2. LITERATURE REVIEW

2.1. INTRODUCTION:

Mankind has been using lead for over 6000 years and solely as a result of anthropogenic activities lead has become the most ubiquitous toxic metal. Lead’s toxicity was recognized and recorded as early as 2000 BC and its widespread use has been a cause of endemic chronic plumbism in several societies throughout history. With the industrial expansion in the last two centuries the problem has become more serious, as evident from the Antarctic and Arctic ice core data showing presence of lead even in such far off places.

Many reviews and references are available in literature related to the health effects of exposure to lead (Pandya et al., 1983; Parikh, 1990; Needleman, 1999).

In contrast with developed countries, where lead exposure is on the decline due to implementation of environmental and occupational regulations (Howson et al., 1995), in developing countries lead poisoning continues to be a serious problem (Romieu et al., 1997; Krishnaswamy and Kumar, 1998). Without proper corrective action, lead exposure would remain a threat to many generations of children in the developing world.

The disease burden of a population, and how that burden is distributed across different subpopulations, are important pieces of information for defining strategies to improve population health. For policy makers, disease burden estimates provide an indication of the health gains that could be achieved by targetted action against specific risk factors. The measures also allow policy-makers to prioritize actions and direct them to the population groups at highest risk. To help provide a reliable source of information for policy-makers, WHO
recently analyzed 26 risk factors worldwide, including lead, in the World Health Report (WHO, 2002).

Policy makers often underestimate the burden of disease caused by relatively low and widespread exposures to lead. For example, loss of IQ points is not considered a disease per se, yet it reflects subtle neurological impairment that will be most marked on the social and psychological development of children who already have a low IQ score. Subtle effects of IQ loss are expected from blood lead levels as low as 5 microgram/dL and the effects gradually increase with increasing levels of lead in the blood.

Enormous effort has been focused over the past two decades and a half on characterizing the behavioral effects of lead in the developing organism. While age-appropriate standardized measures of intelligence (IQ) have been the dependent variable most often used to assess lead-induced cognitive impairment in epidemiological studies, researchers have also used a variety of other methods designed to assess specific behavioral processes sensitive to lead. Increased reaction time and poorer performance on tasks associated with increased lead body burden suggest increased distractibility and short attention span.

Assessment of behavior on teachers’ rating scales identified increase distractibility, impulsivity, non-persistence, inability to follow sequences of directions and inappropriate approach to problems as hallmarks of lead exposure. Robust deficits in learning skills such as reading, spelling, mathematics and word recognition have also been found. Spatial organizational perception and abilities seem particularly sensitive to lead-induced impairment. Thus there is remarkable congruence between the epidemiological and experimental literatures with regard to the behavioral processes identified as underlying the deficits inflicted by developmental lead exposure.

Ph.D. Thesis entitled “Study of Lead Exposure and Outcomes amongst Children in Chennai, India”
2.2. VULNERABILITY OF CHILDREN TO LEAD POISONING:

Children differ from adults in the relative importance of lead sources and pathways, lead metabolism, and the toxicities expressed. The central nervous system effects of lead on children seem not to be reversible.

Children are more vulnerable to lead exposure for three reasons: young children are more at risk of ingesting environmental lead through normal mouthing behaviors (Lanphear et al. 2002), absorption from the gastrointestinal tract is higher in children than adults (Ziegler et al. 1978), and the developing nervous system is thought to be far more vulnerable to the toxic effects of lead than the mature brain (Lidsky and Schneider 2003).

Moreover, peripheral nervous system effects in adults tend to reverse after cessation of exposure (Baker et al., 1985; Yokoyama et al., 1988), whereas the central effects in children seem not to do so (Needleman et al., 1990; White et al., 1993; Tong et al., 1998; Stokes et al., 1998), perhaps because lead perturbs the complex processes by which synaptic connections are selected and modified (Johnston and Goldstein, 1998).

In addition, under many exposure scenarios, the half-life of lead in blood is greater in children than in adults (Manton et al., 2000; Succop et al., 1987).

Hence, studies conducted on adults are likely to be of limited relevance in understanding lead toxicity in children, particularly with regard to nervous system effects.

This organ continues to undergo substantial changes well into the second decade of postnatal life, involving the establishment of hemispheric dominance,
the completion of myelination, particularly in the frontal lobes, synaptic pruning and synaptic reorganization.

2.3. PREVALENCE OF CHILDHOOD LEAD EXPOSURE IN DIFFERENT COUNTRIES:

Today, the major concerns regarding childhood lead exposures are the health risks associated with exposures once considered “normal”. These low-level exposures produce subtle and not readily detectable neurobehavioral effects on personality, intellectual development, behavior and achievement (Mendelsohn et al., 1998; Delville, 1999).

However, measures in European countries have been muted with an overriding feeling that since the banning of leaded gasoline and lead-containing paints, lead exposure no longer poses a significant environmental threat to health. Publication of a study by Canfield et al. in 2003 challenged this view. Their study showed a dose-dependent decline in cognitive function in a cohort of children whose lifetime peak blood lead levels never rose above the current World Health Organization/Centers for Disease Control and Prevention (WHO/CDC) blood lead level of concern (10 microgram/dL) and suggests there is no safety margin at existing exposures.

Hence, the current Centers for Disease Control and Prevention screening guideline (1991) of 10 microgram/dL is only a risk management tool and cannot be interpreted as a threshold for toxicity. In fact, no threshold has been identified, and some data are consistent with effects well below 10.

Blood samples from 200 Saudi Arabian school boys, aged 6 – 8 years, were analyzed for their lead concentrations by Ibrahim et al. in 1989. Mean blood lead concentration was found to be 6.9 (+/- 3.4) microgram/dL. This result
is similar to the results of a number of studies: mean value of 6.4 microgram lead/dL for Finnish children (Taskinen and Hernberg, 1981); mean of 6.0 microgram/dL for Tokyo study (Vahter and Friberg, 1983); mean of 10.4 microgram/dL for Ontario, Canada (Wang, 1988); and mean value of 10.5 microgram lead/dL for Ireland (Grimes et al., 1975). In an earlier study in Jeddah in 1985 by Meteorology and Environment Protection Administration of Saudi Arabia, the mean value was reported to be 10 microgram lead/dL blood for school children in a heavy traffic area (MEPA Report, 1985).

A cross-sectional study was conducted by Veena et al. in 1998 to estimate the mean blood lead levels and prevalence of lead toxicity in a representative sample of school children and children aged 4-6 years residing in an urban slum at Delhi. The mean blood lead was 7.8 microgram/dL (SD 3.9) and the proportion of children with blood lead greater than or equal to 10 microgram/dL was 18.4 per cent.

The study conducted by Carol et al. (2002) evaluated children in three Russian cities: Krasnouralsk, a small city with minimal traffic centered around a copper smelter; and Ekaterinburg and Vogograd, both of which are large cities with multiple factories and heavy vehicular traffic. Overall, 23% of the study children had elevated blood lead levels that were attributed to the use of lead-based automotive fuel, lead-related industrial emissions and old undercoats of lead-based paint.

Jain and Hu (2006) assessed potential correlates of blood lead levels in 1081 children who were below 3 years of age and living in Mumbai or Delhi, India. They examined factors such as age, sex, religion, caste, mother’s education, standard of living, breast-feeding, and weight/height percentile. 76% of the children had blood lead levels between 5 and 20 microgram/dL. Age, standard of living, weight/height percentile and total number of children ever born
to the mother were significantly associated with the log transformed blood lead levels in multivariate regression models.

Jamal et al. (2006) measured blood lead levels in children 2-6 years of age in Israel, Jordan and the Palestinian Authority. The mean blood lead levels in Israel, the West Bank, Jordan and Gaza were 3.2, 4.2, 3.2 and 8.6 microgram/dL respectively. These findings, taken together with data on time trends in lead emissions and in blood lead in children in previous years, indicated the benefits from phasing out of leaded gasoline but also stated the case for further reductions and investigations of hot spots.

At national level, the global burden of disease estimates a regional mean blood lead level of 7.4 µg/dL (SD: 5.6) in urban children out of which, 19.2% of the children were with 5-10 µg/dL of blood lead, 8.8% of the children were with 10-20 µg/dL of blood lead and 8.3% of the children were with more than 20 µg/dL of blood lead. This result was arrived at using the various landmark epidemiological studies that were conducted in India (Awasthi et al., 1996; D'Souza, Narurkar and Narurkar, 1994; Gogte et al., 1991; Lal et al., 1991; Saxena et al., 1994; Shenoi et al., 1991 and Wahid et al., 1997).

2.4. EFFECT OF LOW LEVELS OF LEAD ON CHILDREN’S I.Q.:

The effect of lead on child intelligence quotient (IQ) scores has been extensively studied. Although there appears to be no dispute about the effects of high levels of lead, there has been uncertainty about the effects of low levels of lead exposure on children’s health. The debate has been particularly heated in the United States (Ferber 2002; Wakefield 2002), where data used to support laws and policies relating to lead exposure have become the subject of a number of lawsuits (Bellinger and Dietrich 2002; Mushak 2002; Needleman 2002; Nelson 2002; O'Dowd 2002; Pinder 2002).
Needleman and Gatsonis (1990) identified 24 modern studies of childhood exposures to lead in relation to IQ. From this population, 12 that employed multiple regression analysis with IQ as the dependent variable and lead as the main effect and that controlled for non-lead covariates were selected for a quantitative integrated review or meta-analysis. This quantitative review strongly supported the hypothesis that lead impairs children’s IQ at low dose. The effect is robust to the impact of any single study.

A special issue of Archives of Clinical Neuropsychology in 2001 was devoted to the topic of intelligence quotient (IQ) and low-level lead exposure in children. Five groups of scientists were invited to reply to an article by Kaufman (2001) who posed the question “Do low levels of lead produce IQ loss in children?” (Brown 2001; Hebben 2001; Nation and Gleaves 2001; Needleman and Bellinger 2001; Wasserman and Factor-Litvak 2001). Kaufman argues that parental variables are far more important to a child’s cognitive development than is low-level lead exposure, and that the loss of a few IQ points (if true) is unlikely to have meaningful consequences for society (Kaufman 2001).

In contrast, Needleman argues that lead-induced neurotoxicity has a causal role not only in cognitive loss but also in the subsequent development of juvenile delinquency and socially disruptive behavior (Needleman and Bellinger 2001; Needleman et al. 2002). These two positions represent the opposite ends of a spectrum of opinion on the relationship between low-level lead exposure and child development.

Recently, in 2004, Chiodo et al. reported significant inverse associations between neuropsychological function and blood lead levels less than 10 microgram/dL. In the Canfield et al. (2003) study, moreover, the slope of the association was greater in the subgroup of children whose peak blood lead was
less than 10 microgram/dL than it was in the complete study sample that included children whose peak blood lead levels exceeded 10 microgram/dL. Reanalyses of the Boston prospective study (Bellinger and Needleman, 2003) suggested the same pattern.

2.5. EFFECT OF CONCURRENT BLOOD LEAD LEVEL ON I.Q.:

When blood lead levels do vary over time, age at exposure and magnitude of exposure are often highly confounded, with blood lead level peaking in the age range of 1 to 3 years (Brody et al., 1994). This is probably because this period encompasses both the onset of independent ambulation and the time when a child’s oral exploration of the environment is greatest.

As a result, if a study were to find that blood lead level measured at age 2 is most predictive of some critical neurocognitive outcome at school age, then it would be difficult to ascertain whether this reflects a special vulnerability of the central nervous system at age 2 or that blood lead levels tend to be highest during this period. Some studies support the former hypothesis (Bellinger et al., 1992), whereas others have found that school-age neurocognitive outcomes are most strongly related to recent or concurrent blood lead levels (Dietrich et al., 1993; Tong et al., 1996). The findings of yet other studies fail to provide evidence for the existence of any critical periods of vulnerability (Wasserman et al., 2000).

Among children in the Boston prospective study, for whom the mean blood lead level at age 2 years was 7 microgram/dL, a significant inverse association was found between blood lead level and both IQ and academic achievement at 10 years of age (Bellinger et al., 1992).
One meta-analysis (Pocock et al., 1994) included cross-sectional studies in a separate analysis; those studies also showed an inverse association of blood lead concentration with IQ at more than or equal to six years of age. Another meta-analysis (Schwartz, 1994) included cross-sectional studies in the overall model, but additional analysis of cross-sectional studies showed findings similar to those in the prospective studies.

Very recently, in their article about blood lead and IQ in older children, Chen et al. (2005) made the very important observation that IQ in older children correlates better with their current blood lead level than with levels determined at 2 years of age. They analyzed data from a clinical trial in which children were treated for elevated blood lead concentrations (20-44 microgram/dL) at about 2 years of age and followed until 7 years of age with serial IQ tests and measurements of blood lead. It was found that the cross-sectional associations increased in strength as the children became older, whereas the relation between baseline blood lead and IQ attenuated.

Peak blood lead level thus does not fully account for the observed association in older children between their lower blood lead concentrations and IQ. The effect of concurrent blood lead level on IQ may therefore be greater than currently believed.

2.6. STUDIES ON BLOOD LEAD LEVELS AND IQ:

An evident dose-effect relationship between blood lead level and children’s performance on psychological testing exists: the higher the blood lead level, the lower the intelligence quotient. In Ling et al.’s (1989) study, this relationship remained after confounding factors were controlled by stepwise regression analysis. Partial coefficients for blood lead and verbal IQ, performance IQ and full-scale IQ were -0.85, 0.71 and -0.91, respectively.
Two studies examined higher blood lead levels and IQ, and concluded that above 20 µg/dL, an average loss of 2-5 IQ points could occur (De la Burde and Choate, 1972; Rummo, Routh and Rummo, 1979).

A meta-analysis conducted by Needleman and Gatsonis (1990) of associations between lead burden and IQ suggests that blood lead better predicts IQ than dentine lead.

However, Wasserman et al. (2003) insist that bone lead-IQ associations are stronger than those for blood lead. For each doubling of bone lead, verbal, performance and full-scale IQ decreased by an estimated 4.1, 6.2 and 5.5 points, respectively.

In the study conducted by Todd et al. (2005), the estimated decline in IQ as blood lead concentration increased from 1 to 10 microgram/dL was 6.8-points when controlling for intervention status.

Bellinger et al. (1992) estimated a decline of 5.8 points with an increase in blood lead concentration from 10 microgram/dL to 20 microgram/dL.

Baghurst et al. (1992) estimate that in the age range of 15 months to 4 years, an increase in blood lead concentration from 10 microgram/dL to 30 microgram/dL lead to an approximate deficit in IQ of 4 to 5%.

A previous meta-analysis of Schwartz (1994) suggested a 2.6 point decline in IQ for an increase in lead concentration from 10 microgram/dL to 20 microgram/dL. The results also suggested that the effect is likely to continue below 10 µg/dL.
In the linear model of Canfield et al. (2003), each increase of 10 microgram/dL in the lifetime average blood lead concentration was associated with a 4.6-point decrease in IQ (p=0.004).

There is also some evidence that cognitive effects of lead could occur at blood lead levels below 5 µg/dL (Lanphear et al., 2000).

2.7. STUDIES ON BLOOD LEAD LEVELS AND VISUAL-MOTOR ABILITIES:

De la Burde and Choate (1972, 1975) suggested that asymptomatic lead exposure in children may have latent sequelae in the form of deficits in fine motor function, gross motor development, concept formation and behavior.

In their study, McBride et al (1982) observed that there was a tendency for the children with lower lead levels to perform better than those with moderate blood lead levels in one of the tests of fine motor coordination.

One study (Lerer et al., 1977) has quoted that children with Attention Deficit-Hyperactivity Disorders tend to have a higher incidence of visual-motor problems.

Marecek et al. (1983) established that chronic low-level lead exposure causes neurologic impairment, including decreased intelligence, behavioral and learning disorders and deficits in visuomotor function, perceptual integration and verbal abstraction.

One of the few consistent findings between studies conducted by Harvey et al. (1988) is that of the association between lead level and performance on
tests involving drawing or copying – generally with worse performance being associated with higher lead levels.

In a study conducted by Bellinger et al. (1991) on a cohort of 170 middle and upper-middle class children, the inverse association between lead level and performance was especially prominent for visual-spatial and visual-motor integration skills.

In 1993, Dietrich et al. postulated that motor developmental outcomes may be more sensitive indicators of lead’s adverse effects on the central nervous system as they are probably less confounded with social factors than cognitive and academic outcomes. A comprehensive neuromotor assessment battery was administered by them to 245 six-year-old urban inner-city children enrolled in the Cincinnati Lead Study. In this study, high blood lead levels were associated with poorer scores on assessments of bilateral coordination, measures of visual-motor control, poorer performance on a measure of upper-limb speed and dexterity and a composite index of fine-motor coordination. Low to moderate lead exposure was associated with moderate deficits in gross and especially fine-motor developmental status.

Within a larger comparative environmental health screening program in East and West Germany, neurobehavioral and neurophysiological measures were taken in 367 six-year old children in Leipzig, Gardelegen and Duisburg. After adjusting for relevant confounders and covariates, significant lead-related deficit was found for pattern recognition with respect to blood lead, but not tooth lead (Winneke et al, 1994).

There was an inverse relation between blood lead concentration and visual-motor performance (Baghurst et al., 1995). Even after adjustment for potential confounding factors, blood lead concentrations exhibited a dose-related
inverse association with children’s visual-motor performance. For an increase in life-time average blood lead concentration from 10 microgram/dL to 30 microgram/dL, the estimated deficit in children’s visual-motor performance was 1.6 points. The results indicated that visual-motor integration may be a more sensitive index than global measures of development, such as intelligence quotient, for the assessment of lead effects on child development.

In the preschool period, children with higher lead burdens tend to show their greatest deficits in non-verbal, particularly visual-motor/visual-spatial, abilities (Bellinger et al., 1991; Wasserman et al., 1994, 2000; Dietrich et al., 1991, 1993, 2000; Baghurst et al., 1995).

2.8. STUDIES ON BLOOD LEAD LEVELS AND NEUROBEHAVIOR:

Mental and behavioral disorders in children, characterized as “the new hidden morbidity” (Haggerty, 1988) are now recognized as a major public health problem. Although a broad spectrum of adverse health outcomes have been linked to low-level lead exposure (Needleman and Bellinger, 1991), social and emotional dysfunctions have received very little attention as a potential expression of lead toxicity.

In 1943, Byers and Lord noted that poor school progress among children who were previously treated for lead poisoning was attributable not only to their cognitive deficits but also to their aggression and explosive tempers. Within the past decade, several studies have suggested that even “sub-clinical” lead exposure is a risk factor for antisocial, delinquent behaviors (Bellinger, 2004).

A small number of case-control studies suggested that children with the clinical diagnosis of hyperactivity or attention deficit disorder have histories of
somewhat higher lead exposure (David et al., 1972; Gittelman and Eskenazi, 1983).

In 1977, David et al. suggested associations between child lead levels and symptoms of hyperactivity, including inattention and disruptiveness.

Several studies have reported associations between increased exposure to inorganic lead and parent or teacher ratings of children’s behavior, particularly indices of attention such as distractibility, impulsivity and impersistance (Needleman et al., 1979; Bellinger et al., 1994; Sciarillo et al., 1992).

In their study, Bellinger et al (1994) stated that the risk of behavior problems was unrelated to children’s prenatal lead exposure as reflected by umbilical cord blood lead levels that were nearly all below 15 µg/dL. This is consistent with other evidence that prenatal exposures of this magnitude are less likely than postnatal exposures to have adverse effects that are detectable at school-age (Baghurst et al., 1992; Bellinger et al., 1992; Dietrich et al., 1993).

In the above study, tooth lead level was significantly associated with total problem behavior scores, approximately 2 points in T-score per log unit increase in tooth lead. Significant tooth lead-associated increases in both internalizing and externalizing scores were also observed, approximately 1.5 points in T-score per log unit increase in tooth lead. Weaker associations were noted between tooth lead level and the prevalence of “extreme” problem behavior scores.

Epidemiologic studies provide support for the hypothesis that teachers view children with higher lead burdens as having reduced ability to sustain attention. In the study of Needleman and colleagues (1979) children with high dentin lead levels were rated unfavorably on the following dimensions: distractibility, persistence, dependence, organization, impulsivity, frustration,
tolerance, daydreaming and ability to follow directions (simple or a sequence). Using the same rating scale, investigators in the United Kingdom (Yule et al., 1984) and Greece (Hatzakis et al., 1985) generally replicated these findings.

Schwartz and Otto’s study (1987) indicated that blood lead levels were also significantly related to delays in the age at which children first sat up, walked and spoke and to the probability that a child was hyperactive.

Subclinical elevations of blood or tooth lead levels have been associated with teachers’ ratings of children’s hyperactivity or activity levels on the Conners or Rutter Teachers’ rating scales (Fergusson et al., 1988, 1993).

In two studies of school-aged children (Thomson et al., 1989 and Silva et al., 1988), after control for social confounders, log blood lead was significantly associated with teacher-reported problems; but the impact of blood lead was very small: a 10-fold increase in blood lead increased behavioral scores by around 0.1 points. They have also found associations between blood lead and symptoms of hyperactivity.

In Tuthill’s study (1996), the striking dose-response relationship between levels of lead and negative teacher ratings remained significant after controlling for age, ethnicity, gender and socioeconomic status. An even stronger relationship existed between physician-diagnosed attention-deficit hyperactivity disorder and hair lead in the same children.

In a study conducted by Wasserman et al. (1998), concurrent blood lead explained the independent variance in the destructive and withdrawn behavior problem subscales among 3-year old children, after control for socio-demographic confounders.
Ris et al. (2004) stated that significant interactions were found between gender and lead exposure parameters for both attention and visuoconstruction indicating heightened risk in males.

The results of a study conducted on 246 African American, inner-city children (Chiodo et al., 2004) consistently showed neurobehavioral deficits in relation to low levels of lead in the areas of intelligence, reaction time, visual-motor integration and reasoning skills, fine motor skills, attention, including executive function, off-task behaviors, social behavior and teacher-reported withdrawn behaviors, which have been previously suggested as part of lead’s “behavioral signature”.

In 1993, White et al., claimed that childhood lead poisoning also has long-term neurobehavioral consequences. In their study, adult subjects of around 54 years, with a documented history of lead poisoning before age 4 and matched controls were examined with an abbreviated battery of neuropsychological tests including measures of attention, reasoning, memory, motor speed and current mood. Within the exposed group, performance on the neuropsychological battery and occupational status were inferior and also related, consistent with the presumed impact of limitations in neuropsychological functioning on everyday life. The results suggested that many subjects exposed to lead suffered acute encephalopathy in childhood which resolved into a chronic sub-clinical encephalopathy with associated cognitive dysfunction still evident in adulthood.

Within a sub-cohort from the Collaborative Perinatal Project, Denno (1993) found that a history of lead poisoning was a significant risk factor for both juvenile and adult crime, as well as for disciplinary problems in school.
Some medical researchers believe that as much as 20% of all crime is lead-associated as lead is said to alter neurotransmitter and hormonal systems in a way that may induce aggressive and violent behavior (Needleman et al., 1996).

Needleman and colleagues showed that higher bone lead levels are associated with an increased risk of self-reported antisocial behaviors and were also rated by both their parents and teachers as having scores that exceeded clinical cut-offs on the attention, aggression and delinquent behavior scales (Needleman et al., 1996), and more recently, that being an adjudicated delinquent is associated with an increased risk of having an elevated bone lead level (Needleman et al., 2000).

In a provocative set of historical ecologic analyses spanning, for some endpoints, the last 125 years, Nevin (2000) reported strong associations between the amounts of inorganic lead used in paints and gasoline and rates of violent crime and unwed pregnancies.

2.9. HEMATOPOIETIC EFFECTS OF LOW BLOOD LEAD LEVELS:

In the study conducted by Ibrahim et al. (1989), apart from analyzing the mean blood lead concentrations, the blood samples were also examined for some hematological parameters, total counts of erythrocytes and leucocytes, hematocrit, mean corpuscular volume, hemoglobin, mean corpuscular hemoglobin concentration, and basophilic stippling. All values obtained were within the ‘normal ranges’. However, on assessing the hematological effects of sub-toxic levels of lead in blood by considering the seven cases whose blood lead values were between 15 – 25 microgram/dL, it was found that the values of hematocrit and mean corpuscular volume were marginally below the normal range, the values of mean corpuscular hemoglobin concentration and white blood cell count were within the normal range and the values of red blood cell
count and hemoglobin were at the lower end of the normal range. This predictive pattern indicated that sub-toxic levels of lead in blood may be related to early stages of microcytic anemia.

This finding was also supported by another study conducted by Poulos et al. (1986) on the hematopoietic effects of low blood lead levels. All three hematological parameters: blood lead, hematocrit and hemoglobin, measured by these researchers were within the ‘normal range’ for their entire data. However, within each sub-group of their samples, there was a statistically-significant inverse correlation between blood lead concentrations and the other two values of hematocrit and hemoglobin.

2.10. RELATIONSHIP BETWEEN BLOOD LEAD LEVELS AND SERUM FERRITIN:

Ferritin is a compound composed of iron molecules bound to apoferritin, a protein shell. Stored iron represents about 25% of total iron in the body, and most of this iron is stored as ferritin (Miale, 1982).

Ferritin is found in many body cells, but are especially found in the cells of liver, spleen, bone marrow and in reticuloendothelial cells (Schreiber, 1989).

Ferritin plays a significant role in the absorption, storage and release of iron. As the storage form of iron, ferritin remains in the body tissues until it is needed for erythropoiesis. When needed, the iron molecules are released from the apoferritin shell and bind to transferrin, the circulating plasma protein that transports iron to the erythropoietic cells (Vander et al., 1985).
2.11. ASSOCIATION BETWEEN BLOOD LEAD LEVELS, BODY IRON STATUS AND CHILDHOOD ANEMIA:

One of the substantial problems in Indian children which leads to increased morbidity and mortality is anemia (Bentley and Griffiths, 2003; Brabin et al., 2001; Kapur et al., 2002). Adverse health effects of anemia in children include impaired psychomotor development and renal tubular function, poor cognitive performance, and mental retardation (Hurtado et al., 1999; Lozoff et al., 1987; Ozcan et al., 2003; Palti et al., 1983; Walter et al., 1989). The association of lead toxicity with anemia in children has been explored in the past, primarily in populations at high risk, such as children living near a lead smelter (Landrigan et al., 1976; Schwartz et al., 1990). It has also been shown that there is a link between the high prevalence of lead pollution in India and the hazardous consequences of anemia (Jain et al., 2005).

The anemia of lead poisoning is related to inhibition of hemoglobin production and shortened red cell survival (Beutler, 1977). The former abnormality is due in part to inhibitory effects of lead on porphyrin synthesis and iron incorporation in the porphyrin ring (Goldberg, 1972). Additionally, abnormal globin synthesis has been found in the presence of increased lead levels (White and Harvey, 1972).

Lead in the central nervous system may contribute to dopaminergic dysfunction inducing alteration of dopamine release and dopamine receptor density (Gedeon et al., 2001; Lidsky et al., 2003). Moreover, lead may disrupt the structure of the blood-brain barrier function essential for brain integrity (Dyatlov et al., 1998). Interestingly, Wang et al. (2007) recently reported that iron supplementation protects the integrity of the blood-brain barrier against lead insults. On the other hand, iron deficiency could increase the toxic effect of lead, suggesting a potent neuroprotective effect of iron supplementation on
dopaminergic dysfunction due to lead exposure (Wright 1999, Wright et al., 2003).

The mechanism by which low iron status affects lead uptake is that the binding receptors for iron are made available for lead transport in the face of reduced iron availability. There is also the likelihood, proposed by Watson et al. (1986), that iron deficiency triggers the availability of additional iron uptake receptors in the distal portion of the small intestine, where lead is known to be absorbed as well. This would explain why iron deficiency must first reach a certain level to see enhanced lead uptake and why iron repletion readily suppresses lead uptake; that is, the distal receptors for iron become inactive for both iron and lead uptake (Mushak and Crocetti, 1996).

Iron deficiency anemia develops in sequential changes over a period of negative iron balance. These stages include the iron depletion phase (pre-iron deficiency phase), iron deficient erythropoiesis phase and finally iron deficiency anemia. During the iron depletion phase, the mean corpuscular volume is decreased and the red cell distribution width is increased; however, anemia or decrease of serum ferritin concentrations are not present. In iron deficient erythropoiesis, serum ferritin concentrations and serum iron concentrations are decreased; however, anemia and hypochromia are still not detectable. During the last phase of iron deficiency anemia, along with a decrease in mean corpuscular volume and serum ferritin concentration, a decrease in hemoglobin concentration is also seen.

The global burden of disease estimates that about 5 children for every thousand children (the lower estimate being 2 and the upper estimate being 10) are affected by anemia caused by environmental exposure to lead in the year 2000 (Fewtrell et al., 2003).
2.12. STUDIES ON BLOOD LEAD LEVELS AND GROWTH:

As early as 1930, stunted growth was reported in children who survived lead-induced intoxication (Nyle, 1929). Asymptomatic lead exposure has also been linked to short stature (Mooty et al., 1975; Johnson et al., 1979).

Results of an analysis of data derived from the National Health and Nutrition Examination Survey showed a negative relationship between “low to moderate” levels of lead exposure as indexed by blood lead concentration and stature, in 2695 children, aged 6 months through 7 years (Schwartz et al., 1986). In this study, the correlation of stature, particularly height, with blood lead levels in the range of 5 to 35 microgram/dL was statistically highly significant ($R^2 = 0.905$).

The relationship of blood lead concentration to stature was evaluated by examining data from a sample of 1454 Mexican-American children aged 5 – 12 years, derived from the data sets of the Hispanic Health and Nutrition Examination Survey (HHANES) conducted in 1982 – 1984 by Frinsancho and Ryan in 1991. The results indicated that there is an inverse relationship between blood lead concentration in the range of 0.14 – 1.92 micromoles/L with stature. This finding suggested that growth retardation may be associated even with moderate concentrations of blood lead.

2.13. STUDIES ON BLOOD LEAD LEVELS AND SOCIO-DEMOGRAPHIC FACTORS:

Blood lead concentrations were measured in a group of children from a group of 9- to 10-year-old school children in Aarhus, Denmark. A total of 20% of the variation in blood lead was explained by parents' tobacco smoking, the child’s
number in the sib-ship, gender and consumption of canned food at home (Lyngbye et al., 1990).

Analysis of blood lead levels by father’s occupational type (professional/technical, managerial/administrative/executive, clerical, sales, transport/communication, tradesman/process worker/labourer, service/sport and recreation) showed there was no relationship between the two. The correlation between lead level and sociodemographic status, although significant, was very low. (McBride et al., 1982).

Some occupational studies have suggested a possible relationship between paternal lead exposure and disorders of spermatogenesis among exposed fathers and spontaneous abortion and birth defects among offspring (Lindbohm et al., 1991; Sallmen et al., 1992; Winder, 1993). Few studies have evaluated the relationship between maternal and paternal occupational lead exposures and low birth weight among offspring (Savitz et al., 1989; Kristensen et al., 1993). A population-based case-control study conducted by Yuan et al. in 1996 suggested a possible relationship between maternal and paternal occupational exposures to lead and low birth weight.

A meta-analysis of 10 reports cited in Medline, Toxline, Excerpta Medica and Bio-Med from 1987 through 1994 states that the children of lead-exposed workers had a geometric mean blood lead level of 9.3 mg/dL compared to a U.S. population geometric mean of 3.6 mg/dL (Roscoe et al., 1999).

Pirkle et al. (1994) showed that sociodemographic factors such as low income, low educational attainment are associated with higher blood lead levels.

3 sets of variables were thought to influence the relationship between dust lead and blood lead: demographic variables, child behaviors and maternal
behaviors. Black race, marital status (single parent: \( r = +0.42 \)) and living in rental property were moderately and positively correlated with levels of lead. Contaminated house dust and children’s blood lead levels showed correlation coefficients ranging from +0.18 to +0.44.

In contrast, household income (lower income: \( r = -0.55 \)) and having at least some college education (lower education level of parent: \( r = -0.25 \)) were inversely correlated with children’s blood lead levels, with a range from –0.14 to –0.38. Child behaviors were not strongly correlated with blood lead. Breastfeeding (\( r = -0.19 \)) and vitamin use (\( r = -0.17 \)) were associated with lower blood lead levels. (Bruce and Klaus, 1997).

Lead is also said to migrate from food containers. A study has reported the recoating of the inner surface of brass utensils with a mixture of lead and tin (“tinning”) that is widely practiced by artisans in India. The tin-lead alloy contained 55 to 70\% lead levels, and water-containing tamarind had 400 – 500 micrograms of lead/L after boiling for 5 minutes. Such acidic foods can leach out lead. Lead leaching from Indian pressure cookers while cooking especially from the rubber gasket and safety valve are minor sources of lead concentration of cooked food (Raghunath and Nambi, 1998).

2.14. STUDIES ON BLOOD LEAD LEVELS AND TRADITIONAL MEDICINE:

In recent years there has been an increase in the use of traditional Asian medicines. It is estimated that 30\% of the US population is currently using some form of homeopathic or alternative therapy (Eisenberg et al., 1993). Herbal medications are claimed and widely believed to be beneficial; however, there have been reports of acute and chronic intoxications resulting from their use.
Surma and Kohl is an example of the use of lead as an eye cosmetic or medicine. Surma is available as fine powder or heavy crystal mineral PbS containing 34-92% Pb w/w (Nir et al., 1992; Parry and Eaton, 1991). In a study on Indian and Pakistani children using leaded eye cosmetics, 13 mg/dL mean blood lead level was reported compared to 4.3 mg/dL for those not using such cosmetics (Ali et al., 1978; Abdullah, 1984; Sprinkle, 1995).

Folk and herbal remedies from India have been found to contain high concentration of heavy metals and unsupervised treatment has resulted in toxicity. A patient with hepatitis was found to have lead poisoning where the source was traced to herbal medicines he had been taking for diabetes (Keen et al., 1994). A Western European developed severe anemia after ingestion of several ayurvedic drugs obtained during a trip to India. Laboratory findings showed high blood lead, urinary lead concentrations and an increased urinary excretion of delta amino levulinic acid (ALAD) (Spriewald et al., 1999).

Some ayurvedic medicines containing lead are Saptamrut loh (5.12 mg/g), Keshar gugal (2.08 mg/g), Punarvadi gugal (1.99 mg/g), Trifla gugal (4.18 mg/g), Ghasard (16000 mg/g), Bala goli (25 mg/g), Kandu (6.7 mg/g), Arogyavardhini (63.2 mg/g), Sankhvati (13 mg/g), Brahmiwati (27500 mg/g), Chyavanprash (7.3 mg/g), Trivanga bhasma (261200 mg/g), Diabline bhasma (37770 mg/g) and Hepatogaurd (0.4 mg/g) (Nambi et al., 1997; JAMA Report, 1984).

2.15. STUDIES ON BLOOD LEAD LEVELS AND PAINT:

The addition of lead in paint was once widespread because of its use as pigment, dispersing agent and drying agent but mostly because it provided durability to the paint.
In 1975, Canada’s Hazardous Products Act prohibited the use of paint containing more than 0.5% of lead (dry wt.) for indoor use and on furniture and toys but not on playground equipment. However, the study conducted by Pascal and Bailey (2004) demonstrated that lead toxicity should also be suspected in anyone with pica who eats paint, even if it is “lead-free”.

Dust lead levels were significantly associated with children’s blood lead levels, both indirectly and directly via hand lead. Both soil and paint lead contributed to dust lead levels, but paint contributed significantly more lead to house dust than soil. (Bruce and Klaus, 1997)

In a small survey conducted by van Alphen (1999) in Indian paints, it was observed that the lower lead concentration paints are the white, blue and brown-red paints, while in order of increasing lead concentrations are the green, red, orange and yellow paints. Of the 24 samples analyzed, 17 had lead concentrations exceeding 0.5% lead by weight.

2.16. STUDIES ON BLOOD LEAD LEVELS AND GASOLINE USE:

The growing recognition of lead’s dangerous effects has led to a worldwide initiative to reduce lead content of gasoline (Lovei, 1998). In India, lead levels have been reduced from 0.56 g/L in gasoline (pre 1986) to 0.013 g/L in the year 2000 (CPCB, 1997). Four metropolitan cities became lead free in 1999 as far as exposure through gasoline is concerned.

Studies have revealed a direct link between consumption of leaded gasoline and lead levels in childhood (Thomas et al. 1999). The prevalence rate of lead poisoning in the study conducted by Zou and Zhao et al. (2004) was 24.7% in children aged 0-6 years, which is significantly lower than the previous survey (39.16%) in Hangzhou in 1997 conducted by Yang et al. The researchers
state that this may be due to, at least partly, the using of lead free gasoline from 1998 in Hangzhou.

Since the removal of lead from gasoline, the median blood lead concentration in U.S. children has fallen from 15 microgram/dL in 1978 to 2 microgram/dL in 1999, a triumph for public health (Rogan and Ware, 2003). Not only in children, numerous studies have also shown that reductions in blood lead in the general population parallel decreases in the level of lead in gasoline. In the U.S., for example, average blood lead levels dropped 37% in the early stages of lead reduction programme (Annest, 1983; Annest et al., 1983). Other studies conducted in various countries have shown similar results (Elinder et al., 1996; Wietlisbach et al., 1995; Schuhmacher et al., 1996), with decreases over a five-year period ranging between 30-48%.

Annual volume-weighted mean concentrations of lead in precipitation had decreased from 29 to 4.3 microgram/dL at the urban site and from 5.7 to 1.5 microgram/dL at the rural site in the years 1979 to 1983. Annual lead fluxes in precipitation had decreased from 1979 to 1983: 2000 to 370 (ng/sq.cm)/year at the urban site and 430 to 100 (ng/sq.cm)/year at the rural site. Decreases in atmospheric lead fluxes were closely correlated with decreases in lead used in gasoline in Minnesota. (Steven et al., 1986).

The elemental composition, patterns of distribution and possible sources of street dust are not common to all urban environments, but vary according to the peculiarities of each city. 150g of dust were collected by brushing with a small paint brush the urban surface (sidewalk, road, gutter) from streets and roads of Madrid (Spain) and Oslo (Norway) between 1990 and 1994 in each sampling increment. The fraction below 100 micronmeter was acid-digested and analysed by ICP-MS. The data for lead seem to prove that the gradual shift from leaded to unleaded petrol as fuel for automobiles has resulted in an almost
proportional reduction in the concentration of lead in dust particles under 100 micrometer. (Eduardo de Miguel et al., 1997).

2.17. STUDIES ON BLOOD LEAD LEVELS AND NUTRITION:

During the last three decades, cross-sectional studies have linked iron deficiency with lead toxicity and provided evidence that these two conditions are related. In addition to epidemiological associations, shared aspects of their pathogenesis and a common iron-lead transporter make it likely that an interaction or synergism exists between the two disorders (Kwang et al., 2004). A recent longitudinal study of children has demonstrated an association of iron deficiency with subsequent lead poisoning, suggesting an increased susceptibility to lead poisoning in iron-deficient individuals (Wright et al., 2003). There is also growing evidence that high iron intake and iron-replete status may reduce lead absorption in children (Hammad et al., 1996; Kim et al., 2003, Wright et al., 2003; Wolf et al., 2003).

Iron deficiency among children predisposes them to increased lead absorption thus aggravating further the detrimental effects of lead as observed in a screening study of children carried out in Jammu city (Kaul, 1999) where there was an underlying high prevalence of iron deficiency. Elevated blood lead among iron-deficient children (24% with ferritin less than 12ng/dL) persisted after adjusting for potential confounders by multivariate regression; the largest difference in blood lead levels between iron-deficient and iron-replete children, approximately 3 microgram/dL, was among those living in the most contaminated environments. Asian children had a paradoxical association of sufficient iron status and higher blood lead level, which warrants further investigation (Asa et al., 2001).
Studies have shown that the consumption of certain nutrients in the diet including minerals such as calcium, phosphorus, iron and zinc and vitamins such as vitamin C, E and thiamine can reduce the absorption of dietary lead in children (Sonawane, 1999).

2.18. CONCLUSION:

The ensemble of retrospective studies reviewed here has established the epidemiological basis for the argument that an association exists between low-lead exposure and intellectual deficit, in terms of IQ, visual motor functions and also neurobehavior. This has generated knowledge for use both in setting current policy and future research agendas.