Lead neurotoxicity in children: Is prenatal exposure more important than postnatal exposure?

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Abstract
Numerous studies indicate that low-level lead poisoning causes mild mental retardation and low IQ scores in children. The general mean lead intake in the adult European population corresponds to a reassuring 14% (0.5–56%) of the tolerable daily intake: at this low level of exposure only few children (less than 10%) have blood lead levels (PbB) higher than 10 μg/dl, previously considered the PbB of concern. In more recent years data now suggest that even when ‘the lifetime average blood lead concentration’ is below 10 μg/dl an inverse association exists with intelligence quotient (IQ) scores. Two-thirds (45–75%) of lead in blood, however, comes from long-term tissue stores and this is especially true for newborn infants and pregnant women. Several data suggest that for lead the main toxic event is prenatal exposure: therefore we should focus our attention on maternal lead stores and whenever possible avoid their mobilization during pregnancy. In this regard we should design appropriate studies to confirm whether dietary supplementations can reduce bone resorption and lead mobilization during pregnancy. The hypothesis that the amount of maternal bone lead stores is the relevant parameter for predicting the level of neurotoxicity of this metal gives some optimism for the future: if we study children whose mothers never underwent high environmental pollution (born after the withdrawal of lead from gasoline) and hence have relatively low bone lead stores we could find that, at the population level, lead has little influence on children IQ scores.

Key Words: Children, lead, neurotoxicity, prenatal lead exposure, maternal lead stores

Introduction
Lead exists in the earth’s crust, and occurs naturally in the environment through a variety of mechanisms, including volcanic emissions and geochemical weathering. Lead pollution, however, derives mainly from human activities to extract and exploit the metal.

Severe lead exposure in children (blood lead levels around 350 μg/dl) can cause coma, convulsions, and death. At lower levels of exposure numerous studies [1–6] indicate that lead poisoning causes reduced gestational age and weight at birth, impaired growth in children, impaired synthesis of the active metabolite 1,25-(OH)2 vitamin D, impaired haemoglobin synthesis, anaemia, impaired visual and motor functioning, hearing loss, mild mental retardation, low intelligence quotients (IQs) and attention span, reading and learning disabilities, hyperactivity and behavioural problems, antisocial behaviour and delinquency, decreased ability to maintain steady posture, puberty delays, brain, liver, kidney, nerve and stomach damage, both female and male reproductive impairment, and cancer.

Importantly, lead induces its major deleterious effects on health without causing overt signs of toxicity. At the epidemiological level, lead exposure is estimated to account for almost 1% of the global burden of disease: most of its effects involve children of the developing world [7]. In Europe, the World Health Organization (WHO) estimates that nearly 157 000 days of healthy life are lost in children less than four years of age from lead poisoning [8].
What is the ‘safe’ level of lead exposure in children?

Owing to the reduced use of alkyl leads in petrol and to other interventions in recent decades, blood lead concentrations in children have fallen substantially in a number of European countries (United Kingdom [9], Germany [10], Poland [11]). Lead is also present at low concentrations in most foods. Offal and molluscs may contain higher levels. The main reason for increased lead intake via foodstuffs is lead contamination during food processing. Over recent decades, thanks to source-related efforts to reduce lead emission and improvements in quality assurance of chemical analysis, the lead level in food has also significantly decreased. Present dietary lead levels are well delineated in SCOOP (2004), a survey reporting that the mean daily lead intake from food and beverages of adult populations from 12 European countries is 0.42 μg/kg bw/day. Assuming a provisional tolerable daily intake (TDI) of 3.6 μg/kg bw/day, this average lead intake in the adult European population corresponds to a reassuring 14% (0.5–56%) of the TDI [12].

Dietary lead levels are nevertheless less favourable in certain European countries, and in children and subgroups of European adults or children who consume higher quantities of certain foods. In general, the mean blood lead level (PbB) is estimated to be below 5 microgram/dl in Western and between 5 and 10 microgram/dl in Eastern European countries [12]. These general means include children with increased blood lead levels (e.g., >10 μg/dl) whose prevalence increases significantly when water, soil and dust from the house environment are high and socioeconomic conditions are low. Accordingly, recent studies report that up to 5% of children have blood lead levels >10 μg/dl in England [13].

We must keep clearly in mind that, notwithstanding the continuous improvement in lead exposure in Europe thanks to the concerted efforts on the part of the regulatory authorities, reducing lead exposure in European children further will inevitably be a costly and challenging task. Are these efforts really necessary or can we be satisfied with what has already been achieved? Even though the level of exposure in Europe is indeed far better today than it was 10–20 years ago, pre-industrial humans had an estimated 100- to 1000-fold lower exposure to lead levels than populations of today [14].

Until recently the most reliable information on the effects of lead exposure came from meta-analysis of studies which assessed an estimated mean decrease in the intelligence quotient (IQ) for exposures greater than this level (loss of 2–3 points for an increase from 10 to 20 μg/dl in PbB [14,15]). Until recently, 10 microgram/dl was therefore considered the ‘PbB of concern’. In a recent study, however, using the more meaningful ‘lifetime average lead blood concentration’ to assess its consequences on IQ, Canfield et al. [4], while confirming a loss of 4.6 points of IQ decrement for each increase in PbB of 10 μg/dl, found a larger effect of a loss of 7.4 IQ points for a PbB change between 0 and 10 μg/dl. These data are consistent with the interpretation that the effects of lead on IQ are proportionally greater at lower lead concentrations and strongly suggest that the relationship between PbB and IQ is non-linear with the greatest interval decrements in IQ at PbB less than 10 microgram/dl [4]. From these data we deduce that, for lead, the NOAEL (non-observable adverse effect level) and the LOAEL (lowest observable adverse effect level) are both equal to zero [4]. Hence, there seems to be no threshold below which lead is not toxic to the developing central nervous system [5].

If this is so, then the majority of European children are at risk of losing several IQ points owing to the present level of lead contamination. Lead should therefore still be considered a danger which requires interventions and resources.

Are blood lead levels the best biomarker of lead toxicity?

We report above ample data from the literature showing that blood lead concentrations are inversely and significantly associated with IQs. Even when ‘the lifetime average blood lead concentration’ is below 10 μg/dl (until recently the ‘level of concern’), this inverse association seems to exist, and has become even stronger. These studies, on the basis of the significant and strong correlation between ‘sub-clinical’ blood lead levels and adjusted IQs, assumed that the blood lead level is the biomarker of the ‘internal dose’ biologically effective for neurotoxicity.

Some evidence nevertheless suggests otherwise. In the paper by Canfield et al. [4], the plots of blood lead levels and IQ scores as covariate disclose tremendous scatter around the regression lines with low values of the coefficient of correlation, suggesting that children vary in their response to these low levels of exposure [16]. The potential sources of individual variability in the lead-associated neurodevelopmental risk are many, among them gender, genetic polymorphisms involved in lead metabolism and co-exposure to other toxicants.

One explanation focuses on toxico-kinetic and toxico-dynamic factors. While blood lead levels are largely influenced by concurrent or recent lead exposures it is also true that the blood lead level in general represents only the existing equilibrium between endogenous and exogenous sources of lead. In normal subjects (adults and children) lead leaves the blood to be stored in bone (or other tissues) and
continuously re-enters the blood from tissue deposits; this happens under the influence of several physiological or pathological factors and in these movements lead simply mimics the behaviour of calcium.

By measuring the ratio between different lead isotopes in the blood (four different isotopes of lead exist in nature and their ratios vary in different parts of the world) one research group was able to estimate the contribution of lead stored in bones to the actual blood lead concentration in adult women (20–30 years) who emigrated to Australia from Eastern European countries [17]. These studies demonstrated that in normal adult women two-thirds (45–75%) of blood lead comes from long-term tissue stores: bone lead becomes an even more predominant source of PbB when lead exposure from external sources is low.

We therefore conclude that in general ingested lead contributes to the amount of lead in circulating blood by no more than 35% [18]. This is especially true for newborn infants and women during pregnancy. In a study conducted by Gulson et al. [18] in newborns during the first months of life, the amount of lead coming from maternal milk, from cow’s milk and from beikost contributed only 35% to the lead in circulating blood. An interesting finding in these children was that lead excreted in the urine was three times higher than the dietary lead intake. These findings were explained by the rapid bone turnover which takes place in the newborn; the whole skeleton turns over during the first 12 months of life and this causes a large mobilization of bone lead stored during pregnancy.

PbB in infants is mainly the expression of skeletal lead; the dietary contribution to the PbB level is normally of minor importance especially because at that age the intake of dust is negligible and the lead intake/excretion balance is negative.

During pregnancy, starting from the early stages, maternal calcium requirements increase and continue to rise until delivery [19]. A full-term infant accumulates over 30 g of calcium during the gestation period, most of which is assimilated into the foetal skeleton in the third trimester. Maternal calcium needs are maintained by a fall in the serum albumin concentration [20] and increased gastrointestinal absorption of calcium [21,22], but most importantly through increased bone resorption [23,24]. Increased bone resorption during pregnancy facilitates the active transfer of calcium to the foetus but maternal lead follows a transfer pattern similar to that of calcium and without any barrier at the placental level [25]. This is particularly true during the last part of pregnancy and the lactation period when maternal PbB increases by 25–100%; this increase derives from the further mobilization of lead from bones [26].

The various body compartments in which lead is dissolved are in constant dynamic equilibrium; the bidirectional constants of equilibrium linking different compartments can be very high (rapid lead exchange, e.g. between erythrocytes and plasma) or very low (slow exchanges, e.g. between bone and blood), but in general mother and foetus can be considered separate compartments of the same system throughout pregnancy and these compartments remain in equilibrium. It is not surprising, therefore, that when pregnancy ends an identity exists between the blood-lead concentrations in the mother and child, between the bone lead concentration in the two organisms, etc. [27].

Because blood lead levels in the newborn or child at different ages come under the influence of the child’s bone lead stores, they tend to remain high if the mother was highly contaminated and vice versa. These considerations imply that if we measure PbB several times during the first few years of life (‘lifetime exposure’), we really measure a variable that is heavily influenced by the child’s bone store, a measure that in turn mirrors the mother’s bone stores. Hence evidence that lifetime (postnatal) lead exposure is inversely linked to IQs does not, per se, show that the brain damage took place postnatally; lifetime exposure might simply be the proxy for prenatal lead brain exposure.

In conclusion, maternal bone lead concentration determines the amount of the foetal bone lead stores and in parallel the amount of lead deposited in the foetal brain tissue; foetal brain lead could be the variable associated with lead’s neurodevelopmental toxicity.

**Effects of prenatal lead exposure**

Prenatal lead exposure is a major risk factor for impaired foetal and infant development [28–32]; during the early embryonic and foetal stages lead can pass through the placenta to affect the nervous system [33]. Various toxic mechanisms are purported to explain the lead-induced injuries that damage the developing brain when the brain and spinal cord are growing and differentiating [28–32].

Neurodevelopmental events are initiated in the embryo, ‘fine-tuned’ in the foetus, and elaborated further during the postnatal years into adolescence. It is becoming increasingly apparent that the level of mental acuity (or lack thereof) witnessed in later life is linked to the environments encountered during these formative periods of developmental neurogenesis.

Evidence underlying the importance of early environmental events comes from the results of in vivo studies in adult rats exposed to Pb during the perinatal period [34,35]. In the developing nervous system refinement and stabilization of neuron connections and the fine tuning of synaptic connectivity are dependent on the repetitive activation of
certain biochemical signalling events; this process increases the synaptic strength that underlies learning processes in the mature nervous system (long-term potentiation). In a study investigating early lead toxicity, Gilbert et al. [34] propose that the persistent impairment in cortical plasticity found in adult animals after early exposure to lead may result from toxicant-induced perturbations of activity-dependent plasticity during critical periods of nervous system development.

The foregoing observations clearly do not necessarily exclude the possibility of postnatal lead toxicity. Scientific data which allow to us decide whether, at the epidemiological level, prenatal or postnatal lead exposure is the main neurotoxic event, are scarce. The two possibilities are probably not alternative in the sense that both prenatal and postnatal lead exposure could be important in single individuals, according to the modalities (amount, timing, etc.) of lead exposure itself.

From the viewpoint of prevention, however, the two hypotheses suggest completely different actions. If the determinant toxic event is postnatal exposure, we must operate on the environment, with interventions that as we underlined before, are costly, difficult and of uncertain usefulness. If the determinant main toxic event is prenatal exposure we should direct our main attention to the amount of maternal lead stores and if possible avoid mobilizing these stores during pregnancy.

What actions are needed for the prevention of lead neurotoxicity?

The amount of lead bone deposits depends on lifetime exposure. Lead ingested with air, foods or drinking water is initially taken up by erythrocyte-plasma compartments. With time lead is incorporated into various tissues, especially into bones where lead competes with calcium for the formation of hydroxyapatite crystals. In the bones, lead can be retained indefinitely, with a half-life of the order of decades [36]. Lead can be partially mobilized from bones during aging or other conditions (including osteoporosis, fractures, menopause, and pregnancy).

These data underline that the main way to reduce bone lead stores in young women is to reduce lifetime exposure. Notably, the epidemiological data appearing nowadays in the literature refer to women who underwent high exposure before lead was withdrawn from gasoline, in about 1990. If we study the children of mothers who never underwent high environmental pollution and hence with lower bone lead stores, we will presumably find less severe lead-related IQ deficits.

To answer the question whether we can avoid or reduce lead store mobilization during pregnancy we must consider two sets of data. First, we should consider a set of experimental data demonstrating that nutritional and social factors, together with other unrecognized environmental situations, can deeply modify blood lead levels; the fractional absorption of lead from the environment (referred to as external dose) and the mobilization of lead stores (described as internal dose) can be modified by nutritional status. At least four nutritional conditions increase the effects of environmental lead exposures: irregular food intake (i.e. periods of fasting), high fat intake, marginal calcium ingestion, and subtle iron deficiency [37]. The data are nevertheless difficult to interpret because these marginal nutritional conditions are more common among subpopulations at greater risk of environmental exposure to lead.

Secondly, starting from the notion that fasting and nutritional deficits modify PbB and Pb distribution, studies have been conducted to assess whether a maternal diet rich in calcium could significantly reduce the mobilization of the maternal lead bone stores during pregnancy and lactation. In their study investigating patterns and determinants of blood lead during pregnancy, Hertz-Picciotto et al. [38] reported that higher calcium intake was inversely associated with blood lead levels in the latter half of pregnancy. Also, the paper by Janakiraman et al. [39] documented that dietary calcium supplementations decreased bone resorption in the last trimester of pregnancy. A recent trial of Te`lles-Rojo et al. [40] found that during pregnancy plasma lead levels were inversely related to dietary calcium intake; yet only recently has the idea that dietary supplementation can reduce bone resorption and lead mobilization during pregnancy received due attention. Moreover, calcium could be only one of the many candidate substances (iron, vitamin D, phosphates and probably many more), which could be used in various combinations to attain the maximum result.

Conclusions

Despite the progressive abatement of lead in the environment, concern continues over lead-engendered IQ impairment in children.

The ‘no lower threshold’ notion for this toxic substance forces us to engage in costly efforts aimed at reducing lead exposure levels in children to near zero. Because this is an almost impossible task we should pessimistically envisage that the toxic effects of lead on health will never be overcome.

Conversely, if maternal bone lead storage is indeed responsible for lead-related brain damage in children, then we should focus our efforts on limiting lead mobilization during pregnancy. In the meantime, when women born after the environmental fall in lead in the past 15–20 years become mothers, early lead neurotoxicity in Europe will on its own account almost disappear.
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