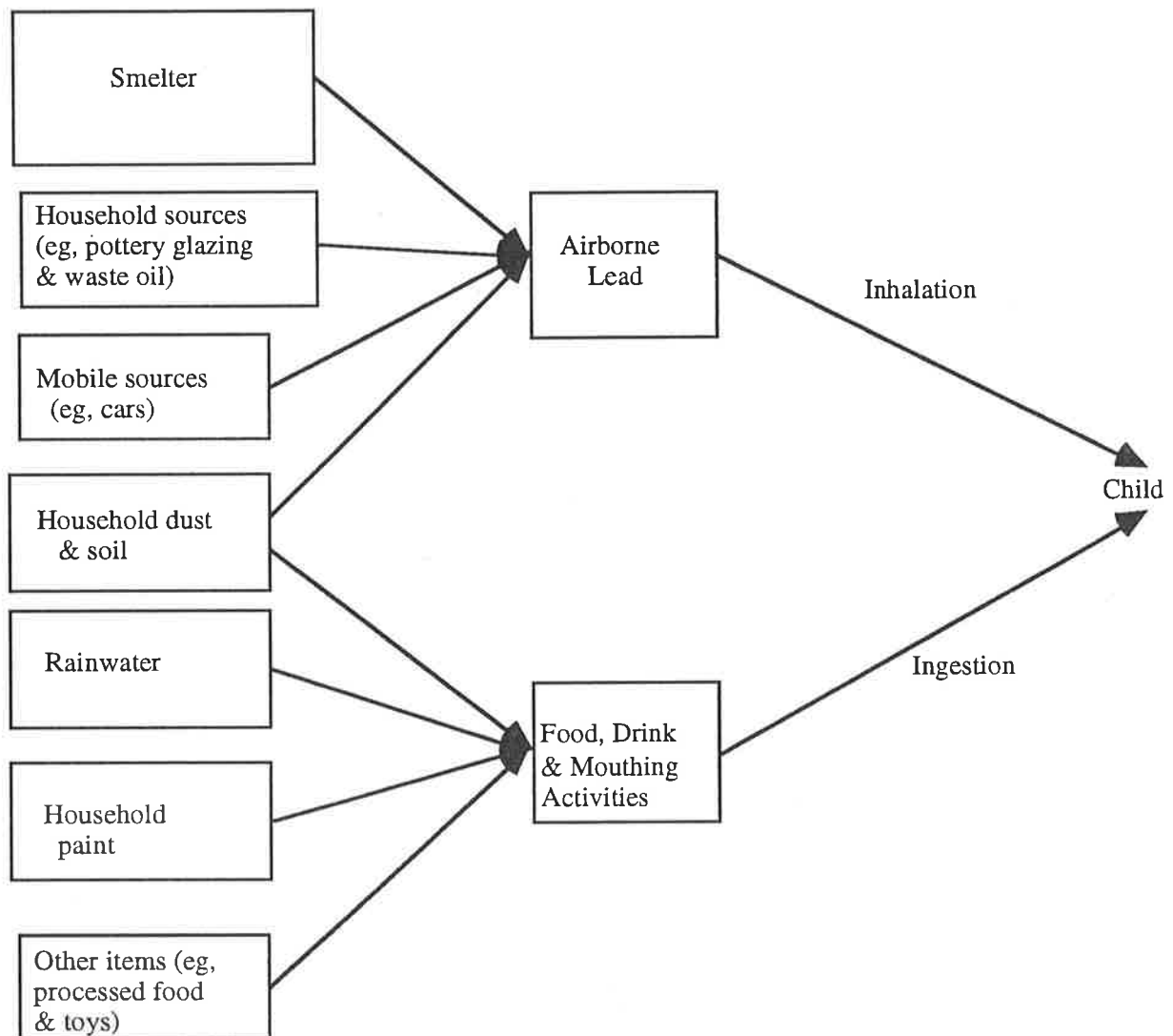


Figure 2.1.2. Sources of lead in a child's environment at Port Pirie.

(1). Industrial sources: A lead smelter - which has been operated by the Broken Hill Associated Smelters Pty Ltd (BHAS) since 1889 - is the major source of lead contamination in the city (Figure 2.1.3). The production of lead at Port Pirie between 1889 and 1982 was in excess of 12.6 million tonnes, and it has been estimated that over 167,000 tonnes of fugitive fume lead emissions from the smelter have been discharged into the atmosphere over the past 100 years. The average total lead concentration in local household dusts and local soils in 1987 were 9,418 ppm and 3,924 ppm, respectively (Body et al., 1988).

Following the introduction of the South Australian Clear Air Regulations in 1972, plant modifications were required (e.g., a 205 metre high main stack was commissioned in 1979). While many of these were aimed at controlling sulphur emissions, they inevitably reduced particulate lead losses. Fugitive fume emissions have been steeply declining with time, and current annual emissions are less than 20 tonnes and still falling. However, a significant additional component may also come from lead-bearing dusts generated by winds passing over uncovered slag heaps and stock piles on the smelter grounds and adjacent wharves and from spillage of railway trucks. Moreover, lead-bearing materials (especially blast furnace slag) have been used extensively for land fill, and thousands of tonnes of lead have been dispersed throughout the Port Pirie environment (Body et al, 1988; Luke, 1991). The re-entrainment of ceiling dusts is also an important exposure pathway for children living in old homes.

(2). Rainwater: Rainwater storage tanks were widely used to supplement the mains water supply obtained from the River Murray at Morgan in South Australia, via approximately 200 kilometre pipeline. Mains water has been shown to contain less than 0.01 mg lead per litre. However, rainwater storage tanks collect water which, in Port Pirie, often contain lead-bearing dusts, and older tanks often contain lead-bearing sludges. The geometric mean lead levels in water in these

tanks were 0.08 mg/litre in 1976 and 0.04 mg/litre in 1982, respectively (SA Department of Environment and Planning, 1986a).

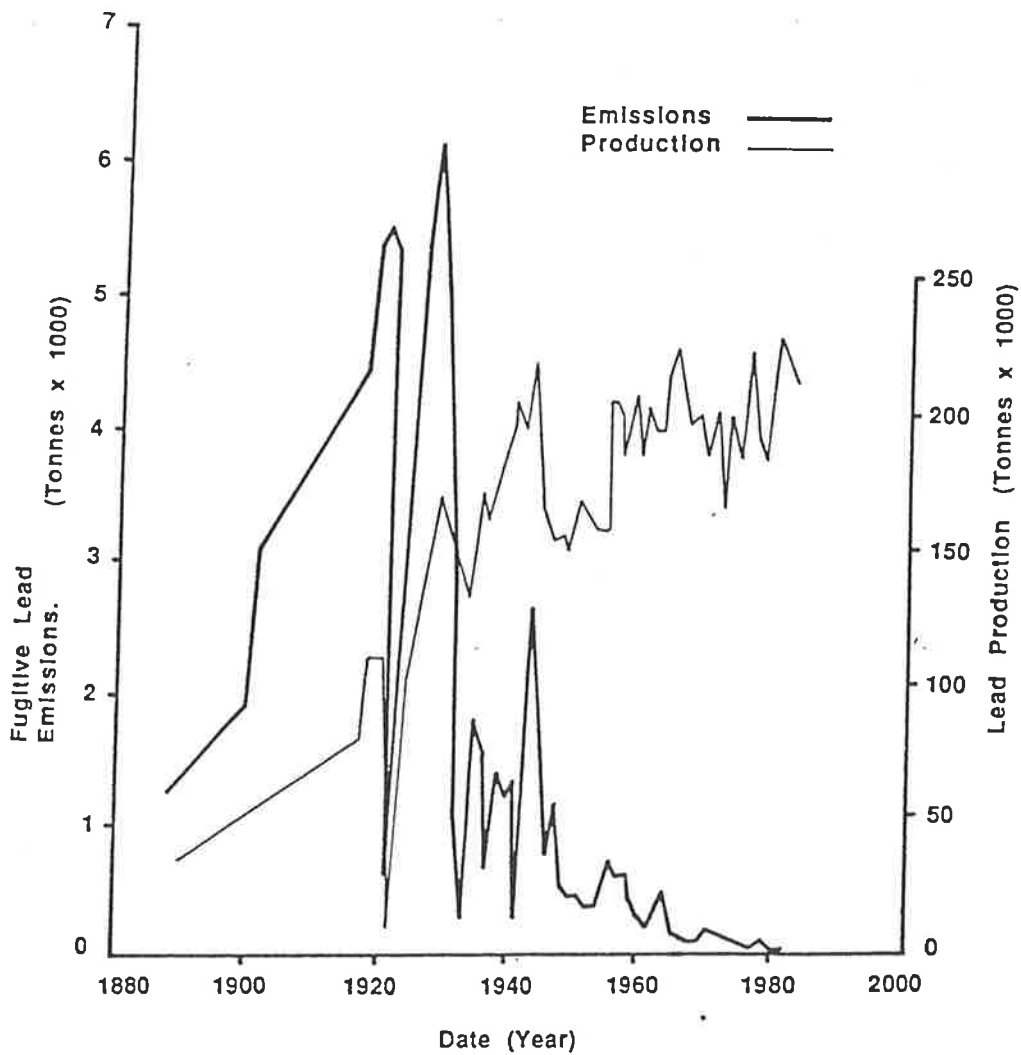


Figure 2.1.3. Annual fugitive lead emissions and production from the Smelter at Port Pirie (adapted with permission from Body et al., 1988)



(3). Mobile sources: Leaded petrol is another source of contamination in the city. Atmospheric emissions of lead from the combustion of leaded petrol at Port Pirie were estimated to be approximately 5 tonnes annually, i.e., 10 to 13 percent of the measured emission from the smelter (SA Health Commission, 1983; Goh et al., 1986). Moreover, ore and concentrate are transported by rail from Broken Hill to Port Pirie, and higher lead levels were found in soils along the railway line and in ore handling places (Body et al., 1988).

(4). Household paint: Lead-based paint was used extensively in houses in Port Pirie prior to the 1960s. In many of the old houses this paint has now deteriorated and is flaking. In this condition, the paint can be picked off and eaten by young children, or it can fall to the ground and contribute to soil lead contamination (SA Department of Environment and Planning, 1986b).

(5). Parental smoking and lead-bearing materials transported home by smelter workers are two other sources of lead exposure in children (SA Health Commission, 1983; Baghurst et al., 1992b). Employment of parents at the smelter, and parental smoking were found to be significantly associated with higher PbB in the Port Pirie children. (Note: Since 1984-85, employees at the smelter have been provided with shower facilities, and work clothes that do not have to be taken home.)

In summary, the Port Pirie environment has been contaminated over the past 100 years by ores, emissions, and fugitive losses from the smelter operations. Lead in dust/soil may be the most important pathway in the child's living space at Port Pirie. Lead in rain water, and house-paint may be important secondary pathways.

## 2.2. STUDY DESIGN

The research design of the extended Port Pirie Cohort Study is shown schematically in Figure 2.1.4. A total of 831 pregnant women were enrolled in the study from May 1979 to May 1982. This enrolment was achieved with the coordinated active support of a network of medical practitioners servicing the community. These women, from Port Pirie (N=646) and the surrounding neighbouring towns (N=185), represented approximately 90% of all newly occurring pregnancies with the specified source population during that period. Inclusions of women from outside Port Pirie, where exposures to lead were expected to be somewhat lower than within the city, provided a second source of comparison beyond that afforded by the inter-individual variation in PbB among women resident in Port Pirie (Baghurst et al., 1987; McMichael et al., 1988).

Eligibility criteria employed in the Port Pirie Cohort Study were: (1) consent by the pregnant woman; (2) no maternal medical conditions associated with congenital anomalies and developmental handicap; (3) residence in Port Pirie and surrounding environs (i.e., townships of Laura, Gladstone, Crystal Brook, Port Broughton and Port Augusta); (4) English as the first language at home.

Of the 831 pregnancies, 723 singleton live infants were recruited into the initial cohort. All of the children in the study are Caucasian.

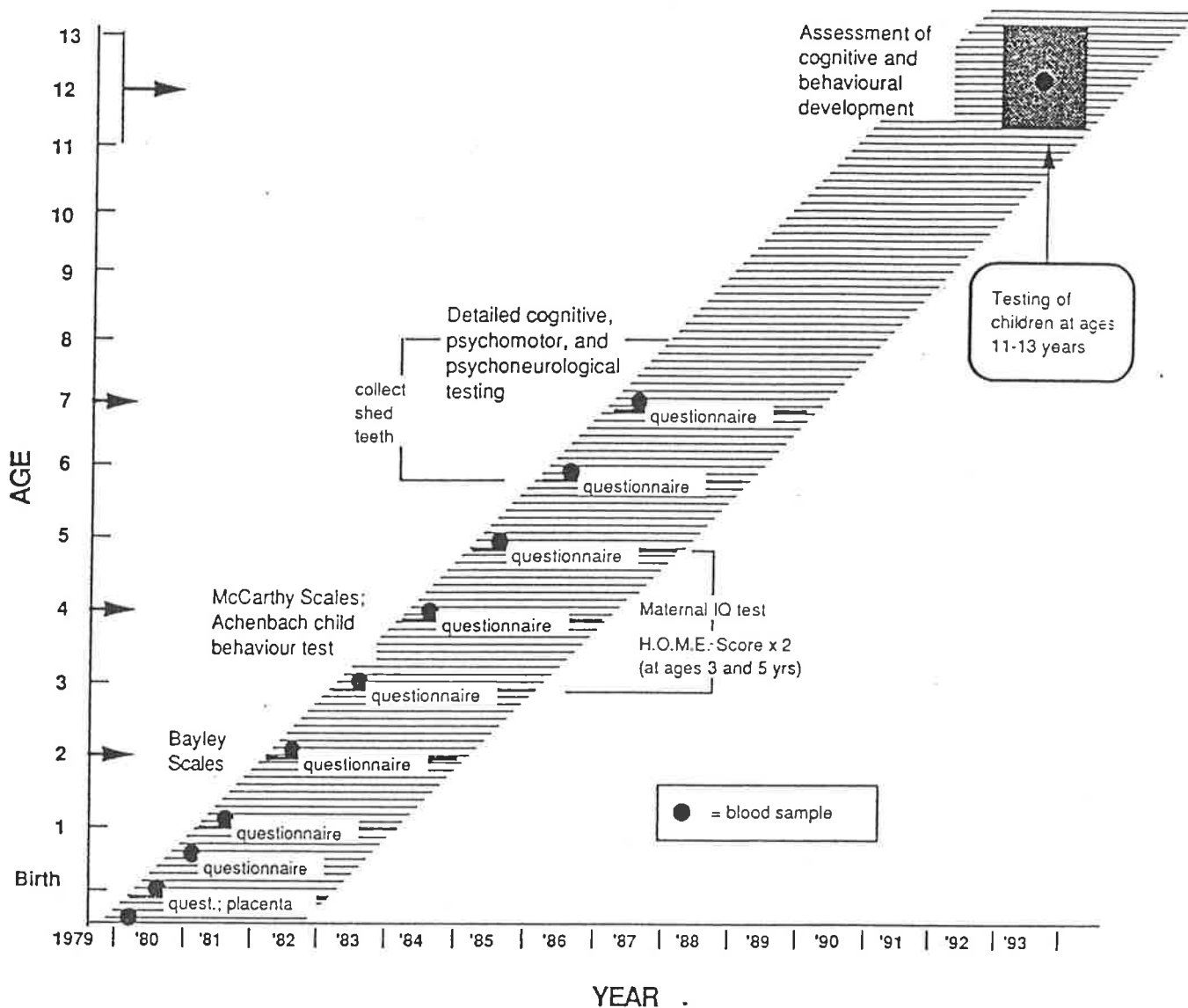


Figure 2.1.4. Research design of the Extended Port Pirie Cohort Study.

Four research nurses collected up to three venous-blood samples from each mother before delivery, and capillary-blood samples from each child at ages 6, 15, and 24 months, and annually thereafter to seven years of age. Hospital staff collected blood samples from the umbilical cord at birth. A pilot study in 47 children who were two to four years of age demonstrated that the lead concentrations in capillary-blood samples collected according to a strict protocol, were highly correlated ( $r=0.97$ ) with the lead concentrations measured in venous-blood samples. Although the "finger stick" method for lead assessment is not considered to be as reliable as the venous sampling method (Schwartz, 1994), it appears that the capillary samples obtained in this study provided a reasonably accurate overall reflection of venous blood lead levels (Calder et al., 1986; McMichael et al., 1988).

The developmental status of each child was assessed with the Bayley Scales of Infant Development, the McCarthy Scales of Children's Abilities, and the Wechsler Intelligence Scale for Children-Revised at ages 2, 4, and 7 years, respectively (Bayley, 1969; McCarthy, 1972; Wechsler, 1974). All assessments were conducted by a clinical psychologist, who was unaware of the lead-exposure and developmental history of individual children.

At the time of each blood sampling, a research nurse also conducted a structured interview to obtain information on a range of demographic, socio-environmental, and biomedical factors.

The present study has extended the follow-up of children in the cohort to ages 11-13 years. In order to take into account any effects of late childhood exposure to lead, an additional venous-blood sample was taken as part of the follow-up at ages 11-13 years.

### 2.3 STUDY POPULATION

The base population in this study was the 494 children who were assessed at age 7 years (Baghurst et al., 1992a). An additional eligibility criterion was employed in the present study to ensure that estimates of lifetime average PbB were reliable, i.e., children to be assessed should not have missed more than two PbB measurements over their first seven years. Twenty one children were excluded for this reason and one further child was excluded because he was found to have had a head injury.

Of the 472 eligible children, 53 (11.2%) had moved, and could not be contacted; 42 (8.9%) refused to participate; and 2 (0.4%) could not be reached, despite intensive efforts (at least 3 attempts). The number of children finally assessed was 375 (79.5%) (Figure 2.3.1.).

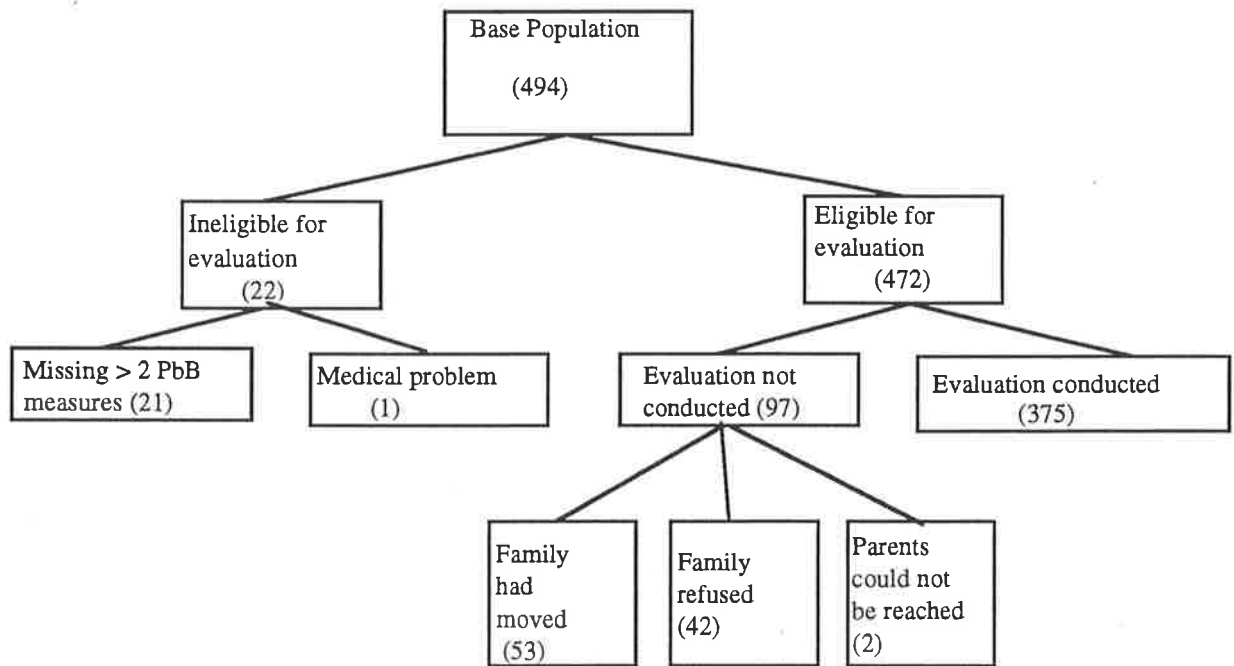


Figure 2.3.1. Sources of attrition of the study population between ages 7 and 11-13 years.

## 2.4. DATA COLLECTION

All parents of the children in the study were sent a letter which described the objectives, nature and process of the study (Appendix 1). Following this, informed consent to participate in the study (Appendix 2) was obtained from the parents by a research nurse. While the nurse collected a venous blood sample from each child (Appendix 3), the mother completed a booklet containing the Family Assessment Device (Byles et al., 1988), the General Health Questionnaire (Goldberg, 1978), and a background information sheet (Appendix 4). A semi-structured interview was also employed to obtain information about the child's life events and medical conditions (Appendix 5).

The cognitive assessments of 342 children (91.2%) were undertaken in local schools. An appropriate assessment room was provided in each school. Nine children (2.4%) were assessed at home because of specific requests by the parents; and 24 (6.4%) were assessed in the CSIRO Division of Human Nutrition because they had moved to Adelaide.

### 2.4.1. BLOOD SAMPLING AND ANALYSIS

Several steps were taken to avoid lead contamination during blood sampling and analysis (see details in Chapter 3.1.1). All equipment and reagents used for the handling and treatment of blood samples were checked and ensured to be free of lead contamination. A standardised method for skin cleaning was employed before a venous blood sample (4 ml) was obtained (Standards Association of Australia, 1988). Blood samples were obtained from 329 children on the day of interview. Insufficient samples were obtained from 5 children and 41 children refused to have blood taken. All samples were placed directly into heparinized polystyrene containers. One ml of each sample was sent to the

Institute of Medical and Veterinary Science at Port Pirie where haemoglobin concentration, packed cell volume, and numbers of erythrocytes, white blood cells and platelets were determined. The remainder of the sample was sent to the Department of Chemical Pathology at the Women's and Children's Hospital in Adelaide for PbB and serum ferritin measurements. PbB was estimated in duplicate by means of electrothermal atomisation atomic absorption spectrometry, after standard complexing and extraction of lead (Standards Association of Australia, 1985).

Measurements of PbB were performed in the Department of Chemical Pathology at the Women's and Children's Hospital. The Laboratory is subject to ongoing internal and external quality control, and participates in inter-laboratory quality control programs at a national and international level (see details in the Chapter 3). Serum ferritin concentration in each sample was measured by the Microparticle Enzyme Immunoassay (Forman et al, 1980). To be consistent with previous practice in this study, individual estimates of PbB at ages 11-13 years were standardised to a packed cell volume of 35%. Estimates were also standardised to a packed cell volume of 50 percent for cord blood and 35 percent for all other samples (McMichael et al., 1988; Baghurst et al., 1992a).\*

\* The objective of hematocrit adjustment is to correct for variation in PbB as a consequence of variation in the concentration of available binding sites of erythrocytes for lead. However, this correction had little effect on the assessment of the relationship studied. For instance, the hematocrit adjusted and unadjusted partial regression coefficients for PbB at ages 11-13 years on IQ were almost identical (adjusted: 3.1; unadjusted: 3.0).



#### 2.4.2. ASSESSMENT OF INTELLIGENCE

The Wechsler Intelligence Scale for Children - Revised (WISC-R) was used to evaluate the children's cognitive development (Wechsler, 1974). This test was chosen because, (i) it is a well-standardised psychological test; (ii) it has been employed in most other studies assessing the effect of lead exposure, and its use enables the results in this study to be compared with those from other studies; (iii) it was used when the children in this cohort were 7 years old, and its continuing use at ages 11-13 years enables direct comparison of the results at these two different ages.

The WISC-R is a test of general intelligence developed for use with children aged 6-16 years. In addition to providing a summary rating of a child's overall intelligence, the WISC-R includes a Verbal Scale which provides a rating of a child's verbal comprehension, and a Performance Scale which provides a rating of a child's perceptual organisation (Wechsler, 1974; Sattler, 1988). The WISC-R contains 12 subtests. Six WISC-R subtests (information, similarities, arithmetic, vocabulary, comprehension and digit span) are employed to estimate the Verbal Scale IQ and the six remaining subtests (picture completion, picture arrangement, block design, object assembly, coding and mazes) are used to estimate the Performance Scale IQ.

All the assessments at ages 11-13 years were conducted by a single trained examiner (Miss J. Mudge, B.A.(Hons) in Psychology), who was unaware of all aspects of a child's lead-exposure and developmental histories. She had not participated in assessing the children at younger ages. Each assessment took about one and half hours to complete, with children being allowed to have brief rests whenever appropriate (see more details in Chapter 3).

### 2.4.3. MEASURES OF COVARIATES

An important consideration was the selection and measurement of covariates that are known or likely to be associated with both childhood cognitive development and lead exposure, and that are not purely intermediate steps in the putative causal path between exposure and outcome. Such covariates are therefore potential confounders in this study.

Measurement of covariates is very important because it can increase the statistical power of a study by reducing the apparent error variance, and because the covariates may confound any true relationship between lead exposure and child development (Confounding is always an alternative explanation of the findings in observational studies, unless it has been carefully considered (Datta, 1993)).

Since iron status in children is now receiving attention in the literature as a potential confounder of the lead-IQ relationship (Lozoff et al., 1991), associations of a serum measure of iron status (i.e., ferritin) with PbB and with children's IQ were also scrutinised. However, serum ferritin was found to be associated with neither PbB nor children's IQ, and therefore is not considered as a potential confounder in this study (The details are presented in Appendices 6 and 7).

In this study, 22 variables were considered for use as covariates which might confound the association between lead exposure and children's IQ. These covariates are as follows:

Demographic variables: It is well known that some demographic variables are related to both lead exposure and developmental status (e.g., child's age). Children of the same age may be in different "grades" at school - which may also

affect developmental measures (Bouchard & Segal, 1985). Moreover, it has been suggested that gender may act as an effect modifier in some studies of low-level lead exposure (McMichael et al., 1988; Rabinowitz et al., 1991). The demographic variables considered in this study were gender, child's age, and child's school year.

Psycho-social and environmental factors: Several psycho-social and environmental factors (e.g., socioeconomic status, the care-giving environment, parent's marital status, and family size) appear to be potential confounders in any assessment of the association between exposure to lead and child development, (Yule, 1986; McMichael et al., 1988; Smith, 1989; Greene & Ernhart, 1991; Ernhart, 1992; Baghurst et al., 1992a). It has also been argued that parental smoking may influence childhood development (Sexton et al., 1990; Tong & McMichael, 1992), and indeed, was found to be associated with PbB in the Port Pirie children (Baghurst et al., 1992b). Moreover, since family functioning and parental psychiatric status may also affect child development, standardised measurements of these covariates were also employed (Goldberg, 1978; Byles et al., 1988). The psycho-social and environmental factors measured in this study were:

- 1). Socioeconomic status (SES): The Daniel Scale (Daniel, 1984), which is based on the prestige of the parents' occupations, was employed as a surrogate measure for social status. The Daniel score is inversely related to prestige (i.e., the higher the Daniel score, the lower the prestige). The SES of each family was evaluated when the child was born and again at ages 2, 4, 7 and 11-13 years. The average Daniel score was used as an indicator of SES.

- 2). Care-giving environment in early childhood: The Home Observation for Measurement of the Environment inventory or "HOME" (Bradley & Caldwell, 1979) was used to assess each child's care-giving environment. The HOME

scores, which were measured at ages 3 and 5 years, were averaged to form an aggregate HOME score. The HOME inventory evaluates the quality of the caregiving environment. The inventory has six subscales: emotional and verbal responsiveness of the parents; parental acceptance of the child; maternal involvement with the child; organization of the home environment; appropriateness of play materials; and variety in daily stimulation (Bradley & Caldwell, 1979).

3). Family functioning: The child's family function was assessed with use of the General Function Scale (GFS) of the Family Assessment Device (Byles et al., 1988). The GFS consists of 12 items and provides an overall measure of the health/pathology of the family with a good reliability and validity.

4). Parents' psychiatric status: The parents' psychiatric status was measured with the 12-item General Health Questionnaire (GHQ). The GHQ has been widely used to assess psychiatric status of respondents in community settings (Goldberg, 1978).

5). Parent's marital status.

6). Parental smoking habit(s).

7). Family size (number of siblings).

8). Life events. The parent was asked: "Has your child experienced any major stress since he/she was 7 years old? (e.g., parental separation, death of close relatives, accidents or serious illnesses.)

9). Period of mother's residence in Port Pirie (years).

10). Assessment site (school, CSIRO and home).

Familial variables: These variables are important predictors of children's intelligence, since they may also associate with the quality of home environment, and therefore, associate indirectly with exposure status (Bouchard & Segal, 1985; Needleman & Bellinger, 1989; Dietrich et al., 1991). They are also potential confounders.

1). Maternal IQ (evaluated with the Wechsler Adult Intelligence Scale-Revised (Wechsler, 1981)).

2). Paternal education (assessed in terms of the number of years of secondary school education).

Biomedical factors: Some of these factors (e.g., birthweight and birth order) are widely considered to be predictors of children's intelligence, and some of them (e.g., maternal age, and using medications, etc.) are putative confounders in studies of lead exposure and child development (Lyngbye et al., 1989; Baghurst et al., 1992a).

1). Maternal age (years).

2). Birthweight (grams).

3). Birth order.

4). Feeding style during infancy (breast, bottle and mixed).

5). Duration of breastfeeding (months).

6). Whether any medication had been used in the last 2 weeks before testing.

7). Whether the child had ever been absent from school for two weeks or longer in any single school term during the last five years.

## 2.5. DATA MANAGEMENT AND ANALYSIS

### 2.5.1. DATA PROCESSING AND MANAGEMENT

Information recorded on questionnaires was coded and entered using a verification procedure. All data were managed with the Scientific Information Retrieval (SIR) database management software (Robinson et al., 1980).

### 2.5.2. DATA ANALYSIS

Statistical methods used to analyse the data from this study included simple univariate, bivariable, and multivariable techniques to evaluate the relationship between blood lead and children's IQ. The major statistical tests employed in this study included ANOVA (for more than two groups) and Student's t tests (for two groups), and all significant tests and 95 percent confidence intervals were two-tailed. A General Statistical Program (Genstat) was used for most analyses (Payne et al., 1987).

The data analyses are generally presented in three stages as follows:

#### (1) Simple univariate analyses

Simple univariate analyses were conducted to summarise the characteristics of each individual variable in the data set. Data distributions of exposure and outcome variables were examined. In order to prevent a small number of very high values of PbB from exerting a disproportionate influence on quantitative estimates of the relation between exposure to lead and children's IQ, statistical analyses were performed on the natural logarithm of PbB, and all reported mean values of blood lead concentrations are geometric. Because the natural logarithm of PbB was used in all simple and multiple regression analyses, the

regression coefficients represent the change in units of IQ points per natural log unit of PbB, expressed in  $\mu\text{g}/\text{dl}$ .

In order to calculate average lifetime blood lead concentrations, a plot of PbB against age was constructed for each child. The lifetime average PbB up to a particular age was estimated by dividing the appropriate area under the curve by the specified age. This method of averaging copes readily with the unequal time periods between successive blood samples.

## (2) Bivariable analyses

For summary descriptions of the data, mean IQ scores were tabulated by tertiles of blood lead concentration at various ages. The unadjusted dose-effect relationships (i.e., without consideration of the potential confounding factors) between PbB and children's IQ were assessed with simple regression models.

## (3) . Multivariable modelling

Multiple linear regression was employed to evaluate the relationship between PbB and children's IQ while controlling for the effects of putative confounding factors. Regression coefficients ( $\pm$ standard errors) of PbB and other independent variables were estimated under the reasonable assumption that IQ scores are normally distributed.

The model-building strategies used in this study include: (a) identification of potential confounders and effect modifiers; (b) assessment of a covariate-adjusted dose-effect relationship between PbB and children's IQ; and (c) evaluation of the relative proportion of variance in IQ attributable to lead exposure, compared with that attributable to other factors.



## Identification of potential confounders

A covariate selection process was carried out separately for each age of blood sampling, since the importance of covariates in an assessment of a lead-IQ relationship may change over time. The selection of covariates was based on both *a priori* and empiric considerations (Dale et al., 1978; Kleinbaum et al., 1982; Mickey et al., 1989; Greene et al., 1991). First, the important antecedents or correlates of developmental outcomes (i.e., children's IQ) were included in the analyses. Second, the variables which were associated with both PbB and developmental outcomes were considered as potential confounders. Finally, the change-in-estimate rule was used as a guide to evaluate an individual effect of each potential confounder (Mickey & Greenland, 1989). A covariate was considered to be a confounder of the lead-IQ relationship if the partial regression coefficient of the lead term varied by more than 10 percent when the covariate was added to or deleted from the model. However, if its' inclusion reduced the error variance substantially, that covariate was retained in the model even though the partial regression coefficient did not differ by more than 10 percent when it was added to or excluded from the model. The combined effect of potential confounders was assessed by the same rule, and was identified by the change in magnitude of the regression coefficients after adjustment for all the potential confounding factors.

All the explanatory variables (except for PbB) which were included in the multiple regression models were categorised, since categorisation of covariates in the model avoids the need to assume a particular functional form (e.g., linear, or exponential, etc) and makes best use of all available data - e.g., the creation of a "missing" category for a particular variable allows for the remaining data to contribute to the analysis. Since the inclusion of subsets with missing data is controversial, this procedure was used only when the number of missing values for any one variable was not too large.

### Assessment of effect modification (interaction)

The possible interactions between blood lead and other covariates were also explored. Stratified analyses were conducted on separate categories of the factors which might act as effect-modifiers on the relations of PbB with children's IQ (Rutter & Russell-Jones, 1983; Bellinger et al., 1989; McMichael et al., 1992). Interaction terms of lifetime average PbB and some possible effect-modifiers indicated by the stratified analyses were then added to the multivariable model. Interactions between PbB and potential effect modifiers allow separate estimates of the changes in the effects of PbB for each level of the effect modifier. The ANOVA test was used to assess effect modification (Payne et al., 1987).

### Assessment of a dose-effect relationship

Multiple linear regression models were employed to assess whether there was a dose-effect relationship between lead exposure (i.e., tertile of PbB) and children's IQ after adjustment for the potential confounders.

### Evaluation of relative importance of the lead "effects" in children's IQ

In order to estimate how well lead exposure can predict IQ, the proportion of the variance attributable to lifetime average PbB was recorded for each regression model. The estimated variance accounted for by lead was compared with that accounted for by the subsets of other variables, including socio-environmental, familial, demographic, and biomedical factors.

### Treatment of missing values

During the process of data analyses, careful attention was given to missing data. Specifically, if a value for a variable was not collected or recorded, the subject was allocated a 'missing' category for that specific variable in regression analyses. As mentioned above, any subject whose age-specific PbB was missing for more than two measures was excluded from the study. Each child's average lifetime blood lead concentration was estimated by trapezoidal integration of the curve of PbB versus age. For subjects with one or two missing values for PbB, trapezoidal integration was performed using the values on either side of the missing value. If the cord PbB was missing, it was replaced by an estimate of  $0.9 \times$  maternal delivery PbB. The factor 0.9 was determined from a separate analysis of the relationship between maternal PbB at delivery and cord PbB.

In accepting the results of this calculation, there is an intrinsic assumption concerning the linearity of PbB versus age across the period in which an observation was missed. In order to evaluate the impact of this assumption, comparison was made between results of analyses in which the subjects with missing PbB were and were not included. The correlations between average

lifetime PbB and children's IQ were very similar for both groups (e.g., -0.32 for the data with missing values, and -0.31 for the data without missing values).

## 2.6. ETHICAL CONSIDERATIONS

This study was approved by the Research and Ethics Committees at the University of Adelaide and the Adelaide Women's and Children's Hospital.

All eligible subjects were provided with an Information Sheet indicating the objectives, methods and procedures of this study (Appendix 1). Written consent for participation (Appendix 2) was obtained from the parents after the nature of the study and their rights and freedoms to withdraw at any time were explained to them by the research nurse. Verbal consent was also obtained from the participating children. Subjects taking part in the study were also given a copy of the Information Sheet and the signed Consent Form.

The personal privacy and confidentiality of each participant were respected throughout the study. For example, the questionnaires used in this study were only identified by a study identification number. Names were not recorded on the questionnaires.

Assurances were also provided that the results of this study would be reported initially in a scientific venue rather than through the mass media, and that the results and their significance would be transmitted to the individual families involved.

## CHAPTER 3. EVALUATION OF VALIDITY AND PRECISION OF THE STUDY

### Summary

*This chapter discusses the validity and precision of the study, the potential sources of bias and confounding, and the quality control procedures employed in the study. Special attention is given to an assessment of the impact of potential bias due to loss of subjects at follow-up and possible misclassification with respect to either exposure or outcome status. The external validity of both exposure and outcome measures, and precision of the research are also examined. Finally, the demographic characteristics of the study population are compared to those of the general population from the latest census and population survey data collected by the Australian Bureau of Statistics .*

### 3.1. VALIDITY

The quality of the information and of the inferences from an epidemiological study is directly determined by the research design and the quality of the data collected throughout the study. Therefore, in presenting results, initial attention is given to the validity and precision of the study, including the potential sources of bias and confounding, an evaluation of the quality control procedures used in the study, and measures used to reduce random errors.

Validity is an expression of the degree to which a test or a study is capable of measuring what it is intended to measure (Beaglehole et al., 1993). The validity of this study, like that of any epidemiological study, is composed of two components: internal and external validity. Internal validity is the degree to which the results of an observation are correct for the particular group of people being studied, i.e., it implies validity of information for the study subjects themselves. External validity,

or generalisability, is the extent to which the results of a study apply to people outside the study population, i.e., it refers to the way in which the findings can be generalised to a wider population (Rothman, 1986; Elwood, 1988; Beaglehole et al., 1993).

### 3.1.1. INTERNAL VALIDITY

#### 3.1.1.1. GENERAL ISSUES

The validity of internal comparisons made within a study population can be impaired either by bias\* or by uncontrolled confounding. Bias occurs whenever the processes of selection and/or observation cause the data to misrepresent the true relationship as it exists within the source population. Selection bias at the time of recruitment is less likely to occur in a prospective cohort study (and is, in any case, a determinant of external, not internal, validity) than in a case-control study, a retrospective cohort study or a cross-sectional study (Rothman, 1986; Hennekens & Buring, 1987; Elwood, 1988), where both the exposure and outcome have already occurred at the time individuals are selected into the study. Selection bias is unlikely to occur in a prospective cohort study because exposure is ascertained before the development of any outcomes of interest. However, bias due to losses to follow-up does occur if the subjects lost to follow-up differ significantly from those still being followed, and the probability of loss is related to either the exposure, or the outcome, or to both. Bias due to losses to follow-up can also affect internal validity (Rothman, 1986; Hennekens & Buring, 1987).

\* There is no consensus regarding either the definition or the categorisation of bias in epidemiological textbooks. However, bias, in an epidemiological context, usually includes all sources of systematic error (Rothman, 1986; Hennekens & Buring 1987; Elwood, 1988; Beaglehole et al., 1993).

Interview bias and misclassification bias are sometimes collectively referred to as observation or information bias. Interview bias occurs when observers who are aware of the study hypothesis are more (or less) likely to record the outcome of interest for individuals known to have the exposure under scrutiny. Misclassification bias arises when subjects are erroneously categorised with respect to either exposure or outcome status. Misclassification of study subjects arises from a lack of validity and/or lack of reliability in the measurement of variables (Rothman, 1986; Hennekens & Buring, 1987; Beaglehole et al., 1993). Non-differential misclassification refers to error in the measurement of outcome that is unrelated to exposure status, or misclassification of exposure unrelated to the individual's outcome status. Regardless of whether the exposure (or outcome) is a continuous variable or is classified as present or absent (i.e., dichotomous classification), non-differential misclassification will always lead to underestimation rather than overestimation of the association of interest, i.e., the estimate of "effect" will always be biased towards the null. When the exposure has more than two levels, non-differential misclassification will have less predictable impacts, and may overestimate or underestimate the association (Mertens, 1993).

Differential misclassification refers to errors of measurement which are related to exposure or outcome status. This is potentially more serious than non-differential misclassification since for both dichotomous and continuous variables, even in the absence of confounding, differential misclassification can distort the estimate of an association under study, and may lead to bias in either direction (Greenland & Robins, 1985; Mertens, 1993).

A further component of misclassification might occur because of lack of validity or reliability in the measurement of covariates. If a misclassified covariate is a confounder, the ability to control confounding in the analysis is hampered, and, misclassification of a confounder will lead to underadjustment for that confounder (Greenland, 1980; Mertens, 1993).



Confounding occurs when an extraneous variable is associated with exposure and is also, independently of that association, predictive of the outcome under study. Confounding can lead to overestimation or underestimation of the relationship under study, depending on the direction of the associations that the confounding factor has with exposure and outcome. Confounding can even change the apparent direction of the relationship under study. Failure to control confounding either by research design (e.g., through the application of randomisation, matching or exclusion criteria) or by data analysis (e.g., by stratification and/or appropriate modelling of confounder terms) will provide misleading estimates of effect (Rothman, 1986; Hennekens & Buring, 1987; Hennekens & Buring, 1987; Elwood, 1988; Beaglehole et al., 1993). Various types of bias and uncontrolled confounding were potentially capable of detracting from internal validity in this study.

#### 3.1.1.2. APPLICATION TO THIS STUDY

(1) Bias due to losses to follow-up: When persons lost to follow-up differ from those who remain with respect to the relationship between exposure and outcome, any observed association will be biased. For example, it is generally acknowledged that children from disadvantaged families have higher PbB and are more sensitive to the effects of lead than those from advantaged families (Rutter, 1983; Bellinger et al., 1989; McMichael et al., 1992). If the socio-economic profile of the children who remain in the study differs from those who are lost to follow-up, bias might occur.

In this study, the 494 children who were assessed at age 7 years comprised the base population. Of these 494 children, 375 (75.9%) were assessed at ages 11-13 years. The characteristics of the children remaining in the cohort and those not followed up were compared (Table 3.1). Although the socioeconomic status of the

children lost to follow-up was slightly lower than that of those remaining in the cohort at ages 11-13 years, the demographic characteristics of the two subsets of children were similar with respect to most of the variables studied. The measures of prenatal and postnatal exposure and the developmental status for the two groups were almost identical. (A similar trend was observed for the children remaining and those lost to follow-up in the first seven years of the study (Baghurst et al., 1992a)). Therefore, bias due to loss to follow-up is unlikely to be a major problem in the study.

Table 3.1. Characteristics of children remaining in the cohort and lost to follow-up at ages 11-13 years.

Characteristic	Children in the cohort (N = 375)	Children lost to follow-up (N = 119)
Sex (%)		
Boys	48.5	46.8
Girls	51.5	53.2
Parental smoking behaviour (%)		
None	52.2	45.9
One	32.8	37.7
Both	15.0	16.4
Feeding style of infants (%)		
Breast	38.8	32.3
Mixed	7.4	8.1
Bottle	53.8	59.7
Number of siblings (%)		
None	43.6	44.6
One	33.2	37.2
≥ Two	23.2	18.2

Table 3.1. Characteristics of children remaining in the cohort and lost to follow-up at ages 11-13 years (Continued)

Characteristic	Children in the cohort (N = 375)	Children lost to follow-up (N = 119)
Maternal age (yrs)	26.0±0.2	25.8±0.4
Mother's residence in Port Pirie (yrs)	13.9±0.6	13.1±1.0
HOME scores	43.4±0.3	43.6±0.5
Daniel scores*	26.1±0.7	28.2±1.2
Length of breastfeeding (months)	3.8±0.1	3.8±0.2
Birth weight (grams)	3394±27	3396±49

Table 3.1. Characteristics of children remaining in the cohort and lost to follow-up at ages 11-13 years (Continued)

Characteristic	Children in the cohort (N = 375)	Children lost to follow-up (N = 119)
Antenatal average PbB (ug/dl)	10.1±0.2	10.0±0.4
Umbilical cord PbB (ug/dl)	9.4±0.2	9.3±0.5
Lifetime average PbB at age 7 yrs (ug/dl)	17.8±0.3	17.9±0.8
Full-scale IQ at age 7 yrs	104.9±0.7	104.1±1.4
Pearson correlation between lifetime average PbB and full-scale IQ at age 7 yrs	-0.25	-0.27

\* Higher Daniel scores mean lower socioeconomic status.

(2) Interview bias: Interview bias arises when systematic differences occur between the subjects with low or high exposure status in the soliciting, recording, or interpreting of information from study subjects. To minimise the potential interview bias, the following quality control procedures were performed throughout the study:

(a) A single observer was used to assess the developmental outcomes of all the children.

(b) The observer was unaware of each child's exposure status and had no access to recorded information on the child's developmental history.

(c) All the interviews and assessments were conducted according to a standardised protocol (Wechsler, 1974).

(d) Children with different exposure status in their early life were interviewed and assessed in an intermixed order.

(3). Exposure misclassification bias: Since body lead burden is very difficult to determine accurately, non-differential misclassification is likely to have occurred in the measurement of lead exposure. This sort of misclassification may have attenuated the estimated strength of the true relationship between the exposure and outcome (see discussions in Section 3.1.1.1). However, if any differential misclassification occurs, it can affect an assessment of the relationship between exposure to lead and cognitive development. Therefore, differential misclassification of exposure was one of the major concerns during execution of the study. The following measures were employed in this study to minimise the misclassification bias of exposure:

As discussed in Chapter 2, venous blood samples (rather than capillary samples) were collected, in order to minimise the potential for lead contamination. The collection, storage and transportation of blood samples were conducted using a standardised protocol (Standards Association of Australian, 1985). All equipment and reagents used for the handling and treatment of blood samples were checked in accordance with an established procedure, and only those materials which were free of significant amounts of the analyte (i.e.,  $< 0.03 \mu\text{mol/l}$ ) were used. Blood was drawn from a vein in the antecubital fossa following a strict cleaning procedure (i.e., wiping the site vigorously with an alcohol impregnated swab and then drying the site using an absorbent sterile gauze swab), and transferred from the syringe to a container as soon as possible. The samples were stored and transported to the Adelaide Women's and Children's Hospital within 24 hours at a temperature of about  $4^\circ\text{C}$ .

Measurements of PbB were performed at the Laboratory of Chemical Pathology, Adelaide Women's and Children's Hospital, using an electrothermal atomization atomic absorption spectrometric method (Atomic Absorption Spectrophotometer: Perkin Elmer Zeeman 5100). Throughout this study, standardised internal quality control procedures were used. A certified commercially prepared product (product number: 14036) was employed to monitor intra-batch accuracy and ensure inter-batch standardisation. The inter-batch precision was high. The coefficient of variability for inter-batch measurements was 5.67% (N=150).

#### (4) Outcome misclassification bias:

Each child's cognitive status was assessed with the WISC-R, which is a standardised psychological test, of known validity and reliability (Wechsler, 1974). However, misclassification can still occur if the quality control procedures are not strictly followed during the process of assessment. The following factors were considered in establishing and maintaining consistency in the assessment:

**Examiner:** In order to avoid inter-examiner variation, a single trained examiner was used throughout this phase of the cohort study. In order to ensure consistency in the testing, pilot assessments were conducted under the supervision of an experienced clinical psychologist with children who were not participants in the study. This pilot testing achieved consistently satisfactory results. The examiner, who had not participated in earlier phases of the cohort study, was unaware of individual children's exposure and developmental histories.

**Subject:** Children were assessed during normal school hours. Each child was asked to rest for at least 5 minutes before the assessment began. Testing of each child took place in one session lasting approximately one and half hours. Testing was postponed if a child was found to have an infection (such as an otitis media or a severe respiratory illness) or was using a medication that might affect performance.

**Procedure:** The Wechsler Intelligence Scale for Children - Revised was administered to each child to evaluate his/her developmental status. This test was conducted according to a standardised format (Wechsler, 1974).



**Assessment environment:** A comfortable, quiet and well lit testing environment was always used, and an atmosphere of friendliness and cooperation was established before each assessment was conducted.

The potential impact of a time dependent drift in the examiner's variability is evaluated in Table 3.2. The results show a slight drift, downward toward the end of the study, in the full-scale IQ. However, the difference was not statistically significant ( $p = 0.13$  from an ANOVA test). Moreover, since the children with different exposure status were assessed in an intermixed order, bias due to intra-examiner variability over time is unlikely to have played an important role in this study.

Table 3.2. IQ scores by date of assessment

Date of assessment	N	Mean $\pm$ SD	95% CI	Range
6.1992 - 1.1993	102	100.6 $\pm$ 12.2	98.3-103.0	70-135
2.1993 - 4.1993	102	101.8 $\pm$ 11.6	99.5-104.0	54-128
5.1993 - 7.1993	108	99.7 $\pm$ 11.9	97.5-102.0	76-145
8.1993 - 10.1993	63	96.6 $\pm$ 13.5	93.2-100.0	59-129

(5) Potential confounders:

Since there are multifactorial influences on cognitive development during childhood, confounding by other coexistent factors is a methodological issue central to this study.

In total, 22 covariates were considered as potential confounders in this study since they may be associated with lead exposure while also being determinants in their own right for children's intelligence. Although the measurement of the covariates may not have been perfect, the possibility of misclassification of these variables was minimised, since, as described above, the single observer used to collect the data was unaware of each child's exposure and developmental history, and all the interviews were conducted in a uniform procedure.

In summary, the possibility of introducing various types of bias was anticipated, and practical steps were taken to minimise their influence during the design and execution of this study. The potential effects of confounding were handled in two stages, viz., through the application of the admissibility criteria at the stage of research planning for re-testing (e.g., exclusion of children with head injuries), and by statistical adjustment for the effects of putative confounding factors as part of data analysis.

### 3.1.2. EXTERNAL VALIDITY

#### 3.1.2.1. GENERAL CONSIDERATIONS

External validity refers to the extent to which the results of a study can be generalised to people outside the study population. The external validity of this study derives principally from its use of a population-based sample of study subjects that was truly representative of the potential source population - that is, all the children living in the lead smelter town and environs of Port Pirie. The children in the original cohort comprised an estimated 90 percent of all singleton live births occurring in the community during the three year period May 1979 - May 1982.

Moreover, the results from this study may be applicable to larger populations (i.e., target population) because of the following two factors:

1. In blood lead determination, external quality control was ensured by participation in three major programs: the Standards Australia Trace Element Quality Assurance Program, the US Pennsylvania Blood lead Proficiency Testing Program, and the UK Quality Assurance Program for Lead in Blood. The quality of measurement of PbB was warranted at the national and international level through participation in these quality control programs.
2. For the purpose of the developmental assessment, the WISC-R - a well standardised psychological test - was employed. The WISC-R has been widely used in other studies of lead effects, and therefore, the results of this study can be directly compared with those of other studies. The mean Full-scale IQ in the study was 100.0 (95% confidence interval: 98.8 - 101.2) which is identical to the expected mean. However, the mean scores on Verbal and Performance IQs were

different from the expected values. The explanation for this is not clear, although differences in characteristics of this study sample and the standardising population may be contributory.

The ability to generalise the results of this study to other community populations may be limited by the fact that the study population had its own distinctive lower/middle-lower socioeconomic profile (see details in Chapter 3.1.2.2) and life-long (including antenatal) exposure to environmental lead in a smelter town.

The standard deviations of IQ scales (12.3 for Full-scale IQ, 10.8 for Verbal IQ, and 14.1 for Performance IQ) within this study population were a little smaller than the expected values (15 for all IQ scales), perhaps due to the absence of the very high or very low IQs encountered in the US sample used to standardise the test scores.

### 3.1.2.2. SOCIODEMOGRAPHIC CHARACTERISTICS OF THE STUDY POPULATION

#### Age and sex

The study population consisted of children aged 11-13 years. The mean age at testing was 12.0 years (standard deviation: 0.67). The male to female ratio in the sample was 0.94, which is slightly lower than that of the South Australian and Australian population, viz. 1.05 and 1.06, respectively (Table 3.3). The original male to female ratio of 723 children was 1.02. There were more boys than girls in the families which had moved during the earlier stage of the study, and the majority of the children lost to follow-up (80%) were in families that left the Port Pirie district (McMichael et al, 1988; Baghurst et al., 1992a). For 42 children who refused to participate in this study, 22 were girls, and 20 were boys. The major reasons for refusal were that parents were either too busy to participate or no longer interested in the study. Therefore, there is no evidence of any gender bias behind the decision to discontinue participation in the present study.

Table 3.3. Comparison of the demographic characteristics of the Port Pirie cohort children with the general population\*

	Port Pirie Cohort	South Australia	Australia
Boys/Girls	0.94	1.05	1.06
Family Type (%)			
Two parents	85.2	79.8	80.7
Single parent/guardian	14.8	20.2	19.3
Parents' Occupation (%)			
Professional	19.0	23.6	24.6
Para-professional	5.1	7.0	6.8
Others†	75.9	69.4	68.6
Parents' Secondary Educational			
Attainment ≥ 5 years (%)	15.9	--	58.0‡

\* From the latest census and population survey data collected by the Australian Bureau of Statistics (1991) and the Labour Force Status and Educational Attainment, Australia (1993).

† Including variety of occupations, e.g., cleaner, baby-sitter, house-keeper, pensioner.

‡ People in the rural and remote areas only comprised 16.5% of the population (Commonwealth Department of Human Services and Health, 1994).

### Family composition

Approximately 85% of children lived in two-parent families (Table 3.3). In the majority of single-parent families, the child lived with the mother (89.1%); with only a very small percentage of children from single-parent families (10.9%) living with the father. The percentage of two-parent families in the study (85.2%) is higher than that reported for the general population (South Australia: 79.8%; Australia: 80.7%). A relatively lower percentage of single-parent families in rural areas appears to be the major reason for the difference in family composition between this study sample and the general population (Australian Bureau of Statistics, 1989, 1993).

### Educational attainment and occupational type of parents

The proportion of parents (15.9%) who had completed secondary (or higher) education was much lower than that of the Australian population (58.0%), and the proportion of parents employed in professional (e.g., managers, doctors, lawyers, scientists, and teachers) or para-professional (e.g., technicians, police and firemen) categories was slightly lower than that of the general population (Table 3.3). In terms of parental educational attainment and employment categories, therefore, this study sample consists predominantly of subjects of lower or middle-lower socioeconomic status. The relevance of this observation to the interpretation of results will be discussed in Chapter 5.

### 3.2. PRECISION OF STATISTICAL ESTIMATES

The primary way to reduce sampling error, and thus increase precision of population estimates in an epidemiologic study is to enlarge the size of study (Rothman, 1986; Elwood, 1988). The minimum desirable study size can be assessed using standard statistical formulae. Before the formulae can be employed, however, information on the following variables is required for calculation of the size of sample in this study:

- (1) The desired level of statistical significance of the expected result ( $\alpha$ );
- (2) The acceptable probability of missing a real effect ( $\beta$ );
- (3) The minimum magnitude of the postulated effect which the investigator wishes to be able to detect ( $\delta$ );
- (4) The standard deviation of the variable under study ( $\sigma$ ).

Power calculations have been used widely to assess desirable study size in epidemiologic studies. Power is the complement to the Type II error ( $\beta$ -error): It is the probability of detecting (as "statistically significant") a postulated level of effect (Rothman, 1986).

According to the results of analyses already published, the estimated deficit in IQ at age 7 was around 4 units for every (natural) log unit increase of PbB (Baghurst et al., 1992a). Within the cohort, the mean blood lead level in the upper tertile of exposure was typically around 2.5 times higher than the mean PbB in the lower tertile at various ages. The expected difference in IQ between these tertiles might therefore be expected to be around 3.7 points. A crude power calculation (using a standard deviation for IQ of 13.6) then reveals that around 212 children in each of two groups would be needed to detect a difference of 3.7 points with 80% power (and a conventional rejection probability of 0.05).



Given that the Port Pirie children exhibit a range of exposures, this is only a crude approximation, but the power calculations for detecting a partial regression coefficient greater than a specified magnitude involve many assumptions concerning the nature of the variance-covariance structure of the covariates, and hence only the simpler method was attempted. The results of this calculation do indicate, however, the desirability of obtaining new data from as many children as possible from the 494 who were assessed at age 7.

## CHAPTER 4. LEAD EXPOSURE AND CHILDREN'S INTELLIGENCE

### Summary

*The profiles of serial blood lead concentration, and children's intelligence are described, and the relationship between these two variables is examined. There was a statistically significant and inverse relationship between blood lead concentrations at ages between 3 and 7 years and IQ scores at ages 11-13 years. This relationship was still apparent after adjustment for confounding factors. A dose-effect relationship is demonstrated in both the simple and multivariable analyses. It is estimated that a hypothetical increase in blood lead concentration from 10 to 20 ug/dl is associated with a 3 point deficit in full-scale IQ.*

### 4.1. BLOOD LEAD CONCENTRATION

Age-specific blood lead concentrations (with or without hematocrit adjustment) exhibit a skewed distribution at all ages, with only a few children recording very high values (Figures 4.1.1 - 4.1.6), and therefore, analyses were performed on the natural logarithm of PbB (Note that the results reported for ages 7 and under are only for those children who remained in the cohort until age 11-13). All reported means and standard deviations are geometric. The log transformation of PbB also prevents a small number of extreme values from exerting a disproportionate influence on the quantitative assessment of the relationship between the lead exposure and child development.

Since the range of PbB varied with children's age, different intervals of PbB were used to plot its distribution at various ages (Figures 4.1.1 - 4.1.6).

Figure 4.1.1. Distribution of lead concentration in umbilical cord blood samples

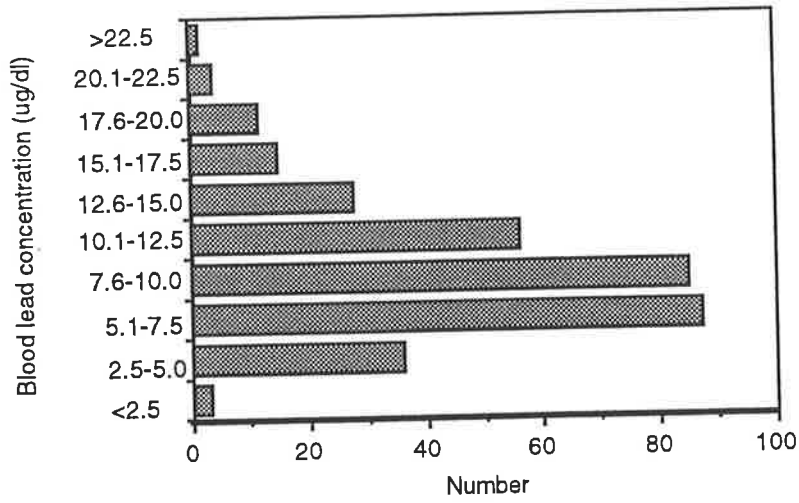


Figure 4.1.2. Distribution of blood lead concentration at age 15 months

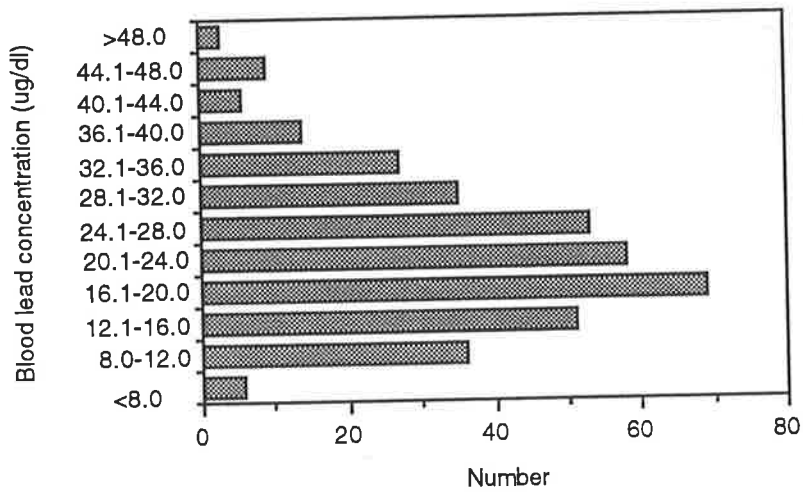


Figure 4.1.3. Distribution of blood lead concentration at age 3 years

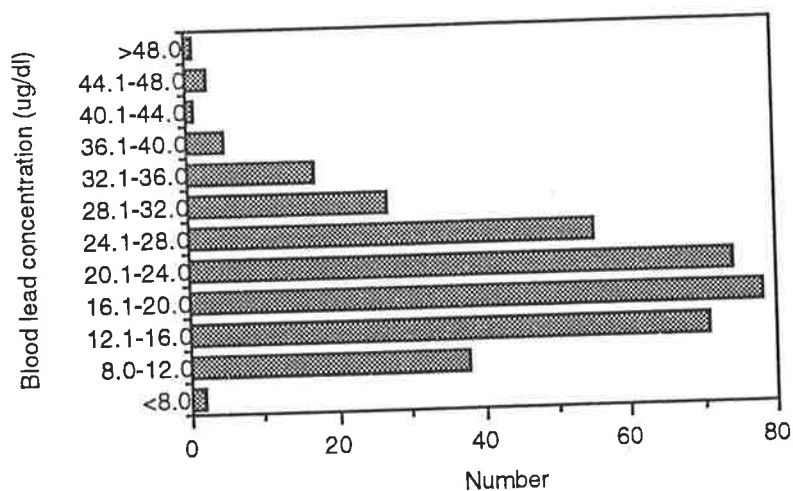


Figure 4.1.4. Distribution of blood lead concentration at age 5 years

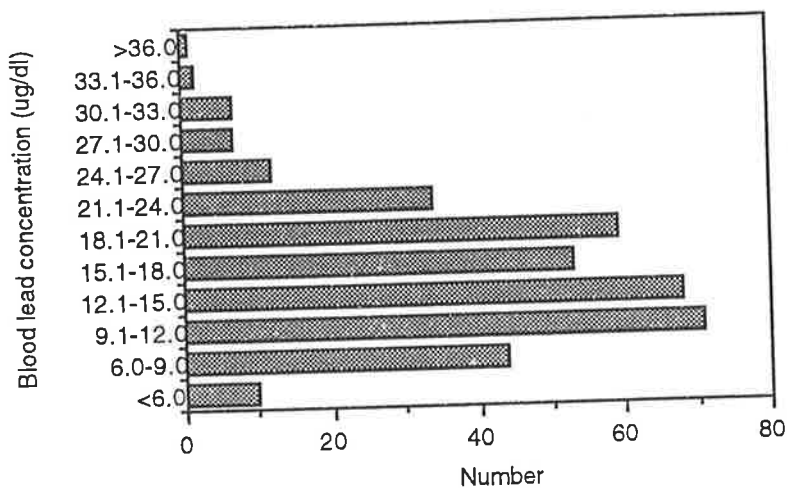


Figure 4.1.5. Distribution of blood lead concentration at age 7 years

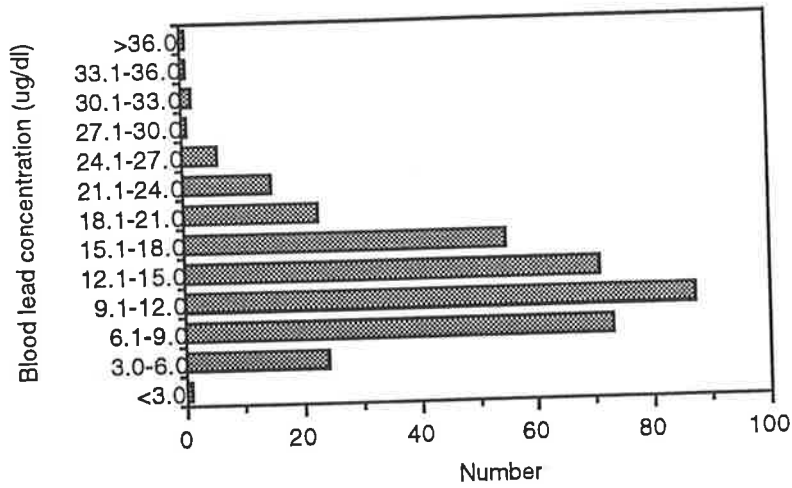
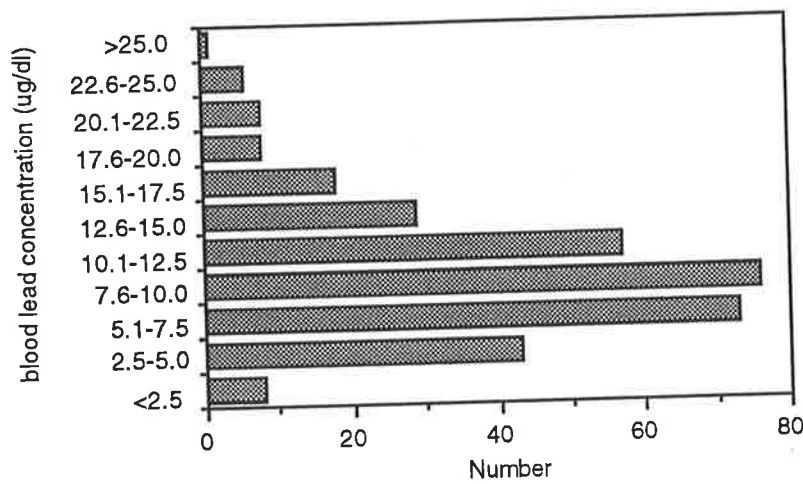


Figure 4.1.6. Distribution of blood lead concentration at ages 11-13 years



The mean lead concentrations in maternal blood collected antenatally, in cord blood at birth, and in blood samples collected throughout childhood are shown in Table 4.1.1. The children's PbB increased sharply over the first two years of life, and then declined. By the age of 11-13 years, the mean PbB was 7.9 ug/dl, and had fallen by 63 percent from its peak value that occurred at age 2 years (mean: 21.4 ug/dl). The mean PbB at ages 11-13 years was slightly lower than the level recorded at birth.

Table 4.1.1. Mean lead concentration (ug/dl) in blood samples taken antenatally and throughout childhood

Time of Sampling	N*	Geometric mean†	SD factor	Range
Antenatal	367	9.6	1.4	3.7-33.2
Cord	328	8.5	1.6	0.9-36.7
6 ms	367	14.4	1.5	2.3-36.9
15 ms	367	21.0	1.5	5.1-51.8
24 ms	372	21.4	1.4	8.8-52.0
3 yrs	372	19.3	1.4	6.4-62.2
4 yrs	369	16.3	1.5	5.6-40.5
5 yrs	368	14.3	1.5	4.8-40.7
6 yrs	356	12.7	1.5	4.8-34.1
7 yrs	360	11.7	1.5	2.0-37.7
11-13 yrs	326	7.9	1.6	0.7-30.8
Lifetime average	326	14.1	1.4	5.0-31.9

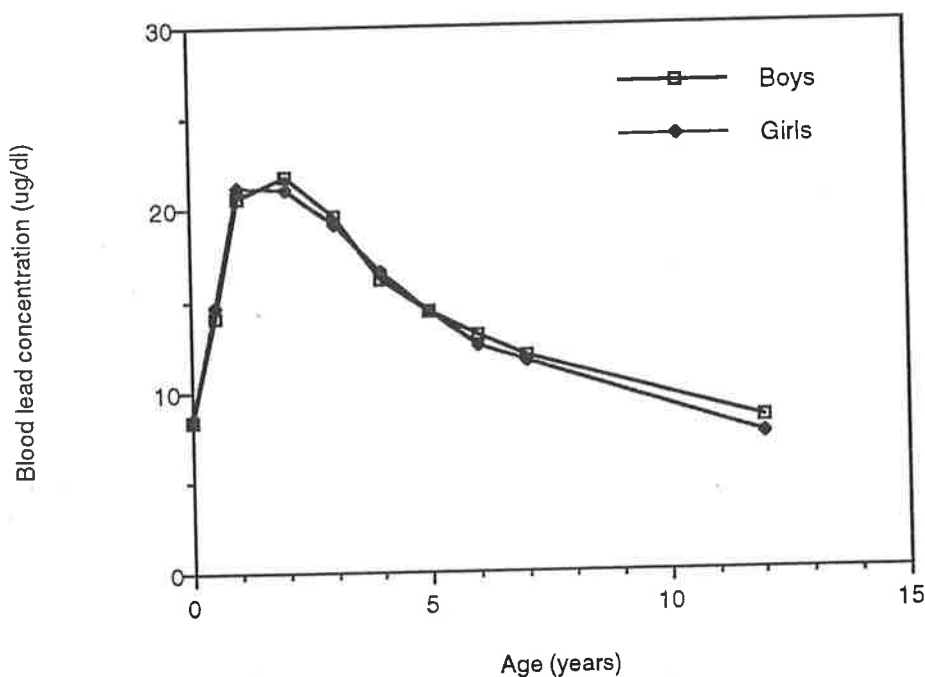
\* The total number of the children who were followed through to age 11-13 was 375.

†Hematocrit adjusted values.

Geometric mean blood lead concentration by age and sex is shown in Figure 4.1.7. At all ages from birth to seven years, the difference in PbB between boys and girls was minimal and was not statistically significant ( $p \geq 0.21$ ). At ages 11-13 years, mean PbB in boys (i.e., 8.4 ug/dl) was slightly higher than in girls (7.5 ug/dl), and the difference was statistically significant ( $p = 0.02$ ).

The following data analyses were based on the combined data from both boys and girls, because, firstly, no significant difference in PbB was found between boys and girls at any age except for 11-13 years; secondly, multivariable analysis indicated no significant interaction between gender and lead exposure in children's IQ after taking the confounding factors into account (see more details in Chapter 5).

Figure 4.1.7. Geometric mean blood lead concentration by age and sex.



In order to summarise the data in tabular form and assess the dose-effect relationship between PbB and children's IQ, tertiles of lead exposure were used. The mean PbB and ranges for these tertiles are shown in Table 4.1.2.

Table 4.1.2. Mean blood lead concentration (ranges) within tertiles in maternal samples taken antenatally and in children's samples at different ages

Tertile	Antenal	Cord	15 ms	3 yrs	5 yrs	7 yrs	11-13 yrs	Lifetime average
	[ug/dl]							
Low	6.9 (3.7-8.6)	5.1 (0.9-7.3)	13.0 (5.1-18.4)	12.8 (6.4-16.5)	8.9 (4.8-12.0)	7.3 (2.0-9.6)	5.2 (0.7-7.1)	9.8 (5.0-12.4)
Medium	9.8	8.7	21.7	19.8	14.9	11.9	9.0	14.8
High	13.3 (11.1-33.2)	13.7 (10.5-36.7)	32.8 (26.3-51.8)	28.4 (23.4-62.2)	22.3 (18.1-40.7)	18.5 (14.5-37.7)	14.6 (11.0-30.8)	21.0 (17.5-31.9)



## 4.2. CHILDREN'S INTELLIGENCE

The distribution of the children's IQ scores is shown in Figures 4.2.1-4.2.3. The WISC-R scores conform reasonably well with the Normal or Gaussian distribution, and therefore, analyses were performed on untransformed IQ scales and subscales.

Figure 4.2.1. Distribution of children's verbal IQ

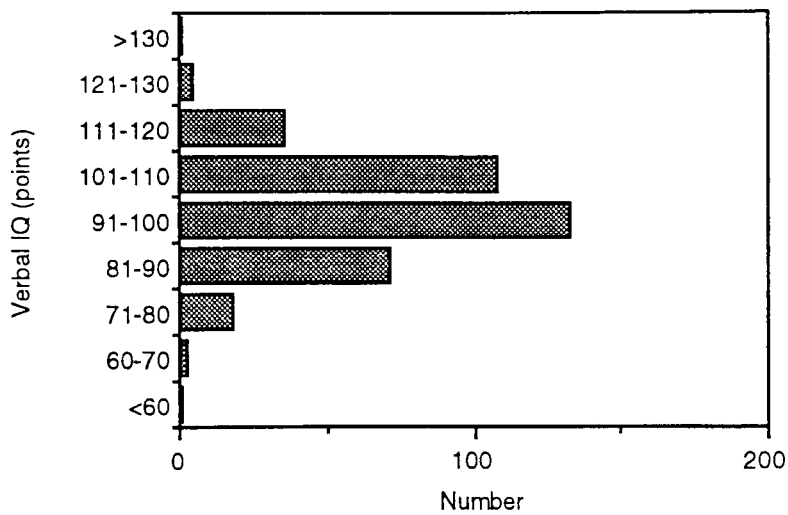


Figure 4.2.2. Distribution of children's performance IQ

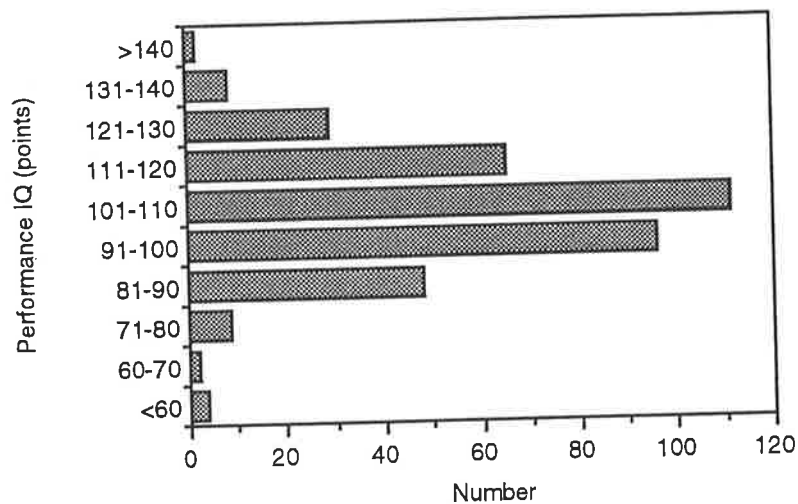
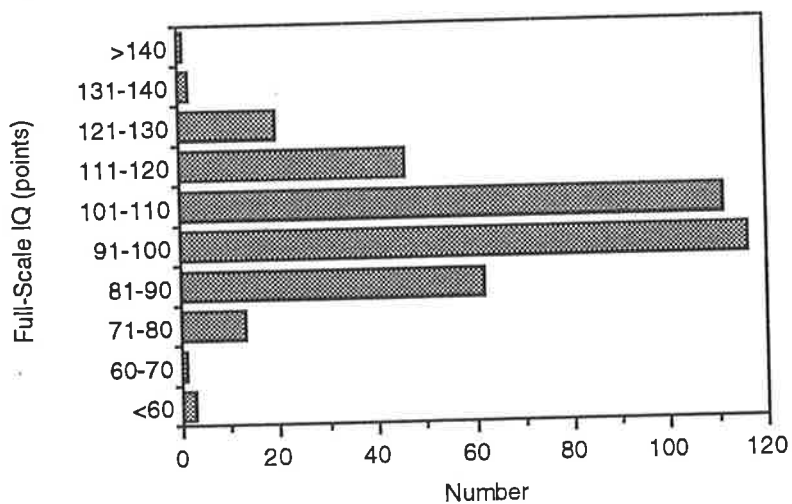


Figure 4.2.3. Distribution of children's full-scale IQ



The mean scores for the 12 WISC-R subscales ranged from 9.2 (95% CI: 2.0-17.0) for "Comprehension" to 11.3 (1.0-19.0) for "Block Design", and the mean scores for verbal, performance and full-scale IQ were 97.6 (95% CI: 96.6-98.7), 103.0 (95% CI: 101.6-104.4) and 100.0 (95% CI: 98.8-101.2), respectively (Table 4.2.1).

In the US population in which the test was standardised, the mean IQ ( $\pm$ standard deviation) was 100 ( $\pm$ 15) points for each age. In this study, the mean full-scale IQ was identical with the expected mean value, while verbal and performance IQs were 2.4 points lower and 3 points higher than their mean values in the general population, respectively. The average verbal-performance IQ discrepancy was 5.4 points. A verbal-performance IQ discrepancy may not have any significance unless it is greater than 12 points in either direction (Kaufman, 1979). All the IQ scale standard deviations were smaller than the expected values, which suggests that there were fewer extreme values in this sample than in the standardising population (Table 4.2.1).

Table 4.2.1. Mean scores for the WISC-R subscales and IQ scales in 375 children at ages 11-13 years

Items	Mean	SD	Range
Full-Scale IQ	100.0	12.3	54.0-145.0
Verbal IQ	97.6	10.8	57.0-139.0
Information	9.9	2.0	1.0 - 17.0
Similarities	9.8	2.4	1.0 - 17.0
Arithmetic	10.0	2.6	2.0 - 18.0
Vocabulary	9.4	2.2	2.0 - 17.0
Comprehension	9.2	2.1	2.0 - 17.0
Digit Span	9.3	2.9	2.0 - 19.0
Performance IQ	103.0	14.1	54.0-145.0
Picture Completion	10.2	2.4	4.0 - 19.0
Picture Arrangement	10.1	2.7	1.0 - 18.0
Block Design	11.3	3.3	1.0 - 19.0
Object Assembly	11.2	3.1	3.0 - 19.0
Coding	9.6	2.9	1.0 - 18.0
Mazes	10.7	2.8	1.0 - 18.0

#### 4.3. BLOOD LEAD CONCENTRATION AND CHILDREN'S INTELLIGENCE

There was a consistent inverse relation between blood lead concentration and the scores obtained for all the IQ scales (Table 4.3.1). Children's IQ was significantly associated with tertile of PbB at all ages except at birth (umbilical cord sample). The mean IQ scores differed by 1.5 (cord PbB and performance IQ) to 9.1 (lifetime average PbB and full-scale IQ) points between the highest and lowest tertiles for PbB.

The magnitude of the deficit in IQ with lead exposure was quite similar for both verbal and performance scales. Although there was an inverse and statistically significant association between children's IQ and PbB measured at most of ages, the relatively larger IQ deficits seemed to be associated with PbB measured at earlier postnatal ages or with lifetime average PbB (Table 4.3.1).

Table 4.3.1. Mean IQ scores by tertile of blood lead concentration\*

Blood lead tertile	Time of blood sampling							
	Antenatal	Cord	15 ms	3yrs	5yrs	7yrs	11-13yrs	Lifetime average
	Full-Scale IQ							
Low	103.1	101.8	103.4	104.4	104.3	104.0	103.0	104.1
Medium	100.2	99.6	100.9	99.8	99.8	100.4	100.2	101.3
High	97.5	99.3	96.0	96.2	96.1	95.8	97.3	95.0
	(0.002)	(0.25)	(<0.001)	(<0.001)	(<0.001)	(<0.001)	(0.002)	(<0.001)
	Verbal IQ							
Low	100.1	99.1	100.5	101.5	101.8	101.2	100.4	101.4
Medium	97.6	98.4	98.7	97.5	98.0	98.3	97.8	98.7
High	95.8	96.3	93.9	94.4	93.1	93.5	95.4	93.2
	(0.007)	(0.14)	(<0.001)	(<0.001)	(<0.001)	(<0.001)	(0.003)	(<0.001)
	Performance IQ							
Low	106.0	104.7	106.4	107.2	106.7	106.9	106.0	106.9
Medium	103.5	101.2	103.6	102.8	102.2	102.7	103.1	103.9
High	100.2	103.2	99.4	99.4	100.4	99.4	100.3	98.4
	(0.005)	(0.18)	(<0.001)	(<0.001)	(<0.001)	(<0.001)	(0.002)	(<0.001)

\*The p values from the ANOVA are shown in parentheses, and indicate if there is a statistically significant relation between the tertile of blood lead concentration and children's IQ.

The crude (i.e., unadjusted) relations between children's IQ and PbB (including age-specific PbB at ages 11-13 years and lifetime average PbB) are shown in figures 4.3.1 - 4.3.2. Generally, for each IQ scale, there was an inverse gradient across the whole range of PbB without an apparent threshold. The trend is quite similar for each IQ scale. The proportion of the variance of full-scale IQ that could be attributed to PbB at different ages (without consideration of the potential confounders) varied from 0.8% (for cord PbB) to 10.1% (for lifetime average PbB).

Figure 4.3.1. Blood lead concentration and IQ, both at ages 11-13 years

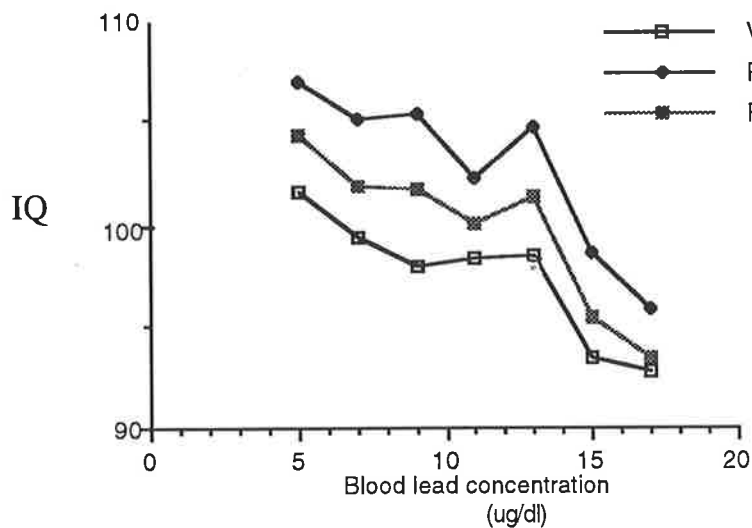
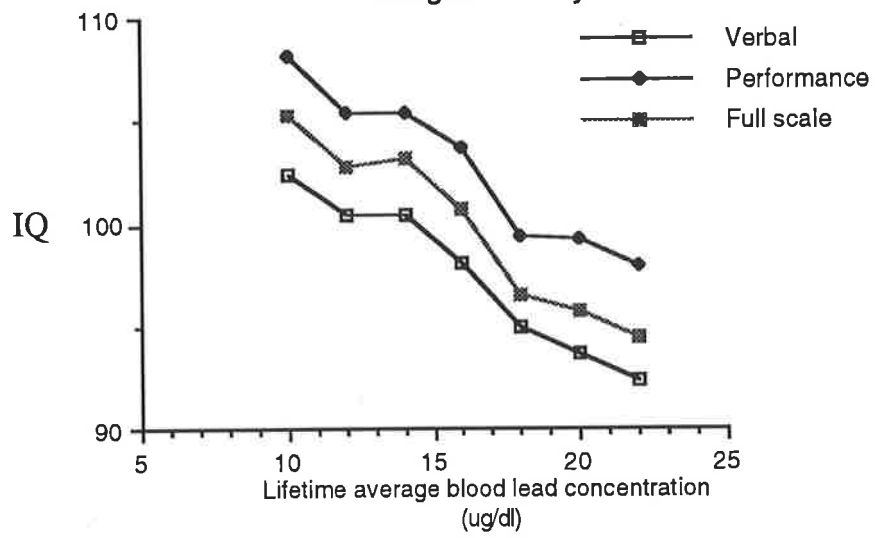


Figure 4.3.2. Lifetime average blood lead concentration and IQ at ages 11-13 years





#### 4.4. IDENTIFICATION OF CONFOUNDERS

Mean IQ scores and blood lead concentration by categories of covariates that may be potential confounders are shown in Table 4.4.1. Many sociodemographic and biomedical factors were associated with both blood lead concentration and child's IQ ( $p \leq 0.25$ )\*. In simple regression analyses, socioeconomic status, quality of home environment, and maternal intelligence were the variables most strongly associated with both exposure and outcome measures and accounted for 18.3, 23.6, and 11.0 percent of variance of the lifetime average PbB, and 15.5, 20.8, and 16.9 percent of variance of the full-scale IQ, respectively.

The Pearson correlation coefficients between all pairs of continuous covariates were estimated (Table 4.4.2). The results show that these covariates were not highly correlated although the estimated coefficients of maternal IQ with Daniel scores and HOME scores were -0.52 and +0.50, respectively.

\* While this is not a formal test for the presence of confounding, it is indicative (Mickey & Greenland, 1989).

Additional regression analyses were carried out to assess the general impact of the confounder selection strategy on estimation of the main effect of lead. The estimated regression coefficients of PbB were decreased to differing extents when each of these variables was added to the simple regressions of verbal, performance or full-scale IQ. For example, the magnitude of the estimated regression coefficient of lifetime average PbB was decreased by 11.0-35.2 percent when the HOME scores, socioeconomic status, maternal IQ and parents' smoking behaviour were individually included in the model (which indicate that these variables may be the real confounders in this study). The effect estimates were changed by less than 10 percent when other covariates were separately added into the regression analyses. In order to minimise the criticism of under-adjustment, all the potential confounders (i.e., those factors associated with both exposure and outcome measures) were included in the final multiple regression analyses.

Table 4.4.1. Children's IQ and blood lead concentration by covariates\*

Covariates	IQ [points]			Blood lead concentration [ug/dl]							
	Verbal	Perf.	Full	Antenatal	Cord	15 ms	3 ys	5 ys	7 ys	11-13 ys	Lifetime
<b>Sex</b>											
Boys	98.8	103.7	101.0	9.4	8.4	20.7	19.6	14.4	11.9	8.4	14.4
Girls	96.6	102.4	99.1	9.8	8.5	21.2	19.1	14.3	11.6	7.5	13.8
	(.04)	(.39)	(.15)	(.27)	(.78)	(.57)	(.52)	(.87)	(.63)	(.01)	(.23)
<b>Age (years)</b>											
11	97.6	102.2	99.6	9.5	8.4	21.4	19.0	14.0	12.1	8.5	14.5
12	97.6	103.7	100.3	9.9	8.8	20.7	19.9	14.6	11.5	7.3	13.8
13	98.0	106.8	102.7	8.8	7.4	18.2	18.7	16.2	10.1	6.5	11.9
	(.98)	(.31)	(.61)	(.39)	(.36)	(.26)	(.22)	(.28)	(.25)	(.02)	(.11)
<b>Grade</b>											
5-6	96.4	100.9	98.2	9.7	8.6	22.6	19.8	14.2	12.3	8.6	14.9
7-8	99.0	105.4	102.1	9.5	8.4	19.2	18.9	14.5	11.2	7.3	13.3
	(.040)	(.005)	(.007)	(.88)	(.86)	(<.001)	(.44)	(.72)	(.14)	(.05)	(.01)
<b>Years resident in Port Pirie</b>											
≤15	97.9	103.9	100.6	8.7	7.3	18.8	17.6	12.8	10.3	7.0	12.7
>15	97.8	102.6	99.9	10.6	9.7	22.9	21.0	15.9	13.1	8.9	12.5
	(.88)	(.36)	(.56)	(.03)	(<.001)	(<.001)	(<.001)	(<.001)	(<.001)	(.02)	(<.001)
<b>Daniel scores</b>											
<45	102.2	107.2	105.0	8.4	6.9	17.5	15.5	11.3	9.2	5.8	11.2
45-55	99.6	105.9	102.5	9.1	8.2	19.5	18.5	13.9	10.6	7.4	13.2
>55	94.5	99.3	96.2	10.7	9.5	23.4	21.4	15.9	13.6	9.0	15.8
	(<.001)	(<.001)	(<.001)	(<.001)	(<.001)	(<.001)	(<.001)	(<.001)	(<.001)	(<.001)	(<.001)

\* P values are shown in parentheses (Student t test for two categories and ANOVA for others).

Table 4.4.1. Children's IQ and blood lead concentration by covariates (Continued)

Covariates	IQ [points]			Blood lead concentration [ug/dl]							
	Verbal	Perf.	Full	Antenatal	Cord	15 ms	3 ys	5 ys	7 ys	11-13 ys	Lifetime
<b>HOME scores</b>											
<40	92.0	98.0	94.1	10.9	9.7	24.6	23.6	18.0	14.8	9.6	17.3
40-45	98.1	104.0	100.8	9.4	8.4	20.4	18.7	14.1	11.1	7.7	13.6
>45	103.4	108.0	106.1	8.5	7.2	17.9	15.9	11.3	9.7	6.7	11.5
	(<.001)	(<.001)	(<.001)	(<.001)	(<.001)	(<.001)	(<.001)	(<.001)	(<.001)	(<.001)	(<.001)
<b>Family functioning</b>											
Lower	98.5	104.6	101.3	9.7	8.5	20.6	18.7	14.5	11.5	7.6	13.9
Middle	98.5	104.2	101.1	9.4	9.0	19.2	18.1	13.3	10.6	7.7	13.1
Higher	97.0	101.8	99.0	9.6	8.2	21.9	20.3	14.6	12.3	8.2	14.6
	(.22)	(.10)	(.12)	(.85)	(.32)	(.07)	(.15)	(.25)	(.17)	(.29)	(.21)
<b>Parents' general health</b>											
Lower	96.0	102.1	98.7	9.7	8.6	20.6	19.2	13.9	11.8	7.5	13.8
Middle	98.7	103.5	100.8	9.6	8.6	21.3	18.7	14.0	11.4	7.6	13.9
Higher	98.4	103.9	100.9	9.5	8.3	20.6	19.8	14.9	11.8	8.5	14.4
	(.06)	(.15)	(.07)	(.84)	(.82)	(.29)	(.43)	(.44)	(.56)	(.42)	(.31)
<b>Parents' marital status</b>											
Married	98.2	103.5	100.6	9.4	8.2	20.3	18.7	13.8	11.3	7.6	13.6
Non-married	95.1	101.3	97.6	10.7	9.8	25.0	23.1	17.3	14.2	10.1	16.9
	(.01)	(.27)	(.09)	(.04)	(.03)	(<.001)	(<.001)	(<.001)	(<.001)	(<.001)	(<.001)

Table 4.4.1. Children's IQ and blood lead concentration by covariates (Continued)

Covariates	IQ [points]			Blood lead concentration [ug/dl]							
	Verbal	Perf.	Full	Antenatal	Cord	15 ms	3 ys	5 ys	7 ys	11-13 ys	Lifetime
Parental smoking behaviour											
None	100.2	105.2	102.7	9.2	8.3	19.6	18.3	13.3	10.7	7.5	13.3
One	96.1	100.3	97.7	9.7	8.2	21.9	19.6	14.8	12.5	8.0	14.5
Both	92.6	101.8	96.4	10.9	9.8	24.6	22.7	17.2	14.1	9.3	16.4
	(<.001)	(.007)	(<.001)	(.01)	(.04)	(<.001)	(<.001)	(<.001)	(<.001)	(.008)	(<.001)
Sibling number in the household											
None	96.1	100.4	97.8	10.1	9.6	22.2	20.3	16.1	12.8	8.6	14.9
One	98.2	104.7	101.2	9.7	8.8	21.1	19.4	14.4	11.5	8.0	14.2
≥2	98.0	102.9	100.2	9.3	7.8	20.3	18.8	13.6	11.4	7.6	13.7
	(.14)	(.04)	(.07)	(.33)	(.10)	(.13)	(.20)	(.04)	(.16)	(.34)	(.28)
Life event											
Yes	96.3	101.4	98.4	10.0	9.0	21.9	20.0	14.7	12.4	8.4	14.8
No	98.5	104.3	101.1	9.4	8.2	20.4	18.9	14.1	11.3	7.7	13.7
	(.09)	(.06)	(.04)	(.28)	(.24)	(.005)	(.05)	(.36)	(.04)	(.32)	(.04)
Testing site											
Schools	97.6	103.1	100.0	9.4	8.2	19.9	18.6	13.7	11.3	7.7	13.5
Others	98.3	102.9	100.3	10.5	9.6	27.0	23.6	18.3	14.4	9.1	17.5
	(.63)	(.90)	(.87)	(.02)	(.01)	(<.001)	(<.001)	(<.001)	(<.001)	(.01)	(<.001)

Table 4.4.1. Children's IQ and blood lead concentration by covariates (Continued)

Covariates	IQ [points]			Blood lead concentration [ug/dl]							
	Verbal	Perf.	Full	Antenatal	Cord	15 ms	3 ys	5 ys	7 ys	11-13 ys	Lifetime
<b>Maternal IQ</b>											
<85	93.1	96.4	94.1	11.0	9.8	26.0	23.5	18.0	14.0	9.5	17.0
86-100	98.5	104.7	101.5	9.5	8.6	21.0	19.3	14.4	11.8	7.8	14.1
>100	105.7	109.1	107.8	8.5	6.3	18.1	16.1	11.8	9.5	6.7	11.7
	(.001)	(.001)	(.001)	(.001)	(.001)	(.001)	(.001)	(.001)	(.001)	(.001)	(.001)
<b>Paternal secondary education (years)</b>											
≤ 3	96.7	103.6	99.8	9.9	8.6	20.6	19.7	14.2	11.7	8.0	14.1
> 3	101.0	105.7	103.3	9.0	8.0	19.8	18.1	13.7	11.0	7.3	13.2
	(.001)	(.17)	(.001)	(.10)	(.16)	(.36)	(.04)	(.42)	(.18)	(.14)	(.10)
<b>Maternal age (years)</b>											
≤25	95.8	102.8	98.9	10.2	9.0	22.0	20.9	15.8	12.6	8.5	15.0
>25	99.3	103.2	101.0	9.1	8.0	20.1	18.0	13.1	11.0	7.5	13.3
	(.002)	(.79)	(.10)	(.06)	(.07)	(.04)	(.001)	(.001)	(.001)	(.06)	(.001)
<b>Birthweight (g)</b>											
≤2500	97.3	100.6	98.5	10.5	7.5	24.2	23.1	16.8	13.4	9.6	15.8
2501-3500	97.3	103.0	99.8	9.7	8.6	20.8	19.1	14.5	11.5	7.7	14.0
>3500	98.2	103.5	100.6	9.4	8.4	20.6	19.3	13.9	11.7	8.0	13.9
	(.71)	(.49)	(.60)	(.46)	(.44)	(.06)	(.13)	(.12)	(.47)	(.39)	(.36)

Table 4.4.1. Children's IQ and blood lead concentration by covariates (Continued)

Covariates	IQ [points]			Blood lead concentration [ug/dl]							
	Verbal	Perf.	Full	Antenatal	Cord	15 ms	3 ys	5 ys	7 ys	11-13 ys	Lifetime
<b>Birth rank</b>											
First	97.3	103.6	100.2	10.0	8.9	21.5	19.4	14.5	11.4	8.2	14.3
Second	97.2	103.0	99.6	9.3	8.5	20.1	19.5	14.6	11.7	7.8	14.0
≥Third	99.2	102.2	100.5	9.3	7.7	21.5	18.9	13.6	12.4	7.7	13.9
	(.36)	(.53)	(.59)	(.36)	(.12)	(.20)	(.48)	(.37)	(.35)	(.46)	(.53)
<b>Feeding style of infants</b>											
Breast	100.0	104.8	102.1	8.9	8.1	19.9	17.6	13.0	10.3	7.2	13.0
Mixed	98.3	103.6	101.3	8.6	6.8	19.4	16.8	12.5	9.8	6.6	12.4
Bottle	95.8	101.6	98.3	10.3	9.0	22.0	21.1	15.7	13.2	8.8	15.3
	(<.001)	(.04)	(.007)	(.11)	(.01)	(.03)	(<.001)	(<.001)	(<.001)	(.02)	(<.001)
<b>Duration of breast-feeding (months)</b>											
0	94.6	100.6	97.0	10.1	9.1	21.4	21.1	16.1	14.1	8.7	15.3
1-6	97.6	102.5	99.7	10.1	8.7	22.1	20.0	14.6	12.2	8.4	14.7
>6	99.2	105.0	101.9	8.6	7.8	18.9	17.3	13.1	10.1	6.9	12.6
	(.006)	(.008)	(.05)	(.07)	(.08)	(.01)	(<.001)	(<.001)	(<.001)	(.05)	(.004)
<b>Medication in the last 2 weeks</b>											
Yes	97.9	102.7	99.9	9.6	8.2	20.3	18.6	13.8	11.3	8.0	13.7
No	97.6	103.3	100.2	9.6	8.7	21.4	19.8	14.7	12.0	7.9	14.3
	(.81)	(.65)	(.83)	(.99)	(.32)	(.24)	(.21)	(.26)	(.36)	(.88)	(.39)
<b>Absence from school (≥ 2 weeks)</b>											
Yes	94.6	102.0	97.7	10.4	9.2	23.5	20.7	16.2	13.6	9.3	15.9
No	98.6	103.4	100.8	9.4	8.3	20.2	18.8	13.8	11.2	7.6	13.6
	(.007)	(.40)	(.04)	(.05)	(.07)	(<.001)	(.003)	(<.001)	(<.001)	(.004)	(<.001)

Table 4.4.2. Pearson correlation between each pair of covariates

	Age	Maternal	Dwelling	Daniel	HOME	FAD	GHQ	Sibling	Maternal	Birth	Duration of
	age		length	scores	scores			no.	IQ	weight	breast-feeding
	1	2	3	4	5	6	7	8	9	10	11
2	-0.14										
3	-0.21	0.01									
4	-0.12	-0.26	0.16								
5	0.06	0.36	-0.07	-0.50							
6	0.06	-0.08	-0.01	0.12	-0.20						
7	0.03	-0.01	0.01	0.06	-0.07	0.29					
8	0.08	-0.05	-0.11	-0.12	0.15	-0.05	0.00				
9	0.01	0.36	-0.14	-0.52	0.50	-0.11	-0.08	0.09			
10	-0.15	0.21	0.08	0.05	0.07	0.05	0.05	-0.02	0.04		
11	0.10	0.16	-0.19	-0.38	0.34	-0.02	-0.02	0.22	0.35	-0.02	
	1	2	3	4	5	6	7	8	9	10	



Covariates that were considered as potential confounders in the assessment of relationship between PbB and children's IQ, according to the above-mentioned strategy for identification of confounders, are shown in Table 4.4.3. From a *priori* considerations (Bouchard & Segal, 1985; Yule, 1986; Cohen et al., 1988), the covariates which may have been important antecedents or correlates of children's intelligence but which were not selected as potential confounders by the above process were also included in the multiple regression models (e.g., child's age at testing, school year, birthweight, and birth rank). Finally, a unique set of 14 to 18 variables was included in the model of assessing the relationship between PbB measured at different ages and child's IQ. There were 14 covariates that were associated ( $p \leq 0.25$ ) with both lifetime average PbB and full-scale IQ, and four antecedents of children's IQ described above were also included in the multivariable analysis. Thus, a total of 18 variables were taken into account in the assessment of the relationship between lifetime average PbB and full-scale IQ. These covariates included sex, age at testing, socioeconomic status, HOME scores, maternal intelligence, family functioning scores, parents' marital status, parental smoking status, life events, paternal secondary education, maternal age at birth, number of siblings, birthweight, birth order, feeding style in infancy, duration of breastfeeding, school year, and prolonged absence at school for any single school term during the last five years.

Table 4.4.3. Confounding of sociodemographic factors with each of IQ scales and blood lead concentration measured at various ages

Covariates	Antenatal	Cord	15 ms	3 ys	5 yrs	7 yrs	12 yrs	Lifetime
Sex							*	*
Grade			**			**	**	**
Socioeconomic status	**	**	**	**	**	**	**	**
HOME scores	**	**	**	**	**	**	**	**
Family functioning			**	**	**	**		**
Parents' marital status	*	*	*	*	*	*	*	*
Parental smoking status	**	**	**	**	**	**	**	**
Sibling number		**	**	**	**	**		
Life event		**	**	**		**		**
Maternal IQ	**	**	**	**	**	**	**	**
Paternal secondary education	**	**		**		**	**	**
Maternal age	*	*	*	*	*	*	*	*
Feeding style	**	**	**	**	**	**	**	**
Duration of Breast-feeding	**	**	**	**	**	**	**	**
Absence at school	*	*	*	*	*	*	*	*

\* Potential confounders for verbal and full-scale IQ.

\*\* Potential confounders for verbal, performance, and full-scale IQ.

#### 4.5. LINEAR REGRESSION ANALYSES OF BLOOD LEAD CONCENTRATION AND CHILD'S INTELLIGENCE

In simple regression analyses, all measures of PbB except for the cord sample were significantly inversely associated with children's verbal, performance and full-scale IQ ( $p < 0.01$ ). The magnitude of the estimated regression coefficients of verbal IQ on PbB was quite similar to that for the performance IQ estimates (Table 4.5.1).

In the multiple regression analyses, the inverse associations between PbB and child's IQ were attenuated markedly after adjustment for the effects of potential confounders. In particular, the apparent associations of IQ with the maternal and cord PbB became insignificant. The covariates contributing most to this attenuating effect were those identified as being most closely related to both PbB and child's IQ, i.e., socioeconomic status, quality of home environment, and maternal intelligence. However, the inverse associations between various measures of PbB from age 15 months to ages 11-13 years and child's IQ (mainly verbal IQ and full-scale IQ) remained statistically significant ( $p < 0.05$ ) or marginally significant even after taking all the potential confounders into account. Lifetime average PbB was found to be the exposure measure most strongly associated with IQ. An increase in PbB from 10 to 20  $\mu\text{g}/\text{dl}$  (0.48 to 0.97  $\mu\text{mol}/\text{l}$ ) was associated with a deficit in verbal IQ that varied, according to the age at which the blood sample was taken, from 1.6 to 2.7 points, and in full-scale IQ the estimated deficit ranged from 2.0 to 3.0 points.

Table 4.5.1. Estimated regression coefficients ( $\pm$ SE) in IQ points per log unit of blood lead concentration from simple and multiple regression analyses

Time of blood sampling	Crude			Adjusted†		
	Verbal IQ	Performance IQ	Full-scale IQ	Verbal IQ	Performance IQ	Full-scale IQ
Antenatal	-6.3 $\pm$ 1.8	-7.7 $\pm$ 2.4	-7.6 $\pm$ 2.0	-0.1 $\pm$ 1.8 (.96)	-2.3 $\pm$ 2.6 (.37)	-1.1 $\pm$ 2.2 (.61)
Cord	-2.9 $\pm$ 1.3 (.03)	-1.8 $\pm$ 1.6 (.25)	-2.7 $\pm$ 1.4 (.06)	1.0 $\pm$ 1.3 (.43)	1.2 $\pm$ 1.8 (.48)	1.2 $\pm$ 1.5 (.41)
15 months	-6.4 $\pm$ 1.3	-5.2 $\pm$ 1.7	-6.2 $\pm$ 1.5	-2.9 $\pm$ 1.3 (.03)	-0.6 $\pm$ 1.9 (.76)	-1.8 $\pm$ 1.6 (.24)
3 years	-8.5 $\pm$ 1.5	-9.4 $\pm$ 2.0	-9.8 $\pm$ 1.7	-2.6 $\pm$ 1.6 (.11)	-4.2 $\pm$ 2.3 (.07)	-3.8 $\pm$ 1.9 (.05)
5 years	-8.4 $\pm$ 1.3	-7.2 $\pm$ 1.7	-8.9 $\pm$ 1.5	-3.7 $\pm$ 1.4 (.01)	-3.7 $\pm$ 1.9 (.06)	-4.0 $\pm$ 1.6 (.02)
7 years	-7.9 $\pm$ 1.3	-8.6 $\pm$ 1.7	-8.9 $\pm$ 1.5	-2.8 $\pm$ 1.4 (.05)	-3.8 $\pm$ 2.0 (.06)	-3.4 $\pm$ 1.7 (.04)
11-13 years	-5.7 $\pm$ 1.3	-6.2 $\pm$ 1.7	-6.5 $\pm$ 1.4	-2.4 $\pm$ 1.3 (.06)	-2.0 $\pm$ 1.8 (.12)	-2.9 $\pm$ 1.5 (.06)
Lifetime average	-10.8 $\pm$ 1.6	-10.8 $\pm$ 2.2	-11.6 $\pm$ 1.9	-3.9 $\pm$ 1.8 (.03)	-4.7 $\pm$ 2.6 (.07)	-4.3 $\pm$ 2.1‡ (.04)

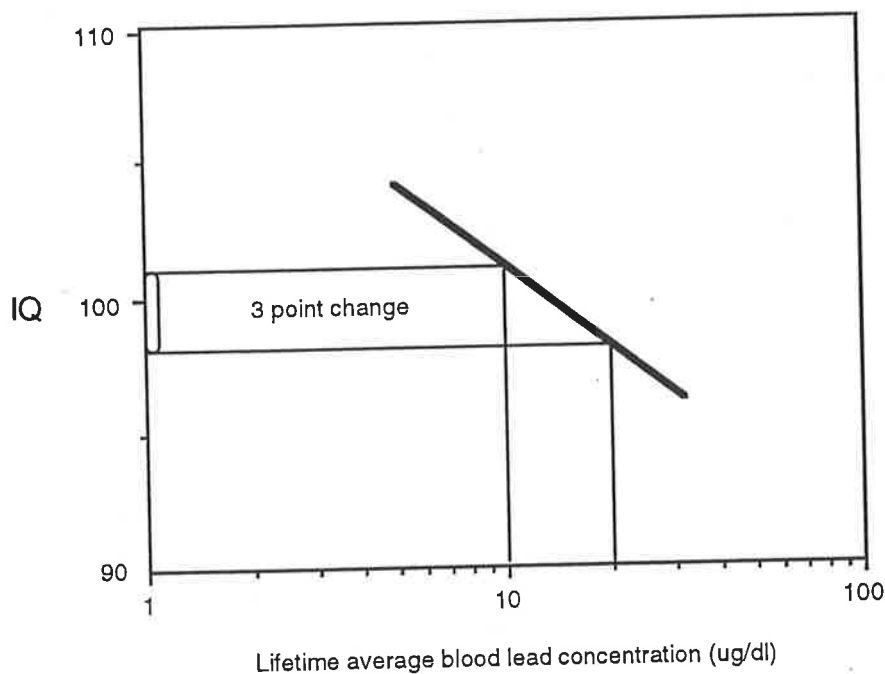
\* P values are shown in parentheses; All simple regression coefficients are statistically significant ( $p < 0.001$ ) except for that of cord blood lead concentration.

† Adjusted for 10 to 18 covariates as described in the text (pages 131-40).

‡ Analyses were based on the natural-log unit of blood lead concentration in ug/dl; This means that the expected deficit in full-scale IQ associated with an increase in lifetime average blood lead concentration from 10 to 20 ug/dl (0.48 to 0.97  $\mu$ mol/l) is 3.0 points:  $4.34 \times (\ln[20] - \ln[10]) = 3.0$ .

A covariate-adjusted dose-effect relationship between lifetime average PbB and full-scale IQ at ages 11-13 years is shown in Figure 4.5.1. The line of best fit (as estimated by multiple regression analysis) indicates that, within the range of exposure in this cohort, there was a dose-dependent relationship of lifetime average PbB with IQ. From the estimated regression coefficient, it can be demonstrated that, for an increase in lifetime average PbB from 10 to 20 ug/dl (0.48 to 0.97 umol/l), the deficit in full-scale IQ would be expected to be 3.0 points.

Figure 4.5.1. Adjusted estimated relation between lifetime average blood lead concentration and full-scale IQ at ages 11-13 years.



#### 4.6. BLOOD LEAD CONCENTRATION AND THE WISC-R SUBSCALES

The results of regression analyses on the WISC-R subscale scores showed that the mean subscale scores varied inversely with the lifetime average PbB (Table 4.6.1). However, there were differences in the magnitude of the associations of the WISC-R subscales with lifetime average PbB. The associations with the Information, Arithmetic, Block Design, and Maze subscales were stronger than those for any other subscale. The Information subtest involves a broad range of general knowledge which requires memory and ability to store and retrieve information; the Arithmetic subtest measures numerical reasoning and computational skill which requires attention and concentration; the Block Design subtest measures visual-motor coordination and ability of nonverbal concept formation; the Mazes subtest appears to measure planning ability and perceptual organisation (Kaufman, 1979; Sattler, 1988). As described above, some fundamental neuropsychological functionings such as memory, concentration and attention, and visual-motor coordination are involved in these four subtests (Kaufman, 1979; Sattler, 1988).

Table 4.6.1. Mean age-adjusted subscale scores ( $\pm$ standard deviation) and estimated regression coefficients in points of subscale scores per log lifetime average blood lead concentration

Subscale	Blood lead tertile			Coefficient*		
	Lower	Medium	Higher	Estimate	SE	P value
Information	10.4 $\pm$ 1.9	10.1 $\pm$ 1.7	9.2 $\pm$ 2.1	-0.90	0.35	0.01
Similarities	10.0 $\pm$ 2.3	10.2 $\pm$ 2.3	9.2 $\pm$ 2.6	-0.02	0.46	0.96
Arithmetic	10.9 $\pm$ 2.7	10.0 $\pm$ 2.5	9.0 $\pm$ 2.4	-1.62	0.50	<0.01
Vocabulary	10.0 $\pm$ 2.2	9.6 $\pm$ 2.1	8.7 $\pm$ 2.1	-0.51	0.39	0.19
Comprehension	9.6 $\pm$ 1.9	9.3 $\pm$ 2.2	8.9 $\pm$ 2.0	0.03	0.40	0.98
Digit span	9.9 $\pm$ 3.0	9.3 $\pm$ 2.6	8.7 $\pm$ 3.0	-0.63	0.58	0.27
Picture completion	10.7 $\pm$ 2.4	10.2 $\pm$ 2.4	9.6 $\pm$ 2.4	-0.53	0.47	0.26
Picture arrangement	10.4 $\pm$ 2.7	10.2 $\pm$ 2.6	9.8 $\pm$ 2.6	0.14	0.53	0.48
Block design	12.2 $\pm$ 3.0	11.3 $\pm$ 3.2	10.3 $\pm$ 3.4	-1.39	0.62	0.03
Object assembly	11.7 $\pm$ 3.1	11.4 $\pm$ 3.4	10.5 $\pm$ 2.9	-0.75	0.62	0.22
Coding	9.9 $\pm$ 2.9	10.0 $\pm$ 2.8	8.9 $\pm$ 3.0	-0.84	0.58	0.14
Maze	11.3 $\pm$ 2.8	10.6 $\pm$ 2.9	10.3 $\pm$ 2.7	-1.13	0.51	0.03

\*The coefficients for the subscales of verbal IQ (i.e., first six subscales) and performance IQ (i.e., last six subscales) were adjusted for the same covariates as those used in the multivariable analysis of relations between lifetime average PbB and verbal/performance IQ, respectively.

The percentage and direction of significant verbal-performance IQ 'discrepancies' in relation to the tertile of lifetime average blood lead concentration were also examined. A verbal-performance discrepancy is defined as a difference between verbal and performance IQs greater than 12 points in either direction (Kaufman, 1979). Significant verbal-performance discrepancies may indicate deficiencies in processing information and/or modes of expression or subtle brain damage (Kaufman, 1979; Sattler, 1988). However, they should not be used to infer neurological dysfunction without consideration of the child's entire performance and clinical data (Sattler, 1988). The overall percentage of children with a verbal-performance IQ discrepancy greater than 12 points in this study sample was 30.4 percent (Table 4.6.2), as compared to 34 percent in the standardising sample (Kaufman, 1979). There was a trend for both the frequency and the direction of discrepancy to vary with lifetime average PbB. Verbal-performance discrepancies were less frequent among children in the high tertile of blood lead concentration than among children in the medium and low tertiles (26.6% vs. 30.6% and 33.9%, respectively). The performance IQ which was greater than the verbal IQ accounted for 32/37 (86.5%), 26/33 (78.8%), and 22/29 (75.9%) of all discrepancies among children in the low, medium, and high tertiles of lifetime average blood lead concentration, respectively. However, there was no significant difference in the frequency of verbal-performance IQ discrepancies among children with different levels of lead exposure in this sample ( $X^2_{(df=4)} = 2.74$ ;  $p = 0.60$ ).



Table 4.6.2. Percentage of children with WISC-R verbal - performance IQ discrepancies by tertile of lifetime average blood lead concentration

Blood lead tertile*	Performance IQ relative to Verbal IQ†		
	P > V	P - V	P < V
Low	29.4	66.1	4.6
Medium	24.1	69.4	6.5
High	20.2	73.4	6.4

$X^2(df=4) = 2.74; p = 0.60.$

\* Geometric mean of lifetime average blood lead concentration in lower, middle, and higher tertiles was 9.8, 14.8, and 21.0, respectively.

† P > V: Performance IQ exceeds Verbal IQ by 12 or more points;

P - V: Performance IQ and Verbal IQ differ by fewer than 12 points;

P < V: Verbal IQ exceeds Performance IQ by 12 or more points.

The frequency of WISC-R subtests deviating significantly from the mean subscale scores (where a significant deviation is defined as a difference of 3 or more points from the mean subscale score (Kaufman, 1979)) in relation to the tertile of lifetime average blood lead concentration is shown in Table 4.6.3. There was no significant association between the subscale deviations and blood lead concentration.

Table 4.6.3. Percentage of WISC-R subtests deviating significantly from subtest mean, classified by tertile of lifetime average blood lead concentration

Blood lead tertile*	Number of subtests						
	0	1	2	3	4	5	6+
Low	5.5	16.5	22.9	24.8	11.9	7.3	11.0
Medium	2.8	18.7	24.3	22.4	18.7	7.5	5.6
High	7.3	15.6	20.2	27.5	12.8	6.4	10.1

$X^2(df=12) = 7.58; p = 0.82.$

\* Geometric mean of lifetime average blood lead concentration in lower, middle, and higher tertiles was 9.8, 14.8, and 21.0, respectively.

Factor analyses of the WISC-R usually result in three factors reflecting Verbal Comprehension, Perceptual Organization, and Freedom from Distractibility. The Verbal Comprehension factor score measures verbal knowledge and understanding obtained informally and through formal education, and the Perceptual Organization factor score measures the ability to interpret and organise visually perceived material within a time limit; while Freedom from Distractibility is a factor that may be considered more “behavioural” than “intellectual” (Kaufman, 1979; Ownby & Matthews, 1985; Sattler, 1988). Additional analyses were conducted to examine the association between lifetime average blood lead concentration and estimated deviation quotients for the Verbal Comprehension, Perceptual Organization, and Freedom from Distractibility factors.

The results show that the lifetime average blood lead concentration was not significantly associated with the deviation quotients for verbal comprehension, perceptual organization, and freedom from distractibility factors. There is no consistent trend in the deviation quotients in relation to blood lead levels (Table 4.6.4).

Table 4.6.4. Estimated WISC-R deviation quotients ( $\pm$ standard deviation) for verbal comprehension, perceptual organization, and freedom from distractibility factors by tertile of lifetime average blood lead concentration

Blood lead tertile	Verbal comprehension	Perceptual organization	Freedom from distractibility
Low	97.2 $\pm$ 11.6	105.0 $\pm$ 14.7	96.6 $\pm$ 13.7
Medium	99.6 $\pm$ 9.6	106.0 $\pm$ 13.2	99.6 $\pm$ 14.1
High	96.5 $\pm$ 10.8	102.0 $\pm$ 13.9	96.8 $\pm$ 14.0

## CHAPTER 5. INTERACTIONS BETWEEN BLOOD LEAD AND OTHER FACTORS ON CHILD'S INTELLIGENCE, PERSISTENCE OF APPARENT LEAD EFFECTS AND EXPLANATORY POWER OF LEAD EXPOSURE

### Summary

*The possible interactions between blood lead and other factors (including gender, parents' occupational prestige (as a surrogate of socioeconomic status), quality of home environment, and maternal IQ) on children's intelligence quotients are examined. Persistence of apparent lead effects and the relative proportion of variance in children's IQ attributable to the lead exposure are also explored. The results show that no statistically significant interaction between blood lead and any of these covariates was found in this study, although there is a suggestion that children of lower socioeconomic status appear to be more sensitive to the effects of lead than those of higher socioeconomic status, and that girls may be more sensitive to lead than boys. There is no statistically significant correlation between changes in blood lead concentrations and changes in cognitive performance during childhood. The relative proportion of variance in children's IQ attributable to lead is small.*

### 5.1. INTERACTIONS BETWEEN LIFETIME AVERAGE BLOOD LEAD CONCENTRATION AND OTHER FACTORS ON CHILDREN'S IQ

Analyses were conducted stratifying on those other factors which were most strongly related to both PbB and child's IQ (i.e., parents' occupational prestige, HOME scores, and maternal IQ) and on gender which has been found to act as an effect-modifier at ages 4 and 7 years (McMichael et al., 1992; Baghurst et al., 1992a).

Table 5.1.1 shows the variation of IQ with lifetime average PbB within boys and girls separately. The association between lifetime average PbB and children's IQ appears to be more pronounced for girls than for boys (Table 5.1.1).

Table 5.1.1. Mean IQ ( $\pm$ standard deviation) according to lifetime average blood lead concentration and gender.

Lifetime average Blood lead (ug/dl)	Gender		p value
	Boys	Girls	
$\leq 12.0$	103.3 $\pm$ 12.7	105.0 $\pm$ 11.1	0.03
12.1-17.0	101.9 $\pm$ 11.4	100.2 $\pm$ 11.7	
$> 17.0$	97.9 $\pm$ 12.7	91.5 $\pm$ 9.3	

In Table 5.1.2 it is apparent that the impact of lead exposure on children's IQ was stronger amongst the children from the families of lower socioeconomic status than those in higher socioeconomic status families.

Table 5.1.2. Mean IQ ( $\pm$ standard deviation) according to lifetime average blood lead concentration and socioeconomic status\*.

Lifetime average Blood lead (ug/dl)	Socioeconomic status		p value
	Higher	Lower	
$\leq 12.0$	105.6 $\pm$ 12.5	103.1 $\pm$ 10.4	
12.1-17.0	104.4 $\pm$ 10.4	100.6 $\pm$ 12.6	<0.001
> 17.0	101.5 $\pm$ 11.4	90.9 $\pm$ 10.9	

\* Socioeconomic status was defined by Daniel's scale of parents' occupational prestige.

Further, an inverse association of lifetime average PbB with children's IQ seemed apparently stronger among the children who had poorer quality of home environment (Table 5.1.3), and those whose mothers had lower IQ (Table 5.1.4).

Table 5.1.3. Mean IQ ( $\pm$ standard deviation) according to lifetime average blood lead concentration and HOME scores.

Lifetime average Blood lead (ug/dl)	HOME scores		p value
	Higher	Lower	
$\leq 12.0$	105.1 $\pm$ 11.2	99.7 $\pm$ 11.4	0.23
12.1-17.0	102.2 $\pm$ 10.9	96.9 $\pm$ 10.7	
$> 17.0$	99.7 $\pm$ 10.1	92.5 $\pm$ 10.0	

Table 5.1.4. Mean IQ ( $\pm$ standard deviation) according to lifetime average blood lead concentration and maternal IQ.

Lifetime average Blood lead (ug/dl)	Maternal IQ		p value
	Higher	Lower	
$\leq 12.0$	106.8 $\pm$ 10.9	98.8 $\pm$ 11.5	0.14
12.1-17.0	104.9 $\pm$ 11.6	99.3 $\pm$ 11.2	
$> 17.0$	103.9 $\pm$ 10.3	93.3 $\pm$ 10.1	



The interactions between blood lead and the covariates suggested by Tables 5.1.1 - 5.1.4 were further examined using regression modelling. Simple regression analyses also indicated that gender and socioeconomic status were potential effect-modifiers of lead exposure, i.e., girls seemed to be more sensitive to the lead effect than boys, and children in lower socioeconomic status families appeared to be more affected by exposure to lead than those from an advantaged background, although no statistically significant interaction between lead and HOME scores or maternal IQ was found (Table 5.1.5).

Multiple regression analyses indicate that the magnitude of association between lifetime average PbB and children's IQ at different levels of socioeconomic status or gender was, in each case, markedly attenuated after adjustment for potential confounders. However, the adjusted regression coefficients (boys: -2.6 IQ points per log unit of PbB\* [95% CI: 2.9 to -8.0]; girls: -7.4 [95% CI: -1.7 to -13.1]; lower SES: -9.6 [95% CI: -2.5 to -17.7]; higher SES: -2.9 [95% CI: 3.8 to -9.6]) were still suggestive of higher sensitivities in girls and in children of lower socioeconomic status.

\* For example, for each natural log unit increment in PbB, children's IQ is estimated to decline by 2.6 points for boys and 7.4 points for girls.

Table 5.1.5. Estimated regression coefficients of potential effect-modifiers of the relation between blood lead concentration and children's IQ

Covariate	Crude			Adjusted*		
	Estimate †	SE	P value	Estimate †	SE	P value
<b>Gender of child</b>						
Boys	-7.7	2.7	0.03	-2.6	2.8	0.19
Girls	-15.8	2.6		-7.4	2.9	
<b>Parents' occupational prestige</b>						
Lower	-19.6	3.8	<0.01	-9.6	3.6	0.16
Higher	-4.3	2.9		-2.9	3.4	
<b>HOME scores</b>						
Lower	-10.2	2.9	0.23			
Higher	-6.7	2.9				
<b>Maternal IQ</b>						
Lower	-9.4	3.2	0.14			
Higher	-2.7	3.6				

\* Adjusted for the same covariates as in Table 4.6.1.

† Regression coefficient represents the change in IQ for each natural log unit change in hematocrit adjusted PbB.

## 5.2. PERSISTENCE OF AN ASSOCIATION BETWEEN BLOOD LEAD CONCENTRATION AND CHILD'S DEVELOPMENT

### 5.2.1. LEAD EXPOSURE AND DEVELOPMENTAL STATUS AT VARIOUS AGES

Although the significant association between PbB and cognitive development observed at earlier ages continues to be evident at ages 11-13 years within this cohort, it is still unclear to what extent the apparent "effects" at early years persist into the later years of children's lives. If an 'adverse effect' of lead can be demonstrated in the same group of children at each stage of development, it would substantially strengthen the conclusion that the lead 'effect' is persistent, and would also improve our understanding of the dynamic pattern of lead 'effects' on childhood development.

Accordingly, the children followed at ages 11-13 years were divided into low, medium, and high exposure groups on the basis of their lifetime average PbB at age 2 years (the age when the children's developmental status was assessed for the first time in this cohort study), and the histories of exposure and development in these three groups of the children were then examined.

The differences in lifetime average PbB at ages 2, 4, 7, and 11-13 years between the means of lower versus higher tertile were 13.4, 12.7, 10.9, and 7.6 ug/dl, respectively (Table 5.2.1).

Table 5.2.1. Geometric mean lifetime average blood lead concentrations (ug/dl) at different ages by tertile of lifetime average blood lead concentration at age 2 years

Blood lead tertile at 2 years	Geometric mean (geometric standard deviation)			
	2 years	4 years	7 years	11-13 years
Low	12.5 (1.2)	13.3 (1.2)	11.9 (1.2)	11.0 (1.4)
Medium	18.5 (1.1)	19.5 (1.1)	17.6 (1.2)	14.7 (1.3)
High	25.9 (1.1)	26.0 (1.2)	22.8 (1.2)	18.6 (1.3)

The corresponding (unadjusted) differences in the mean scores of developmental tests were 6.6, 8.9, 8.5, and 7.4 points at each of those ages, respectively (Table 5.2.2).

Table 5.2.2. Mean scores ( $\pm$ standard deviation) of developmental tests at different ages by tertile of lifetime average blood lead concentration at age 2 years\*

Blood lead tertile at 2 years	MDI (2 yrs)	GCI (4 yrs)	Full-scale IQ (7 yrs)	Full-scale IQ (11-13 yrs)
Low	113.3 $\pm$ 14.7	112.5 $\pm$ 14.2	109.9 $\pm$ 13.3	104.3 $\pm$ 12.4
Medium	109.9 $\pm$ 13.2	107.3 $\pm$ 13.4	104.2 $\pm$ 13.0	99.6 $\pm$ 11.7
High	106.7 $\pm$ 14.0	103.6 $\pm$ 14.2	101.4 $\pm$ 12.2	96.9 $\pm$ 11.3

\* Children's developmental status was assessed with use of the Bayley Mental Developmental Index (MDI) at age 2 years, the McCarthy General Cognitive Index (GCI) at age 4 years, and the Wechsler Full-Scale IQ at ages 7 and 11-13 years.

Multiple regression analysis revealed that, for lower versus higher tertiles of blood lead groups, the adjusted differences in developmental scores were 4.0, 4.8, 4.9, and 4.5 points at ages 2, 4, 7, and 11-13 years, after taking potential confounders into account (Figure 5.2.1). These results show that the inverse associations between blood lead concentration and measures of developmental status observed at younger ages in this cohort are still apparent in middle childhood. The strong correlation ( $r=0.78$ ;  $p < 0.0001$ ) of full-scale IQ at ages 7 and 11-13 years suggests that the children who scored poorly at earlier ages had not improved substantially in their overall ranking of development by age 11-13, despite the fact that their blood lead concentrations had declined markedly (Figure 5.2.1; Table 4.2.1 & Table 5.2.1).

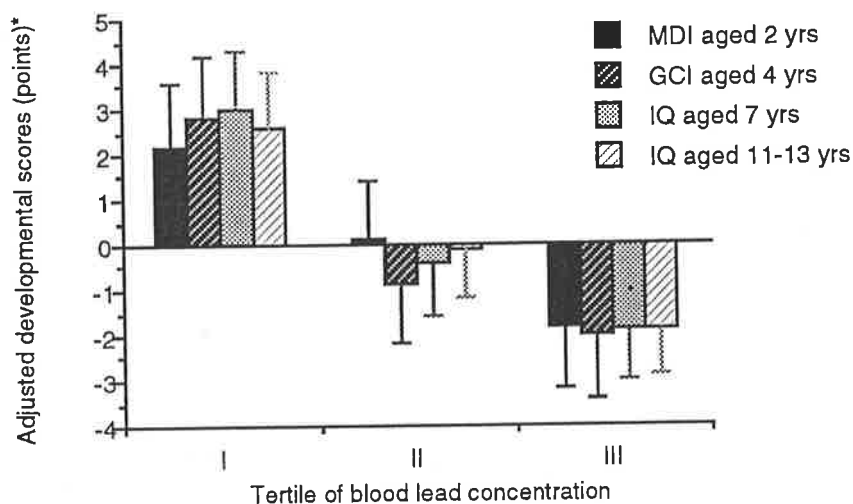


Figure 5.2.1. Developmental status at different ages by tertile of blood lead concentration

(\*Mean ( $\pm$ standard error) adjusted scores for children classified by lifetime blood lead concentration at age 2 years. The potential confounders for which adjustments were made include gender, maternal age at child's birth, socioeconomic status, HOME scores, maternal IQ, parental smoking status, parents living together or apart, birthweight, birth rank, feeding style of infants (breast/bottle), and duration of breast-feeding. These variables were measured at the early stage or various stages of the study. MDI: Bayley Mental Developmental Index; GCI: McCarthy General Cognitive Index; IQ: Wechsler Full-Scale IQ.)

### 5.2.2. DECLINING BLOOD LEAD LEVELS AND COGNITIVE CHANGES

An alternative approach to the question of persistence is to examine the changes in IQ from age 7 to ages 11-13 as a function of the changes in lead exposure. If the "effect" of lead is transient, cognitive performance might be expected to improve most amongst those children whose blood lead level experienced the greatest decline in the later childhood. On the other hand, if the lead "effect" is persistent (or exposure to lead has no real effect), children's performance would not be expected to improve as their exposure declined.

The results show that children's IQ at ages 11-13 years was generally lower than that at age 7 years. The mean changes in blood lead levels between ages 7 and 11-13 years were not statistically significantly related to changes in children's IQ, although there was a trend in the anticipated direction for the relation, i.e., children with the biggest decline in PbB exhibited the least drop in IQ (Table 5.2.3).

Table 5.2.3. Changes in blood lead level and changes in children's IQ between ages 7 years and 11-13 years

Decline in PbB between 7 and 11-13 years (ug/dl)	$\Delta$ IQ*		P value†
	Mean $\pm$ SD	95% CI	
< 2.3	-5.4 $\pm$ 8.3	-3.8 to -7.0	0.45
2.3 ~ 4.9	-5.0 $\pm$ 9.3	-3.2 to -6.8	
> 4.9	-3.8 $\pm$ 7.9	-2.3 to -5.3	

\*  $\Delta$ IQ = (IQ<sub>11-13</sub> - IQ<sub>7</sub>).

†From an analysis of variance.



These analyses were extended to look at changes in cognitive function from earlier ages (2 and 4 years) to the present. As the measures employed varied different ages (e.g., MDI at age 2 years, GCI at age 4 years, and IQ at ages 11 years), it was not possible to meaningfully compare the 'raw' scores at each age. Therefore, Z scores (i.e., [actual score - mean value]/standard deviation) were used to compare the trend of changes in cognitive development, in relation to changes in blood lead levels during childhood. The results show that there was no statistically significant association between either of these pairs of changes in simple analyses, and no obvious trend was apparent (Tables 5.2.4. & 5.2.5).

Table 5.2.4. Changes in blood lead level and changes in cognitive function between ages 2 years and 11-13 years

Decline in PbB between 2 and 11-13 years (ug/dl)	$\Delta$ Z score*		P value†
	Mean $\pm$ SD	95% CI	
< 10.2	0.03 $\pm$ 0.94	-0.15 to 0.21	0.74
10.2 ~ 16.2	0.04 $\pm$ 1.01	-0.15 to 0.23	
> 16.2	-0.01 $\pm$ 1.02	-0.20 to 0.18	

\*  $\Delta$  Z score = (Z<sub>11-13</sub> - Z<sub>2</sub>).

†From an analysis of variance.

Table 5.2.5. Changes in blood lead level and changes in cognitive functioning between ages 4 years and 11-13 years

Decline in PbB between 4 and 11-13 years (ug/dl)	$\Delta Z$ score*		P value†
	Mean±SD	95% CI	
< 6.0	0.05±0.90	-0.12 to 0.23	0.42
6.0 ~ 10.3	0.01±0.91	-0.17 to 0.18	
> 10.3	0.01±0.96	-0.17 to 0.19	

\*  $\Delta Z$  score =  $(Z_{11-13} - Z_4)$ .

†From an analysis of variance.

Pearson correlation and simple regression analyses between changes in blood lead levels and changes in cognitive functioning were conducted (Table 5.2.6). Generally, correlations between changes in PbB and cognitive functioning were very weak ( $|r| \leq 0.12$ ), and not statistically significant, although the changes in IQ from 7 to 11-13 years is suggestive of a slight "recovery" (or a least decrement) amongst those with the greatest fall in PbB between ages 7 and 11-13 years.

Table 5.2.6. Correlation and simple regression analyses between changes\* in blood lead levels and changes in cognitive functioning during childhood

Change in PbB	Correlation	Estimate $\pm$ SE	R <sup>2</sup> %	P value
<b>7 ~ 11-13 years</b>	-0.12	-0.73 $\pm$ 0.43	0.6	0.09
<b>4 ~ 11-13 years</b>	-0.01	0.01 $\pm$ 0.08	0.0	0.94
<b>2 ~ 11-13 years</b>	0.03	-0.01 $\pm$ 0.10	0.0	0.89

\* Change in blood lead =  $PbB_t - PbB_{11-13}$  (t=2, 4 or 7 years); change in cognitive functioning =  $Z_{11-13} - Z_t$  (t=2 or 4), while change in IQ between ages 7 and 11-13 years =  $IQ_{11-13} - IQ_7$ .

It should be noted that the analysis of changes in developmental measures in relation to changes in PbB is a difficult task since individual variation is considerably large (Tables 5.2.3-5.2.5). The ability to detect an "improvement" of cognitive performance is limited in this study. For example, calculations on the basis of the data from the present study show that, at the conventional level of significance of  $p=0.05$ , the power to detect a difference of 1, 2, 3, and 4 points in the mean cognitive change between two groups with lower and higher exposure status was 0.14, 0.42, 0.75, and 0.94, respectively, while the largest difference between the top and bottom tertiles in the present study was only 1.6 points, i.e., the power to detect a difference of this magnitude was less than 40 percent.

Some further comment on the apparent decrease in the unadjusted mean IQ (i.e., without consideration of the confounding effects) from age 7 to ages 11-13 years is also warranted. Possible reasons for this downward IQ drift are that:

(a) the characteristics of this study population are different from the US standardising population, and the expected mean IQ may vary with age in this cohort;

(b) Australia (especially rural Australia), has encountered a severe recession during the last a few years, and therefore, poorer socioeconomic aspects might have had a negative impact on child development (Bouchard & Segal, 1985; Sattler, 1988);

(c) intelligence testing was administered by different examiners at ages 7 and 11-13 years, and inter-examiner differences may have been important.

### 5.3. EXPLANATORY POWER OF LEAD EXPOSURE IN CHILDREN'S INTELLIGENCE

The relative explanatory power of an "independent" (or predictive) factor within a given data set can be defined as the percentage variance in the dependent variable which is accounted for by that factor. Although the percentage variance accounted for depends on the distribution of the independent factor (i.e., exposure range) as well as the magnitude of its effect, and therefore, must be interpreted with great caution, it is, nevertheless, a useful statistical index.

Multiple regression analyses show that in this study, for children's IQ at ages 11-13 years, the variance attributable to the lead exposure is quite modest (1.6%), compared with that of other cofactors (Figure 5.3.1). The Figure indicates that the genotype-environmental effects on the children's IQ are certainly multifactorial. For example, socio-environmental and familial variables accounted for 17.3 and 6.1% of variation in children's IQ, respectively, whereas demographic and biomedical factors explained less than 2% of the variance. There is a large amount of variance of child IQ (i.e., 73.3%) which cannot be explained by any subset of the variables examined in this study. These observations suggest that there are other factors which may be important predictors of the children's IQ and that unraveling the complexity of genotype-environmental influences on IQ still poses a great challenge to neurobehavioural science researchers.

The socio-environmental and familial factors clearly have a larger influence on cognitive development than any other subset of covariates studied, although environmental exposure to low levels of lead does account for approximately 6% of the *explained* variation in children's IQ within this study population.

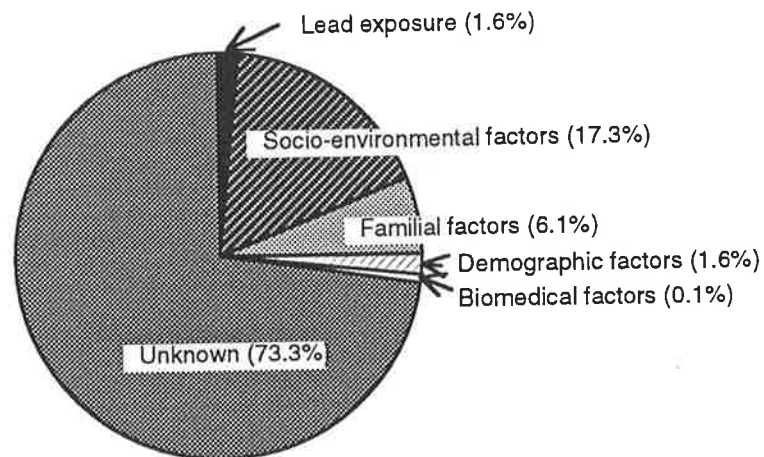


Figure 5.3.1. Relative size of variance in children's IQ

Note: Variables which were included in the model are as follows:

Lead exposure: Lifetime average blood lead concentration at ages 11-13 years.

Socio-environmental factors: Socioeconomic status, HOME scores, family functioning scores, parents' general health status, parental smoking behaviour, parent's marital status, sibling number in the household, life event, length of dwelling in Port Pirie, testing site.

Familial factors: Maternal IQ and paternal secondary education.

Demographic factors: Gender, age and school year.

Biomedical factors: Maternal age at birth, birthweight, birth rank, feeding style during infancy, duration of breast-feeding, whether any medication had been used in the last 2 weeks before testing, whether the child had been absent from school more than 2 weeks in the last 5 years.

## CHAPTER 6. DISCUSSION

### Summary

*Possible explanations for an observed association between low level lead exposure and children's IQ, implications of the findings from this study, and directions for further research are discussed. Based on an integral consideration of chance, bias, confounding, causality and reverse causality, it is concluded that low-level exposure to lead in early childhood is likely to cause a small, but real and detectable effect on cognitive development, and this effect appears to persist into later childhood. It is concluded that the effect of "low" level lead exposure may be irreversible. It is recommended that the formulation of a public health policy for the prevention of the lead problem should be based on a composite optimisation of child health and best use of existing resources.*

### 6.1. THE MAIN FINDING - ASSOCIATION BETWEEN LIFE-LONG EXPOSURE TO LEAD AND CHILDREN'S INTELLIGENCE AT AGES 11-13 YEARS

The main finding of the study is that the inverse associations between lead exposure (i.e., blood lead concentration) and cognitive development observed in younger children are still apparent at ages 11-13 years. After adjusting for a wide range of potential confounding factors, this association is still evident for scores on each IQ scale, but is particularly evident for full-scale IQ scores and for verbal IQ scores. The estimated deficit in verbal and full-scale IQ scores at ages 11-13 years is 2.7 and 3.0 points, respectively, for a shift in lifetime average PbB from 10 to 20 ug/dl (0.48 to 0.97 umol/l).

This study is the longest and largest follow-up study, to date, of children for whom lifetime lead exposure histories are available. Very few studies have been able to examine whether there is a long term effect of exposure to low levels of lead on childhood development.

In the Boston prospective study, a consistent inverse association between PbB (particularly at age 2 years) and cognitive development was found at ages 57 months and 10 years, but it failed to find a persistent association between prenatal exposure to lead and functional performance (Bellinger et al., 1987; 1990; 1991; 1992). It is unclear why children's performance was much more strongly associated with PbB at age 2 years than any other age. An age-specific vulnerability of the nervous system during that period was hypothesised (Bellinger et al., 1992), but it has not been supported by any other prospective study.

In the group followed by Needleman and colleagues, it was shown that exposure to lead in childhood was associated with deficits in neuropsychological functioning that persisted into young adulthood (Needleman et al., 1979; 1990). However, dentine lead concentration was used as the exposure measure in their study, and data describing temporal changes in the children's exposure status were not collected. Moreover, some important confounding factors (e.g., quality of home environment and child's grade at school) were not included in the data analysis, and the possibility that the observed association was spurious cannot be totally excluded (Good, 1991; Ernhart et al., 1991).

The fact that an inverse association between PbB and developmental scores has been observed longitudinally at the ages of two, four, seven and again at eleven to thirteen years within this cohort suggests that environmental exposure to lead may have an independent and enduring effect on childhood development.

Possible explanations for this association are discussed below.



### 6.1.1. CONFOUNDING

Although an association of blood lead concentration with children's IQ remained after controlling for a wide range of putative confounders, some of the pitfalls that can arise when controlling for confounders are discussed here.

#### Overadjustment or underadjustment

Quality of the home environment, and maternal IQ were confounders, and it was shown (see Table 4.4.1) that these factors are indeed correlates of both lead exposure and IQ. These factors are also considered to be direct determinants of children's intelligence (Hanson, 1975; Bouchard & Segal, 1985; Bradley et al., 1989). Three hypothetical models are outlined in Figure 6.1.1.1. Model I satisfies the classical criteria for "confounding" given in standard epidemiology texts (Rothman, 1986; Hennekens & Buring, 1987): a mechanistic association (straight lines with arrow heads) between, say, HOME scores and child intelligence - and a statistical association (straight lines without arrow heads) between HOME scores and PbB. If this represents the true situation, HOME scores *should* be taken into account in an assessment of the lead-IQ relation.

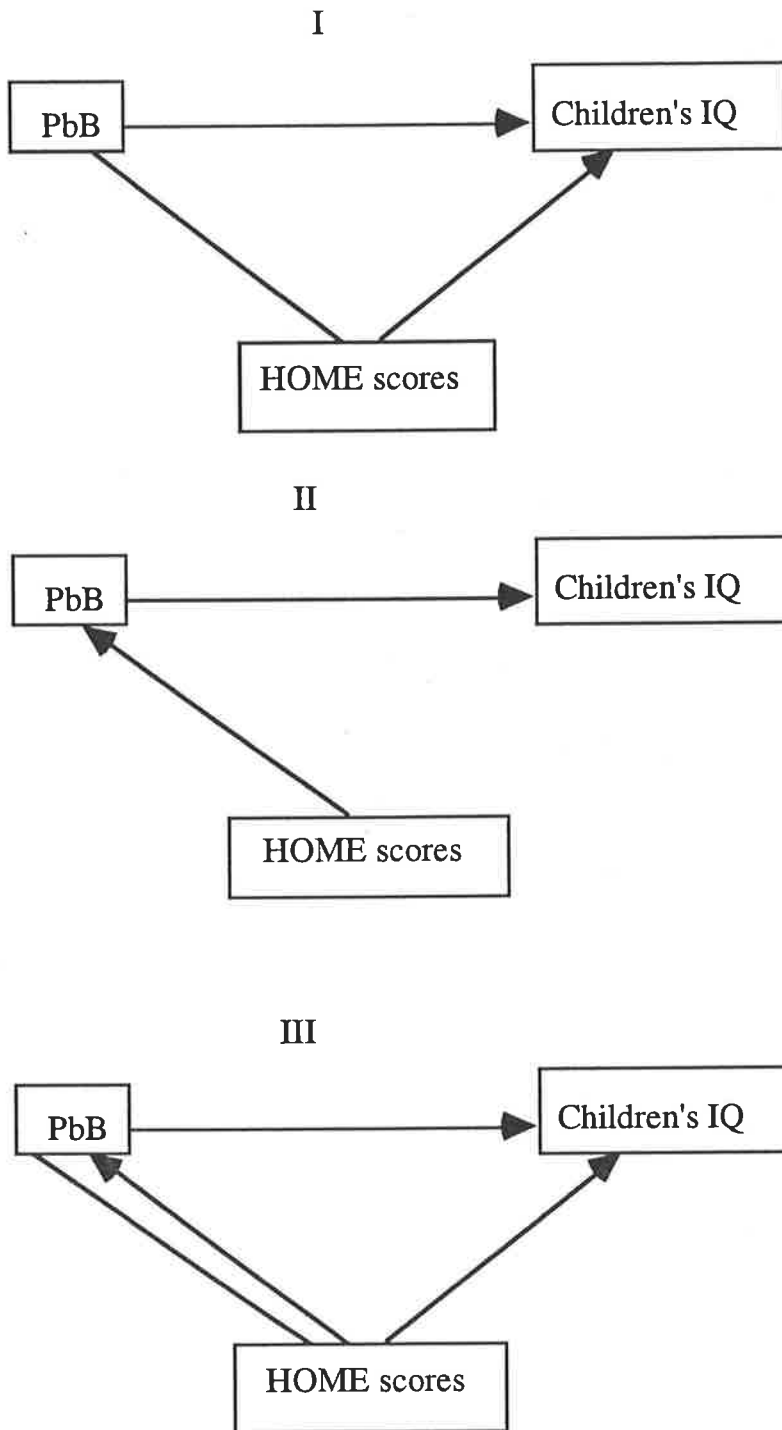


Figure 6.1.1.1. Confounding (I), non-confounding (II) and partially confounding (III)

Model II depicts the hypothetical situation in which the observed impact on children's IQ of HOME scores is mediated *entirely* by the amount of lead in the home environment which was ingested or inhaled. It is plausible that, in homes in which parents are less well educated and in which less attention is given to providing the child with a stimulating environment, less attention is also paid to other aspects of child and family care, such as domestic cleaning and maintenance. If this were the predominant mechanism then it would be utterly *inappropriate* to include HOME score in the analytic model (Baghurst et al., 1987; Weinberg, 1993).

It is entirely plausible, however, that HOME scores may be partly artificial/stochastic, and partly causal correlates of lead exposure (Model III), i.e., the associations of HOME scores with IQ actually consist of two components, one of which is artefactually associated with exposure, the other being causally associated with exposure (Vimpani et al., 1989). Thus, HOME score can play a dual role, serving in part as a classical confounder and also as a mediator of exposure (Joffe & Greenland, 1994; Weinberg, 1994). Within this study's data set the estimated Pearson correlation coefficients of HOME scores with lifetime average PbB was 0.55, which indicates that such considerations may be quite important. It is impossible, however, to distinguish the relative contributions of each component, and the treatment of these variables as pure confounders will therefore underestimate the effect of lead on child development.

In the analyses presented in this thesis, HOME scores and other variables (e.g., maternal IQ, and parental smoking habit) were included in the analyses as pure confounders (Model I). The strength of association of PbB with children's IQ was remarkably attenuated, but the association still remained evident after adjustment (Table 4.5.1). This analytical strategy is conservative in that it assumes that all these 'non-lead' variables are associated with children's IQ via independent (i.e.,

direct) mechanisms that do not involve lead exposure, i.e., they are acting as pure confounders. In fact, it is plausible - even likely - that part of the effect of these variables was mediated via altered exposure to lead (Model III). Although this analytical procedure may have partitioned some variation which was truly attributable to the lead exposure, this may still be the prudent way to proceed until a better understanding of these mechanisms has been reached.

In brief, therefore, it may be concluded that the analytical approach employed in this thesis is likely to *underestimate* rather than *overestimate* an association between the lead exposure and children's IQ.

#### Adequate or inadequate information on confounding

Residual confounding may arise when the data are classified into categories that are too broad (Leon, 1993). Some confounding factors (e.g., HOME score, and maternal IQ) that may be regarded as continuous variables were analysed as categorical variables, in order to avoid making assumptions about the form of their associations with the outcome of interest (e.g., linear, curvilinear, etc.) and to ensure the best use of the data (e.g., by creating a "missing" category, other data on the child can still be used in the regression analysis even if his/her value for that variable was recorded as "missing"). The aggregation of these variables might have resulted in some residual confounding. However, significant associations of PbB with children's IQ remained when these covariates were adjusted for, either in narrower categories (e.g., dividing the HOME scores and maternal IQ from 5- to 2-point groups, and from 15- to 5-point groups, respectively), or as continuous variables.

A poor proxy for, or misclassification of, the underlying confounder(s) of interest may also result in residual confounding. For example, socioeconomic status *per se* may not affect a child's IQ, but it may convey information about many other

factors that are causally associated with children's IQ (e.g., educational stimulation, medical care, etc). Therefore, socioeconomic status is probably acting as a proxy for one or more fundamental underlying variables which are difficult to assess directly and precisely. In this study, the parents' occupational prestige scale (i.e., Daniel score) - which is widely used in Australia - was employed as an index of the socioeconomic status. Several other measurements, e.g., parental education, and quality of home environment, would also have reflected aspects of socioeconomic status. It is unclear how well these proxies may have represented the underlying determinants of IQ, and hence, the results presented in the thesis should be interpreted with caution.

### 6.1.2. INTERACTION BETWEEN BLOOD LEAD AND OTHER FACTORS

In studies of the lead-IQ relationship, most of the results reported have been based on the assumption that lead exposure has the same effect in all subsets of study subjects. This assumption is potentially misleading if there is an interaction between lead and the factor classifying the subsets (e.g., socioeconomic status, gender, etc.).

Possible interactive effects of lead and some key covariates on children's IQ were explored in this study. In stratified analyses, the strength of the association between PbB and children's IQ did in fact vary with the gender, socioeconomic status, HOME scores, and maternal IQ. However, in multivariable analyses, none of the interactions between these variables and lifetime average PbB was statistically significant after adjustment for the other confounders.

### 6.1.3. BIAS

There are a number of factors that could potentially bias the assessment of an association between lead exposure and children's IQ.

One of the major potential problems in any cohort study is bias due to differential loss to follow-up (Rothman, 1986; Hennekens & Buring, 1987). However, for the reasons described in Chapter 3, differential loss is unlikely to have played a significant role in this study. Briefly, the socioeconomic characteristics of the children remaining in the cohort were only slightly higher than for those lost to follow-up. Since children from disadvantaged families may be more vulnerable to the effects of lead than those from more favorable backgrounds (Rutter, 1983; Bellinger et al., 1989), the inverse relation of lead to IQ might have been stronger among the children lost to follow-up than among those remaining in the cohort. However, there was no significant difference between the two groups, in terms of their blood lead levels and cognitive status at younger ages, and the estimated Pearson correlation coefficient of lifetime average PbB and cognitive status at age 7 years was only slightly higher in the children lost to follow-up ( $r = -0.27$ ) than those remaining in the cohort at ages 11-13 years ( $r = -0.25$ ). Therefore, if there was any bias due to the loss to follow-up, the true association is likely to have been underestimated.

Information bias occurs when the individual measurements or classifications of exposure or outcomes are not correct. Since the investigators who were involved in the process of data collection and coding were unaware of the histories of exposure and development for each child, and children with different levels of exposure were assessed in an intermixed order, opportunities for selective differences in the soliciting, recording or interpreting of information from study participants should have been minimal.

Blood lead concentrations were measured using both standardised internal and external quality control procedures. The precision of measurements was quite high (e.g., CV = 5.67%), and external quality control was ensured by participation in three international and national programs (Chapter 3). Developmental status in the children was assessed using a rigorous quality control procedure as described in Chapter 3. Briefly, a single observer was used to collect data; the observer was unaware of each child's exposure and developmental histories; and all the assessments were conducted using the same procedure under a uniform condition. Therefore, potential information bias due to misclassifications of exposure and/or outcomes was (hopefully) minimised.



#### 6.1.4. REVERSE CAUSALITY

A serious and rather special problem for studies of lead exposure and cognitive development is reverse causality. A lead-IQ association may be observed because children with lower IQ are more likely to exhibit behaviours (e.g., playing in dust, lack of handwashing, and thumbsucking) which would result in increased lead intake (Ernhart et al., 1987; Smith, 1989; Pocock & Smith, 1992; Pocock et al., 1994). This is a special issue that arises in an assessment of the relationship between lead exposure and child development because the postulated outcome variable (e.g., IQ) can actually influence behaviour which then determines exposure to lead.

The temporal relationships between lead exposure and children's IQ were examined in both directions in this study. Some measures of PbB several years prior to outcome under study or lifetime average PbB have shown the strongest relations to children's IQ (see Table 4.6.1), while none of the developmental scores at earlier ages was significantly associated with the current (i.e., 11-13 years old) blood lead measure (partial regression coefficients\* for the MDI, GCI, and full-scale IQ, respectively, at ages 2, 4 and 7 years: -0.0014 [95%CI: 0.0031 to -0.0059]; -0.0051 [95%CI: 0.0009 to -0.0092]; and -0.0046 [95%CI: 0.0009 to -0.0083]). Such temporal relations, therefore, provide support for the notion that exposure to lead may have affected children's cognitive development rather than the reverse.

\* Regression coefficient represents the natural log unit change in PbB at ages 11-13 years per unit change in developmental scores.

### 6.1.5. CAUSE AND EFFECT

General evidence in favour of a real (possibly causal) association includes the perseverance of an inverse association between blood lead concentration and children's IQ at ages 11-13 years, following adjustment for a wide range of potential confounders. The strength of the association was only modest, but consistent with the previous findings observed at ages 2, 4, and 7 years within this cohort (Wigg et al., 1988; McMichael et al., 1988; Baghurst et al., 1992a) and with other studies in which the children were followed up to age 10 years, or in which tooth lead was used as an indicator of integrated exposure (Needleman et al., 1990; Bellinger et al., 1992). A dose-effect relationship corresponding to an estimated deficit of 3 points in IQ for an increase in lifetime average PbB from 10 to 20 ug/dl was demonstrated using multiple regression analysis.

The plausibility of an association between low level lead exposure and children's IQ is supported by animal experiments which indicate an effect of exposure to low levels of lead on the central nervous system. Some, but not all studies show a persistent effect after lead exposure ceases or is reduced (Hastings et al., Hopper et al., 1986; 1979; Gilbert et al., 1987; Rice et al., 1988; Rice, 1989; Lilienthal et al., 1988; Levin et al., 1986, 1987, 1989). The possible biological mechanisms by which lead exerts its effect on cognitive development are generally postulated to include alterations in the release processes of neurotransmitters (e.g.,  $\gamma$ -aminobutyric acid, acetylcholine, dopamine, norepinephrine) through interference with calcium metabolism and/or synaptic functioning; as well as specific effects on enzyme activities (e.g., kinase C, tyrosine hydroxylase, choline acetyltransferase, etc.) and on brain energy metabolism (Silbergeld, 1980; Winder, 1984; Rossouw et al., 1987; Rius, 1988; Markovac & Goldstein, 1988; McIntosh et al., 1989; Mushak et al., 1989; Ronnback & Hanson, 1992).

The lead-IQ association appears therefore to meet at least some of the criteria for causality, viz. an appropriate temporal relationship, biological gradient, and biological plausibility. However, because of the modest size of the lead-IQ association and inconsistency of findings in studies with respect to the identification of a lead 'signature' effect and/or an age of maximal susceptibility, considerable caution is still needed in drawing conclusions about the nature of the relationship.

The results from this study show that there was a component of the association of environmental exposure to lead with children's IQ which was apparently independent of the other key socioenvironmental, hereditary, and biomedical factors. Based on the findings of this study and other research, a consideration of the roles of chance, confounding, bias, and reverse causality, and the criteria for causal inference, it appears that environmental exposure to lead may cause a persistent deficit in children's IQ.

## 6.2. OTHER FINDINGS

### 6.2.1. LEAD EFFECT MODELS

It is generally (but not universally) accepted that low-level exposure to lead exhibits some moderate and detectable effects on early childhood development. However, debate continues over whether children with developmental deficits caused by early exposure to lead can “catch up” with others. If not, to what extent do the effects of lead exposure upon early development persist into later life?

Recently, three models which might describe the adverse effect of early exposure to environmental lead on the later cognitive development were proposed by Fergusson & Horwood (1993):

First, the Deterioration Model assumes that children with early elevated lead exposure exhibit a tendency to progressively deteriorate in their cognitive performance so that their cognitive development lags further and further behind other children with the passage of time.

Second, the Constant Decrement Model assumes that cognitive deficits resulting from early lead exposure persist over an extended period of time (or perhaps are irreversible) even when exposure ceases or decreases.

Finally, the Catch-Up Model assumes that with the passage of time, children with cognitive deficits caused by exposure to lead at an early age can “catch up” with other children.

In this study, even though the children's PbB declined remarkably after two years of age, the deficit in developmental indices for higher vs lower blood lead groups

was 4.0, 4.8, 4.9, and 4.5 points at ages 2, 4, 7, and 11-13 years, respectively, after adjustment for a wide range of potential confounders (Note: It should be acknowledged that different outcome measures were used at different ages). The changes in blood lead levels between ages 2 or 4 or 7 years and 11-13 years were not statistically significantly related to the cognitive changes, although there was an indication that a slight “recovery” might have occurred among those whose PbB decreased most from ages 7 to 11-13 years (Table 5.2.2.1). These findings seem to provide support for the constant decrement model, although as noted in Chapter 5, the power to detect such a relationship was sub-optimal.

Data from three other studies also permit examination of the dynamic pattern of the effects of low level lead exposure on cognitive development (see more details in Chapter 1).

In the Massachusetts' study by Needleman and colleagues (1979, 1990), 132 subjects from their original sample of 270 children were re-examined 11 years later, and the neuropsychological deficits associated with elevated PbD in early childhood were found to persist into young adulthood. However, since qualitatively different measures of outcomes and different methods of data analysis were used during the follow-up in that study, it is difficult to judge which model is best supported by their data.

In the Boston study by Bellinger et al (1992), the exposure-related differences at age 10 years were reported to be approximately twice the size of those observed at 57 months, but due to differences in characteristics between the continuing participants and those lost to follow-up, the association at age 10 years may have been distorted.

In the Christchurch study conducted by Fergusson and Horwood (1993), the mean reading test score was consistently 3-points lower in children with higher dentine

lead levels than those with lower dentine lead levels at age 8 and again at age 12, although the temporal change in lead exposure status during that period was not measured.

In summary, these long-term follow-up studies appear to support the results of this study in that they show a persistent effect of exposure to low levels of lead. Since cognitive growth appears to stabilise after middle childhood (Sattler, 1988; Cohen et al., 1988), these results would suggest that the cognitive deficit resulting from early lead exposure may be irreversible (i.e., that the constant decrement model is the most plausible). However, it should be stressed that the duration, intensity, and timing of exposure to lead, as well as other social and familial factors may influence the nature and degree of reversibility.

## 6.2.2. THE CRITICAL PERIOD OF EXPOSURE?

If exposure to environmental lead appears to have a persistent effect on cognitive development, a subsequent question is: Is there the critical period of exposure to lead during childhood development? This study, like two other prospective studies (i.e., the Cincinnati and Cleveland studies), has failed to identify any critical age of exposure. One reason for this may be the phenomenon of "tracking" of PbB - i.e., the tendency for an individual who has a high PbB at one age to have a relatively high PbB at other ages (Dietrich et al., 1991; Baghurst et al., 1992a; Greene & Ernhart, 1993). It is difficult to identify the critical age of exposure if a child's exposure ranking remains reasonably constant over time. However, the strongest association of lead with IQ was found for lifetime average PbB which was heavily influenced by early exposure. Since PbB was greatly decreased after two years of age, exposure to lead during early childhood (possibly including fetus) appears to play a significant role in determining intellectual deficits, and these deficits may persist into late life even though the exposure level is reduced.

Another question is why we did not find an apparent association between prenatal exposure to lead and cognitive development in this study if prenatal exposure to lead has an important impact on childhood development (Grant & Davis, 1989; Goldstein, 1992). There are four explanations for this. First, prenatal exposure to lead at such a low level encountered in this study may have no detectable effect on cognitive development. Second, there was a sharp increase in PbB from birth to two years of age within this cohort (Note: the Port Pirie cohort had the highest postnatal PbB in all the prospective studies), and any adverse effects of prenatal exposure may have been overwhelmed by the much higher postnatal PbB. Third, there was a very much narrower range of exposure prenatally than postnatally in this study, and therefore, the opportunity to detect the effect of prenatal lead exposure was limited. Finally, measures of cognitive performance (e.g., IQ) may

not be sensitive enough to detect the subtle effects of prenatal exposure to lead. This hypothesis is supported by a recent comparison of the relative sensitivity to lead “effects” of children's IQ and visual-motor measures in this cohort (see more details in Chapter 6.2.5).

We should admit, however, that this population may be poorly suited to examining the question of periods of vulnerability because the “tracking” of PbB was so strong (correlation coefficients of PbB at different ages  $\geq 0.41$ ).



### 6.2.3. RELATIVE SIZE OF THE VARIATION IN IQ

A further question of interest is what is the relative size of the variation in IQ that can be explained by lead in comparison with other factors? i.e., how well can exposure to lead predict a child's IQ and how strongly is lead exposure associated with developmental deficits?

A sketch of the relative size of independent contributions of the subsets of factors is presented earlier in this thesis. The socio-environmental factors, familial variables, and lead exposure can account for approximately 65, 23 and 6 percent of *explained* variance in IQ, respectively. However, the percentage variance explained depends on the range of values encountered for the variable under study. Since there was a fairly uniform socioeconomic status (and therefore a small range of lead exposure) in this study population, we should remain cautious in attempting to compare these results with those from other studies. It is likely that more variance in IQ would be explained by lead in a population with a wider range of lead exposure.

#### 6.2.4. EXISTENCE OF A THRESHOLD

If there is a persistent effect of chronic exposure to low levels of lead, an important issue is whether there is a level of exposure below which a biological or toxicological effect may not occur. Within the range of blood lead concentration encountered in this study, however, there is little evidence that such a threshold exists, since plots of IQ versus PbB ( either current or lifetime average) offer little or no support for the existence of a threshold (Figures 4.3.1 & 4.3.2).

Because there are few data available at lower levels of exposure (e.g., lifetime average PbB < 10 ug/dl), the power to detect a threshold is limited in this study. However, if one compares ancient humans, whose body burdens of lead were several-orders of magnitude lower than contemporary populations, it is apparent that a relatively large region still exists on the continuum of lead exposure in which to find a threshold (Davis et al, 1990). If efforts to reduce lead exposure continue, then it may yet be possible to demonstrate a clearcut threshold for the apparent health effects of lead.

In order to solve the threshold issue, it would be necessary to study much larger number of subjects at lower exposure levels.

### 6.2.5. SENSITIVITY OF WECHSLER SCORES

In an assessment of the effects of lead exposure on child development, one of the major issues which is still being debated is what indices of outcome are the most sensitive to lead and the most reliably measured?

Full-scale IQ, despite its short-comings, provides a global estimate of a child's overall mental abilities and gives an indication of the child's relative standing in comparison with his or her age-related peers. Full-scale IQ is still generally regarded as the single most reliable and valid score, and provides a basis and overall context for evaluating other cognitive abilities (Groth-Marnat, 1990; Goldstein, 1992).

In this study, full-scale IQ was found to be inversely and significantly (or marginally significantly) associated with most of the postnatal blood lead measures and lifetime average PbB (see Table 4.6.1). The notion that full-scale IQ is a reliable and valid measure of the lead effects is supported by the fact that, among the Wechsler scores, full-scale IQ has been found to be the developmental measure most consistently associated with exposure to lead (US EPA, 1986; Needleman & Bellinger, 1991).

Although global measures of cognitive functions, such as full-scale IQ, are generally regarded as the most quantitative and convenient index of lead effects, some more specific elements of cognitive functioning appear to be more sensitive to the effects of low-level exposure to lead. For example, among the twelve WISC-R subtests, only four of them (i.e., Information, Arithmetic, Block Design, and Maze) were found to be significantly associated with the lifetime average PbB. Concentration, attention, visual-motor coordination, and memory are considered to be important contributors to these four subscales.

The question of the relative sensitivity to lead of various functional abilities was also explored at age 7 years within this cohort by expressing the estimated partial regression coefficients in units of standard deviations of functional ability per log unit of PbB. The estimated coefficients were -0.26 standard deviation of full scale IQ and -0.47 standard deviation of visual-motor integration scores, per natural log unit of lifetime average PbB. It is readily apparent that for a given change in lifetime average PbB, larger relative shifts may be expected for tests assessing visual-motor skills than for full scale IQ (Baghurst et al, 1995). Similar findings were observed in two other studies (Winneke et al., 1990; Dietrich et al., 1993), but not in the Boston study, in which children's attention and concentration were found to be most strongly associated with exposure to lead (Stiles & Bellinger, 1993).

There is considerable evidence in the clinical and animal literature showing that neuropsychological aspects, such as concentration, attention, visual-motor coordination, and memory, are adversely affected by moderate levels of lead exposure (US EPA, 1986; Davis et al., 1990; Winneke et al., 1990).

In this study, all three IQ scales were found to be associated with lifetime average PbB. However, the number of statistically significant associations between PbB and adjusted subtest scores seemed limited (see Table 4.6.2), which may be for the following reasons:

First, the aspects of cognitive functioning that are influenced by lead have still not been precisely identified and described. Global measures of cognitive functioning, such as full-scale IQ, require high-order organizational skills and integration of various abilities. It is possible that lead has a selective impact on only some of these high-order functions (Stiles & Bellinger, 1993).

Second, due to differences in socioeconomic status, genotype, biomedical factors and nutrition, individual variation in biological vulnerability may vary more widely among the specific subtests which are *not* related to the lead effects than those which *are* related to the effects of lead.

Although associations between exposure to lead and global measures of IQ have been found in most epidemiological studies (Needleman et al., 1979; Schroeder et al., 1985; Fulton et al., 1987; Hatzakis et al., 1989; Hansen et al., 1989; Rabinowitz et al., 1991; Bellinger et al., 1992; Baghurst et al., 1992a; Greene & Ernhart, 1993), efforts to dissect the neuropsychological basis of the adverse effect of lead on IQ have not been entirely successful (Cicuttini et al., 1994). It is possible that chronic exposure to low levels of lead may affect cognitive development through various mechanisms, and these may also interact with each other. Some neuropsychological dysfunctioning in areas such as concentration, attention, visual-motor coordination, and memory may have played an important role in the manifestation of the lead "effects". Another possibility is that contextual factors of subjects, such as genetic, social and environmental characteristics, may affect the form in which a lead effect is manifested.

In summary, full-scale IQ is generally regarded, to date, as the most quantitative and convenient index of the apparent effects of lead, but it may not be the most sensitive measure. In order to determine sensitive indices of lead effects, an elucidation of the biological mechanisms is urgently needed.

### 6.3. LIMITATIONS OF THE DATA

This study, like all others, has limitations which need to be borne in mind in formulating conclusions about the relationship between lead exposure and child development.

First of all, since all the subjects in this study were initially recruited from Port Pirie and neighbouring towns, the majority of them were of lower or middle-lower social class (see Table 3.3). This could be of some importance, if either the magnitude of effect of lead upon childhood development - or the accuracy of estimating it from such a study - is dependent on socioeconomic status.

Second, using blood lead concentration as an index of exposure may not be the best way to assess a relationship between lead exposure and children's intelligence. While blood lead is in dynamic equilibrium with the total body lead, the latter cannot be precisely determined from a blood lead measure. Since the half-life of lead in blood is only about one month (Rabinowitz, et al., 1977), PbB mainly reflects relatively recent exposure. Measures of lead burden other than blood lead determination (e.g., X-ray fluorescence analysis of lead in bone) may be more appropriate (Landrigan et al., 1992; Schindler et al., 1993). However, such measures are more difficult and expensive, and are still under development.

Third, the children's developmental status at ages 11-13 years was assessed with use of the WISC-R. Although the WISC-R is an excellent psychometric instrument (Kaufman, 1979; Sattler, 1988), there are a number of limitations that should be recognised:

(1) Intelligence tests do not necessarily measure innate intelligence, and many hereditary and socio-environmental factors contribute to psychometric assessment of intelligence (Wechsler, 1974; Bouchard & Segal, 1985).

(2) Intelligence tests do not measure all aspects of individual intelligence, although they adequately measure most of the important elements of intelligence (Sattler, 1988). For example, definitions of intelligence emphasise the ability to adjust or adapt to the environment, the ability to learn, or the ability to perform abstract thinking. It has been questioned whether the intelligence tests can directly measure an individual's learning abilities (Kaufman, 1979; Eysenck, 1979; Sattler, 1988).

(3) Intelligence tests do not provide a perfect developmental measure since a psychometric assessment of intelligence can be affected by many factors. The result of the assessment depends on both the intelligence test itself and the inter-relation between a subject, an examiner, and the assessment environment. It is worth noting that non-differential measurement error is always present to some extent in the psychometric assessment (Kaufman, 1979; Fletcher & Taylor, 1984).

## 6.4. CONCLUSIONS

### 6.4.1. ENVIRONMENTAL EXPOSURE TO LEAD AND CHILDREN'S INTELLIGENCE - summary

In this study, children's exposure status to lead was estimated by serial blood lead concentrations measured from before birth to ages 11-13 years. The children's intelligence at ages 11-13 years was assessed with use of the Revised Wechsler Intelligence Scale for Children. An inverse and statistically significant association between environmental exposure to lead and children's IQ was apparent in the simple (or bivariable) analyses, and the association remained, albeit attenuated, after multivariable adjustment for a wide range of confounding factors. Dose-effect relations between PbB and children's IQ were demonstrated in both simple and multivariable analyses. These findings suggest that exposure to low levels of lead is associated with a decrement in children's IQ, and the apparent adverse effects of lead exposure on early cognitive development may persist into middle childhood, despite the fact that average blood lead levels declined by 63 percent from 21.4 ug/dl at age 2 years to 7.9 ug/dl at ages 11-13 years. The lead "effect" observed in this study was not large, viz., an estimated 3 points deficit in IQ for an increase in lifetime average PbB from 10 to 20 ug/dl. However, it is important to note that, on the one hand, the overadjustment which may have occurred in the data analysis is likely to have led to an underestimate of the true lead effect, while on the other hand, the possibility that some of the association after adjustment may still be attributable to a degree of residual confounding and/or unmeasured confounders cannot be totally excluded.



#### 6.4.2. IMPLICATIONS FOR PUBLIC HEALTH POLICY

Since lead is ubiquitous and persistent in the environment, a lead effect of even small extent is of great public health significance. Cognitive deficits due to environmental exposure to lead are clearly small and not clinically identifiable at the individual level. However, it is undesirable for an entire community of exposed individuals to undergo a small downwards shift in the distribution of IQ, because proportionally small decreases in mean IQ may give rise to proportionally much larger increases in the percentage of children who are mentally retarded, and decreases in the percentage of children with superior IQ.

Within the range of blood lead concentration studied, the results of this cohort study provide little evidence of a 'threshold' level of exposure below which there is no apparent effect of lead. This has important implications for public health policy since the determination of the 'acceptable' level of exposure (i.e., 'level of concern'\*) must now depend on an integral consideration of risk assessment and evaluations of social, economic, and environmental impacts.

\* A level of concern is not the same as a threshold. A level of concern, in this case, represents a blood lead level associated with outcomes that are judged to warrant attention from a medical or governmental regulatory standpoint. As such, a level of concern reflects scientific judgment for the purpose of protecting public health. It does not imply that a biological or toxicological effect may not occur at lower levels of exposure (Davis, 1990).

The fact that an inverse relationship between PbB and cognitive development has been observed longitudinally at ages 2, 4, 7, and 11-13 years within this cohort suggests that chronic exposure to low levels of lead may have an independent and persistent effect on childhood development. From a public health perspective, it is necessary to identify, treat and eradicate any adverse effects of lead exposure on children, and as part of such a program, the early detection and abatement of lead in the environment are essential.

On the other hand, the apparent effect of lead needs to be viewed within the context of other determinants of IQ. Compared with other socio-environmental and familial factors, the variance in IQ attributable to lead exposure seems small. A specific policy recommendation is that a comprehensive strategy addressing multifactorial determinants in IQ be adopted in the process of eradicating and preventing lead problem in children. In order to draw up this strategy, considerations would need to be given to the following issues:

- (1). Risk assessment of lead exposure (e.g., who will be exposed and to what extent? what potential hazards will occur? how can we evaluate the risk? which level of risk is acceptable? etc.);
- (2). The multifactorial nature (in particular, the quality of home environment, socioeconomic status, and parental education) of the determinants of a child's cognitive development;
- (3). Community education and public awareness (which is essential for the successful implementation of any program within a democracy);
- (4). Population-wide cost-benefit analyses.

Environmental exposure to low levels of lead continues to be a public health issue. The lead problem is preventable, and yet, if left unattended, can only get worse (Ericson et al., 1979; Patterson et al., 1991; Flegal & Smit, 1992). The formulation of a public health policy for eradicating this problem should be based on a composite consideration of the child's health and the best use of existing resources.

### 6.4.3. FURTHER RESEARCH

Although extensive data have been collected for studying the effects of low level lead exposure on childhood neuropsychological development, many issues remain to be resolved. The following areas are among the most urgent:

#### Exposure index

There is a need to evaluate the adequacy (i.e., accuracy and precision) of the lead exposure index, particularly at low levels (e.g., PbB < 10 ug/dl). It is desirable to develop some more accurate and precise measures of body lead burden at low levels (Flegal & Smith, 1992a). For example, the application of *in vivo* X-ray fluorescence (XRF) to the analysis of lead in bone appears to represent a promising technique for the assessment of total lead accumulation in skeletal tissues. This noninvasive dosimetric technology provides the possibility of improving an understanding of body lead burden. More research is required to improve the precision of the method at the levels commonly encountered in the general population.

There is a lack of reliable data concerning the relation between blood, teeth or bone lead and brain lead, and the impact of the rate of transfer of lead in blood, teeth or bone into the brain. The relationship between lead levels in blood, teeth or bone and those in target organs (e.g., brain, kidney) warrants further investigation.

#### Outcome measures

Various measures of neuropsychological development have been used to study lead effects. Most epidemiological research has focused on the psychometric assessment of mental and motor development, even though other aspects of

development, such as emotional development, social interaction, and other facets of human life, may also be affected by chronic exposure to low levels of lead. Although some attention has been paid to lead effects on social-emotional behaviour (Yule et al., 1984; Thomson et al., 1989; Sciarillo et al., 1992; Bellinger et al., 1994), the majority of these studies have employed only one source of information (e.g., teachers or parents or the children themselves). The validity and reliability of this approach need to be evaluated. Moreover, the possible long-term effects of lead exposure upon social-emotional behaviour have not yet been examined so far. A number of electrophysiological measures of nervous system function have been employed to assess the effects of low level lead exposure. However, the functional significance of these measures still needs to be explored.

#### Threshold and interaction

Lead has no known biological role, so the ideal level of exposure is zero. In pragmatic terms, a lead-free environment is impossible to attain, firstly, because lead is a constituent of the natural environment, and secondly, because the magnitude of lead contamination in the environment, with the emergence of the industrial age, makes a return to the levels of the pre-industrial era impossible. However, the goal of zero exposure may be unnecessary if there is a threshold for lead-induced effects. At present, there is insufficient evidence to draw any conclusion about the possible existence or otherwise of a threshold, since little data are available in the range of what we have now come to regard as very low levels of exposure (e.g., PbB < 5 ug/dl). Due to ubiquitous environmental contamination, however, lead exposure levels throughout many world populations may have already exceeded the threshold for effects, and it may be impossible to detect such a threshold in any epidemiological study (Davis, 1990). Further reductions of environmental lead exposure may be required in order to draw any firm conclusions about the existence or otherwise of a threshold level of exposure.

With regard to the interactions between lead and covariates, a consistent effect modification of socioeconomic status has been reported, although this interaction has not always been statistically significant (Rutter, 1983; Winneke & Kraemer, 1984; Harvey et al., 1984; Lansdown et al., 1986; Dietrich et al., 1987; Pocock et al., 1987; Bellinger et al., 1989; McMichael et al., 1992). There is conflicting evidence among the few studies that have addressed the question of a gender-specific vulnerability to lead exposure (Dietrich et al., 1987; Pocock et al., 1987; Bellinger et al., 1990; Rabinowitz et al., 1991; McMichael et al., 1992). The investigation of interactions between lead and other covariates (e.g., age, nutrition and recreational drug use) is also an area for future research, since it may help to elucidate causal mechanisms and have implications for public health intervention strategies.

#### Mechanism

The mechanisms underlying the cognitive deficits deserve further investigation. It is recognised that molecular biochemical changes attributable to low level lead exposure may not necessarily be specifically or directly related to cognitive deficits (US EPA, 1986; Davis et al., 1990; Goldstein, 1992). An urgent requirement is an understanding of mechanisms by which these changes impinge on cognitive development.

In order to systematically evaluate apparent effects of exposure to lead on cognitive development, the assessment of the critical features of exposure (e.g., timing of exposure, and relative importance of cumulative and peak doses) is very important.

#### Public health policy

As various measures to control the continued transfer of lead to the environment (e.g., phasing-out of lead in paints, fuel, and other consumer products; and tighter control on industrial emissions) are implemented both in Australia and throughout the rest of the world, environmental exposure to lead will continue to decline. However, because of the persistence of lead in the environment, exposure of children to lead will remain a public health problem for a long time, especially in lead contaminated communities, such as Port Pirie. Much research work needs to be carried out in the areas of identifying and treating children with elevated PbB effectively, and reducing subsequent re-exposure. Screening, monitoring, intervention, and evaluation studies are critical for developing rational, cost-effective, and science-based public health policies to achieve these goals.

## **Appendix 1.**

**An information sheet about the objectives,  
nature and process of this study.**



LONG-TERM EFFECTS OF EXPOSURE TO ENVIRONMENTAL LEAD  
-----  
IN CHILDHOOD -- EXTENDED FOLLOW-UP OF PORT PIRIE COHORT  
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INFORMATION SHEET FOR PARTICIPANTS  
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You are no doubt aware of the public and scientific interest in the effects of lead in our environment on the growth and development of children. As you know, your child's growth, development and exposure to lead was followed from birth to age seven years in the Port Pirie Cohort Study.

The study showed that lead can affect childhood development, although the effects do not appear to be large. Those research results are assisting governments to make decisions about the control of environmental lead in South Australia and throughout the world. Nevertheless, no research anywhere has yet followed children through to the end of their primary schooling. With the information which we already have on your child's early-life exposure to lead, we are in a unique position to find out if these effects persist into later life. But for this we will need your help.

Research staff from CSIRO, the University of Adelaide, and the Adelaide Medical Centre for Women and Children are cooperating in this study to assess your child's intellectual and behavioural development. Your participation in this study will involve the following procedures which will be carried out at your child's school:

- . assessment of your child by a research assistant supervised by a trained psychologist;
- . collection of a small blood sample from your child by Sister Maureen Wauchope (probably known to you for her 22 years at Port Pirie Hospital);

and you will also be asked to complete a short checklist about your child's behaviour, and to fill in a questionnaire about your lifestyle and occupation because they are important factors in the development of children.

Please note that there is no obligation on you to take part in this study and your refusal will not prejudice you or your child in any way. You are free to withdraw from the study at any time.

All information resulting from your participation in this study will be stored and analysed in a computer, but your name will not be included. Only the researchers will know that the information is related to you. The results of the study may be published in the medical literature, however your identity will not be revealed. The information will be made available to you at the end of the study should you wish.

We will be in contact with you shortly, and we hope that you will be interested in taking part in this extension of our important study. Should you have any questions in the meantime please contact Professor Tony McMichael in the Department of Community Medicine at University of Adelaide (phone 2284637) or Dr. Peter Baghurst at the CSIRO Division of Human Nutrition (phone 2241811).

## **Appendix 2**

**An informed consent to participate in the study.**

**THE UNIVERSITY OF ADELAIDE  
THE CSIRO DIVISION OF HUMAN NUTRITION  
THE ADELAIDE MEDICAL CENTRE FOR WOMEN AND  
CHILDREN**

**FORM TO BE COMPLETED BY PARENT OR GUARDIAN  
(See also Information Sheet attached)**

1. I \_\_\_\_\_ (please print) hereby consent to allow my child to take part in the research project entitled: *LONG-TERM EFFECTS OF EXPOSURE TO ENVIRONMENTAL LEAD IN CHILDHOOD - EXTENDED FOLLOW-UP OF PORT PIRIE COHORT.*
2. I have read and understood the Information Sheet entitled: *LONG-TERM EFFECTS OF EXPOSURE TO ENVIRONMENTAL LEAD IN CHILDHOOD - EXTENDED FOLLOW-UP OF PORT PIRIE COHORT*, and have had the project fully explained to me by the research worker. My consent is given freely.

IN ADDITION, I ACKNOWLEDGE ON BEHALF OF \_\_\_\_\_  
THE FOLLOWING:

3. I have been informed that the information he/she provides will be kept confidential.
4. I understand that he/she is free to withdraw from the project at any time.
5. I am aware that I should retain a copy of this Consent Form, when completed, and the relevant Information Sheet.

SIGNED \_\_\_\_\_ DATE \_\_\_\_\_  
(Relation to child: PARENT/GUARDIAN)

NAME OF WITNESS \_\_\_\_\_ DATE \_\_\_\_\_

I, \_\_\_\_\_ have described to \_\_\_\_\_  
the nature of the procedure to be carried out. In my opinion he/she  
understood the explanation.

SIGNED \_\_\_\_\_ DATE \_\_\_\_\_

STATUS IN PROJECT \_\_\_\_\_

## **Appendix 3**

**A protocol for collection, storage, and transportation of  
blood samples.**

## A PROTOCOL FOR COLLECTION, STORAGE, AND TRANSPORTATION OF BLOOD SAMPLES

1. Preparation of the sampling site: see Australian Standard 2636-1988.

2. Collection of 4 ml venous blood:

At the time of sample collection, please write down the name AND ID number of each child, PPCS (abbreviation for Port Pirie Cohort Study), and date of collection on the label of tube.

3. Transfer of the sample to the tube and storage of the sample:

1 ml blood should be transferred into the tube with pink top for a complete blood picture (CBP); 1 ml into the tube with pink top for the blood lead measurement (PbB); and 2 ml into the tube with white top for the determination of ferritin.

4. Transportation of samples:

All samples need to be taken to the IMVS in Port Pirie Hospital with the least possible delay. On arrival at the IMVS please give the 1 pink-top tube to Mr. Greeneklee for CBP and arrange for the other pink-top tube and white top tube to be transported to Ms. Elaine Whitham, Department of Chemical Pathology at Adelaide Medical Centre for Women and Children (Adelaide Children's Hospital) by courier. Please put the samples in an appropriate insulating container (e.g. foam 'six-pack' holder) marked with the sticky label (provided).

## **Appendix 4**

**Questionnaire for background information.**

BACKGROUND INFORMATION

OFFICE USE

1. YOUR SEX: MALE FEMALE

1

2. WHICH OF THE FOLLOWING DESCRIBES YOUR RELATIONSHIP WITH THE CHILD IN THIS STUDY? (PLEASE CIRCLE)

2

- (1) NATURAL MOTHER
- (2) NATURAL FATHER
- (3) STEPMOTHER
- (4) STEPFATHER
- (5) OTHER (PLEASE SPECIFY) \_\_\_\_\_

3. HOW MANY CHILDREN (INCLUDING THE CHILD IN THIS STUDY) UNDER AGE OF 18 YEARS LIVE IN YOUR HOUSEHOLD? \_\_\_\_\_

3

4. WHICH OF THE FOLLOWING BEST APPLIES TO YOU (PLEASE CIRCLE):

5

- (1) MARRIED
- (2) WIDOWED
- (3) SEPARATED/DIVORCED
- (4) NEVER MARRIED
- (5) OTHER (PLEASE SPECIFY)

5. WHAT IS YOUR USUAL OCCUPATION? (PLEASE SPECIFY) \_\_\_\_\_

6

6. ARE YOU CURRENTLY WORKING? (PLEASE CIRCLE) YES/NO

8

7. IF YOU LIVE WITH A SPOUSE/PARTNER, WHAT IS THEIR USUAL OCCUPATION? (PLEASE SPECIFY) \_\_\_\_\_

9

8. IS YOUR SPOUSE/PARTNER CURRENTLY WORKING? (PLEASE CIRCLE) YES/NO

11

9. DO YOU SMOKE AT ALL? (PLEASE CIRCLE) YES/NO

12

9.1. IF YES, HOW MANY CIGARETTES DO YOU SMOKE A DAY? \_\_\_\_\_ CIGARETTES/DAY

13

9.2. IF NO, HAVE YOU EVER SMOKED REGULARLY? (PLEASE CIRCLE) YES/NO

15

IF YES, IN WHICH YEAR DID YOU QUIT? YEAR \_\_\_\_\_ AND HOW MANY CIGARETTES DID YOU SMOKE A DAY? \_\_\_\_\_ CIGARETTES/DAY

16

10. DOES YOUR SPOUSE/PARTNER SMOKE AT ALL? (PLEASE CIRCLE) YES/NO

18

10.1. IF YES, HOW MANY CIGARETTES DOES HE/SHE SMOKE A DAY? \_\_\_\_\_ CIGARETTES/DAY

20

10.2. IF NO, HAS HE/SHE EVER SMOKED REGULARLY? (PLEASE CIRCLE) YES/NO

21

IF YES, IN WHICH YEAR DID HE/SHE QUIT? YEAR \_\_\_\_\_ AND HOW MANY CIGARETTES DID HE/SHE SMOKE A DAY? \_\_\_\_\_ CIGARETTES/DAY

23

24

26

## **Appendix 5**

**Life events and medical conditions' questionnaire.**



QUESTIONS FOR SISTER WAUCHOPE TO ASK

CHILD'S ID

OFFICE USE

DATE OF ASSESSMENT: \_\_\_\_\_ DATE \_\_\_\_\_ MONTH \_\_\_\_\_ YEAR

1. CHILD'S DATE OF BIRTH: \_\_\_\_\_ DATE \_\_\_\_\_ MONTH \_\_\_\_\_ YEAR

2. CHILD'S SEX: (PLEASE CIRCLE) 1=MALE 2=FEMALE

3. CHILD'S SCHOOL: \_\_\_\_\_

4. CHILD'S SCHOOL YEAR: \_\_\_\_\_

5. HAS YOUR CHILD EXPERIENCED ANY MAJOR STRESS DURING THE LAST 5 YEARS (e.g. separation of parents, death of relatives, accidents or serious illnesses)?

Yes/No

If yes, please describe:

- (1)
- (2)
- (3)
- (4)

6. HAS YOUR CHILD MISSED MORE THAN TWO WEEKS OF SCHOOL IN ANY SINGLE SCHOOL TERM SINCE HE/SHE WAS 7 YEARS OLD? (PLEASE CIRCLE) Yes/No

If yes, please describe:

- (1)
- (2)
- (3)
- (4)

7. HAS YOUR CHILD RECEIVED ANY LEAD CHELATING TREATMENT? (PLEASE CIRCLE) Yes/No

If yes, in which year? Year \_\_\_\_\_

8. IN THE PAST HAVE YOU BEEN INVOLVED IN THE HOME LEAD DECONTAMINATION PROGRAM? (PLEASE CIRCLE) Yes/No

If yes, in which year? Year \_\_\_\_\_

1	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
7	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
13	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
19	<input type="checkbox"/>					
20	<input type="checkbox"/>					
21	<input type="checkbox"/>					
22	<input type="checkbox"/>					
23	<input type="checkbox"/>					
24	<input type="checkbox"/>	<input type="checkbox"/>				
26	<input type="checkbox"/>					
27	<input type="checkbox"/>	<input type="checkbox"/>				

# QUESTIONS FOR MS. JANE MUDGE TO ASK

OFFICE USE

NAME \_\_\_\_\_

ID NUMBER: \_\_\_\_\_

1

1. SEX: (PLEASE CIRCLE) 1=MALE      2=FEMALE

7

2. DATE OF BIRTH: \_\_\_\_\_ DAY \_\_\_\_\_ MONTH \_\_\_\_\_ YEAR

8        
DD MM YY

3. DATE OF TESTING: \_\_\_\_\_ DAY \_\_\_\_\_ MONTH \_\_\_\_\_ YEAR

14        
DD MM YY

4. SCHOOL: \_\_\_\_\_

20

5. SCHOOL YEAR: \_\_\_\_\_

22

6. PLACE OF TESTING: \_\_\_\_\_

7. TIME TESTING COMMENCED \_\_\_\_\_

23

8. HOW LONG SINCE YOU LAST ATE ?

\_\_\_\_\_ HOURS

27

9. HAVE YOU TAKEN ANY MEDICATION IN THE LAST TWO WEEKS? (e.g. inhalers/injections/tablets etc.)

(PLEASE CIRCLE) YES/NO

30

IF YES/WHAT MEDICATION HAS BEEN USED?

\_\_\_\_\_

## **Appendix 6**

**Mean Bayley Mental Developmental Index by tertile of ferritin level at ages 6 and 15 months.**

Mean Bayley Scale Scores by Tertile of Ferritin Level at Age 6 Months\*

Tertile	Mean+SD	95% CI	P value
Mental Developmental Index			
Lower	107.5+13.4	104.3 - 110.7	0.58
Medium	108.3+11.8	105.4 - 111.1	
Higher	109.9+16.2	106.1 - 113.8	
Psychomotor Developmental Index			
Lower	107.6+14.7	104.1 - 111.1	0.70
Medium	109.4+12.8	106.4 - 112.5	
Higher	109.2+12.9	106.1 - 112.2	

\*Mean ferritin level (range) within lower, medium, and higher tertile was 18.2 (3.0-30.0), 40.3 (30.1-54.0), and 79.3 (54.1-210.0), respectively; Number of children in each tertile was 68.

## **Appendix 7**

**Cognitive/developmental status by tertile of haemoglobin levels by age.**

Cognitive Developmental Status by Tertile of Haemoglobin Levels at various Ages

Tertile	Mean Score (Standard error)									
	Cord	6 ms	15 ms	2	3	4	5	6	7	11-13 ys
IQ at ages 11-13 years										
Lower	100.2 (1.1)	100.4 (1.1)	100.4 (1.2)	101.1 (1.2)	99.7 (1.1)	100.1 (1.2)	99.9 (1.2)	99.1 (1.3)	99.2 (1.2)	99.5 (1.3)
Medium	101.8 (1.2)	100.1 (1.1)	99.5 (1.1)	99.0 (1.0)	99.9 (1.1)	99.8 (1.1)	99.0 (1.2)	99.8 (1.1)	99.3 (1.1)	100.7 (1.1)
Higher	98.8 (1.2)	99.8 (1.1)	100.6 (1.1)	100.2 (1.2)	100.9 (1.2)	100.3 (1.1)	100.8 (0.9)	100.6 (1.1)	100.7 (1.1)	100.6 (1.3)
IQ at age 7 years										
Lower	105.7 (1.3)	105.7 (1.2)	105.4 (1.2)	105.5 (1.2)	104.3 (1.2)	105.0 (1.4)	104.7 (1.3)	104.0 (1.4)	104.1 (1.3)	
Medium	106.7 (1.1)	105.1 (1.3)	105.7 (1.2)	105.9 (1.2)	106.1 (1.2)	104.4 (1.1)	104.3 (1.2)	104.4 (1.2)	104.6 (1.2)	
Higher	103.5 (1.3)	104.8 (1.2)	104.3 (1.2)	103.9 (1.3)	104.9 (1.3)	105.5 (1.3)	105.4 (1.2)	105.6 (1.2)	105.8 (1.2)	
GCI at age 4 years										
Lower	108.2 (1.4)	109.2 (1.2)	106.7 (1.5)	108.8 (1.4)	106.5 (1.4)	110.7 (1.4)				
Medium	109.2 (1.5)	107.8 (1.6)	109.3 (1.3)	107.2 (1.5)	109.6 (1.5)	105.3 (1.5)				
Higher	106.9 (1.5)	107.1 (1.4)	108.2 (1.4)	108.1 (1.3)	108.1 (1.3)	107.8 (1.3)				
MDI at age 2 years										
Lower	109.7 (1.3)	111.6 (1.3)	107.8 (1.3)	109.7 (1.3)						
Medium	111.4 (1.4)	110.2 (1.5)	111.2 (1.2)	108.9 (1.3)						
Higher	107.9 (1.5)	107.4 (1.2)	109.9 (1.4)	110.7 (1.4)						

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