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EFFECTS OF LOW DOSES OF LEAD ON CHILDREN'S HEALTH

G. ABBRITTI, G. MUZI, C. CICIONI, M.P. ACCATTOLI, T. FIORDI and P. MORUCCI

Istituto di Medicina del Lavoro, Università degli Studi, Perugia, Italy

Summary. - *An investigation has been carried out of the blood lead levels of children resident in three different municipalities of Umbria: Corciano, selected as a control area; Perugia, the largest town in Umbria (approx. 150,000 inhabitants), with intense automobile traffic, and Deruta a town in which there is a flourishing ceramic industry. The mean blood lead levels were found to be higher in children in Perugia (96 µg/l) and Deruta (97 µg/l) with respect to Corciano (83 µg/l); in Deruta the mean blood levels were raised in those children whose families are occupationally exposed to lead (107 µg/l). The concentration of lead in the air in Deruta was higher than in Corciano (0.19* vs *0.11 µg/m³, respectively). The lead concentrations in house dust were higher in Deruta (2.8 µg/m²) than in Corciano (0.8 µg/m²) and the difference was greater in the houses were the inhabitants were exposed to lead in factories (2.7 µg/m²) or in workshops which were adjacent to the houses (4.7 µg/m²). The blood lead levels of children included in this study have been compared with those obtained during a similar investigation in 1978. Over the last eight years primary school children in Corciano and Deruta have shown a marked reduction in blood lead levels (> 50%). This improvement should not lead to false optimism: in fact, it is impossible to establish the blood lead level at which no adverse effects are induced, especially in children. Numerous sudies suggest that even sub-clinical levels of lead can cause alteration in heme synthesis, peripheral nervous system, kidney, immune system, skeleton and growth. Furthermore, with regard to the central nervous system, low blood lead levels can provoke neuropsychological deficits, which can result above all, in a decreased I.Q., and behavioural alterations.*

Riassunto (Effetti del piombo a basse dosi sulla salute dei bambini). - *E' stata condotta una indagine sui livelli di piombemia sui bambini residenti in tre diversi comuni dell'Umbria: Corciano, paese preso come zona di riferimento; Perugia, la maggiore città dell'Umbria (circa 150.000 abitanti), con intenso traffico automobilistico; Deruta, paese in cui è fiorente la produzione di ceramica artistica. I livelli medi di piombemia sono risultati significativamente più alti nei bambini di Perugia (96 µg/l) e in quelli di Deruta (97 µg/l) rispetto a quelli di Corciano (83 µg/l); a Deruta i valori di piombemia più elevati si sono riscontrati nei bambini i cui familiari erano professionalmente esposti a piombo (107 µg/l). Nell'aria di Deruta la concentrazione di piombo è risultata significativamente più alta rispetto a Corciano (0,19* vs *0,11 µg/m³). Nella polvere di casa la concentrazione di piombo era più elevata a Deruta (2,8 µg/m²) che a Corciano (0,8 µg/m²) e la differenza era più marcata per le abitazioni degli esposti a piombo in fabbrica (2,7 µg/m²) o in laboratori annessi all'abitazione (4,7 µg/m²). I livelli di piombemia dei bambini ottenuti in questo studio sono stati confrontati con quelli ottenuti nel corso di una simile indagine nel 1978. In questi otto anni nei bambini delle scuole elementari di Corciano e di Deruta si è avuta una nettissima riduzione dei valori di piombemia (> 50%). Il miglioramento dimostrato non deve indurre ad un facile ottimismo: infatti è impossibile stabilire il livello di piombemia che sicuramente non provoca effetti avversi all'organismo, specialmente nei bambini. Numerosi studi suggeriscono che anche livelli subclinici di piombemia possono indurre alterazioni della sintesi dell'eme, del sistema nervoso periferico, del rene, del sistema immunologico, dell'apparato scheletrico e della crescita. Inoltre, a carico del SNC, bassi livelli di piombemia possono provocare deficit neuropsicologici, rappresentati soprattutto da una diminuzione dell'I.Q. e da alterazioni comportamentali.*

Introduction

Lead is an element that is widely distributed in the biosphere [1]; in the prehistoric age traces of lead deriving from the "natural" mobilization from the earth's crust were already detectable in the environment [2]. Man's discovery of the metal, its mining and processing date back several centuries [3]; its usage increased considerably during the Industrial Revolution, in the second half of the Eighteenth Century and even more so after 1920, when tetraethyl lead was introduced as an anti-knock in petrol. At present, lead is employed in a large number of industrial and artisan activities such as making batteries, bullets, cables, collapsible tubes, lead alkyls, white lead and many others. The ever-widening use of lead, as anti-knock in petrol and in industries, may cause widespread environmental contamination mainly in areas closest to the sources of pollution. Man can absorb lead from air, water and food [4]. Whatever the origin is, lead particles deposit on the earth surface and on vegetables and may reach man directly (i.e. through vegetables and fruit) or indirectly, by eating meat of animals coming from polluted areas. An increased lead content in foodstuff may be due to the conservation in improperly soldered cans and, occasionally, the cooking and storage of acidic food in lead-glazed pottery, which has not been fired at a high temperature. With respect to the adult population, children are at a greater risk; they have more numerous sources of exposure to lead, more chances of ingestion due to their behaviour and a greater susceptibility to the poison [5-8].

Sources of exposure and children's susceptibility to lead. Some epidemiological data

Lead exposure begins already before birth; during gestation the fetus is exposed to a lead concentration that is very close to that in maternal blood as the poison can cross the placental barrier [9-10].

This is a very important issue considering that young women can be occupationally exposed to lead in a large variety of activities. Moreover, the fetus seems to be particularly susceptible to the effects of lead during the phase of rapid growth [1]. The newborn can ingest lead through the maternal milk which contains one tenth of the blood lead concentration and, although less frequently in developed countries, through dried-milk preserved in cans welded with lead alloys or dissolved in contaminated water [11].

In young children ingestion is the principal route of lead absorption whereas inhalation is of minor importance. Lead exposure is mainly due to typical behaviour of the age group (in particular between 6 and 18 months); at this time children's hand to mouth activity is very common and in some cases may assume the configuration of pica ("indiscriminate ingestion of non-food substances") [12]. A great number of sources are possible; the most important include dust and soil contaminated by automotive exhaust or industrial emissions. In some industrial areas such as El Paso (USA) or Port Pirie (Australia), sites of large and long-standing lead-smelting facilities, an extensive environmental contamination with lead has been shown, reaching levels of 2000 ppm or more in the dust [13-14]. It has been estimated that each increase of 100 ppm in the lead content of surface soil, above a level of 500 ppm, is associated with a mean increase in children's whole blood lead levels of 10 to 20 µg/l. A number of cases of lead poisoning have also been described in children having parents or cohabitants working with lead either at home (batteries, ceramics) or in plants (foundries, battery factories), as they can bring lead at home on hair, skin and clothing [15-16].

In some countries relevant risks are related to local situations. In the USA the most important risk of undue lead absorption, for preschool children, remains [17] the ingestion of lead paint chips, deriving from the deterioration of the interior and exterior surfaces of the houses. Even the improper deleading of these surfaces for preventive purposes has been demonstrated to be dangerous [18].

Less common lead sources are indoor hobbies, implying the utilization of lead compounds (i.e. ceramics), old toys and furniture, some cosmetics from Asia, containing white lead or lead sulfide, imported food contained in improperly soldered cans [17].

The high susceptibility of children to the toxic effect of lead is due to several factors [12, 19]. They have a high intestinal absorption of the metal (about 50% of the ingested quota, whereas in adults it is about 10%), immature enzymatic systems and blood brain barrier, and a typical distribution of the poison. In the growing organism the compact bone is by percent lower than in adults [20]; therefore, there is a larger labile pool and a greater possibility for lead of reaching dangerous concentrations in target organs. Finally, there are several animal and human studies demonstrating that deficiencies in iron, proteins, calcium and zinc, relatively common in childhood, can increase lead toxicity [21].

For many decades pediatric lead poisoning has been considered, expecially in USA, a health problem confined to poorest children, living in the slums of the biggest towns [22]. It was believed that the main reason for the increased lead absorption was the ingestion of lead paint chips, deriving from the interior and exterior surfaces of old houses. However, many recent studies demonstrated increased blood lead levels also in children living in small towns [23], in polluted areas surrounding plants and mines [13, 24-26], in regions where the water supply pipelines are made of lead [27-28]. Data obtained from National Health and Nutrition Examination Survey (NHANES II) [29] allow one to estimate that between 1976 and 1980 about 675,000 children in USA, aged 6 months to 5 years, had a blood lead level higher than 290 µg/l and in about 1.5 million the CDC (Center for Disease Control) limit of 240 µg/l [30] was overstepped [31]. This data might induce a pessimistic view; this is not the case. In fact, over recent years a consistent reduction of blood lead values has been reported, both in adult people and in children, in different countries. In the United States, Annest *et al.* [32] studied 27,800 people aged 6 months to 74 years and demonstrated a 37% blood lead reduction between 1976 and 1980; in children younger than 5 years the overall decrease was 41-42%. In Boston, in the period 1979-1981, Rabinowitz *et al.* [33] observed an 11% decrease of lead level in blood sampled from umbelical cord. Also in more homogeneous populations such as Sweden similar results were obtained [34-35].

In Italy, pediatric lead poisoning does not seem to be a major health problem, even though several researchers have demonstrated, in different areas, the existence of conditions causing an increased lead absorption in children [36-39].

Lead absorption in children living in Umbria. Comparison of 1978-1986 blood lead levels

In 1978, a survey performed by our group in Umbria (a region in central Italy) showed that primary school children, living in an area with a high concentration of pottery factories (Deruta), had higher blood lead levels than children living in a medium size city (Terni) or in a small town (Corciano), without any known source of environmental pollution [39].

In 1986 we carried out a new survey with the following aims:

a) to examine the blood lead levels of nursery and primary school children living in three different communities and the possible influence of parents' occupation and environmental pollution on these levels;

b) to analyze environmental and domestic lead pollution in two small towns, one of which with a high concentration of ceramic workshops;

c) to ascertain the variation of blood lead levels in children of the same areas over a 8-year period.

Children living in three different communities in Umbria were examined. The communities were Corciano, Perugia and Deruta. Corciano was designated as control area; it has 12,500 inhabitants, with an essentially rural economy, far from heavy traffic roads. Perugia was chosen to verify the effect of pollution caused by traffic in a medium size city (146,500 inhabitants in June 1986) on children blood lead levels. Deruta was chosen to evaluate whether a large gathering of small ceramic plants and workshops could be responsible for an increased lead absorption in resident children; we also wanted to study the importance of parents' and cohabitants' occupations. Deruta is a small community (7500 inhabitants) with an economy based mainly on the production of ornamental ceramic handicrafts and pottery; work is mainly performed in small factories, next to the houses or even in the houses themselves, where laboratories are usually located on the ground floor, while artisans' families live on the upper floors.

All the children attending nursery and primary school in Corciano and Deruta were enrolled in the study. In Perugia the children were attending one nursery school and one section of a primary school, located in the old part of the town. Children participating in the study were living in the urban area of the town, where there are neither industrial plants nor other known sources of lead pollution other than traffic.

None of the parents or cohabitants of children from Corciano or Perugia were occupationally exposed to lead. Deruta children were divided into two classes: with (Deruta I) or without (Deruta II) parents or cohabitants working on ceramic plants or workshops next to or in the houses.

Methods for lead determination in blood and environment are described in detail elsewhere [40].

The study concerned 539 children (275 males and 264 females) aged 3-12 years. Among them, 156 attended nursery school (infant school) and 383 attended primary school.

In the total population mean blood lead levels were slightly higher in males than in females; this difference was more relevant in children living in Perugia (102 μg/l *vs* 89 μg/l) than in children living in Deruta (101 μg/l *vs* 93 μg/l) or in Corciano (86 μg/l *vs* 80 μg/l). However, as the difference was negligible and the sex distribution very similar in the three groups, the results obtained in both males and females were pooled and analyzed together. No differences were found in mean lead blood levels between nursery school and primary school children. Consequently, children of different ages, living in each town, were considered as a single population.

Mean blood lead levels of children living in Perugia, Corciano and Deruta are shown in Table 1. Values are significantly higher in children living in Deruta ($p < 0.05$) and in Perugia ($p < 0.05$) in comparison with children living in Corciano. No difference was found between children living in Deruta and children living in Perugia.

Table 2 reports the influence of the parents' and cohabitants' occupation on blood lead levels of children living in Deruta. Children whose relatives were not occupationally exposed to inorganic lead (named Deruta I group) had blood lead levels similar to children living in Corciano. In contrast, in children belonging to Deruta II group, who had relatives occupationally exposed to inorganic lead, blood lead levels were significantly higher in comparison to Corciano children. Furthermore, the mean blood lead levels of Deruta I group children was significantly lower than values in Deruta II group (90 μg/l *vs* 107 μg/l, $p < 0.05$).

The analysis of lead concentration in the air in Corciano and Deruta (Table 3) showed very low values. In Corciano the geometric average of 21 samples was 0.11 μg/m^3 (SD = 0.02). In Deruta three different air-sampling positions were set up; in all of them the geometric mean of samples was in any case higher than the value recorded in Corciano. Moreover, the mean value obtained considering the samples all together (A + B + C) was significantly higher than the value observed in Corciano ($p < 0.05$).

Table 4 shows the mean concentrations of lead in the dust collected from children's houses in Deruta and Corciano. In the Deruta houses considered all together, mean lead concentration in the dust was more prominent than in the Corciano houses ($p < 0.01$). This value was higher in the houses of children whose cohabitants worked in potte-

Table 1. - *Blood lead levels in children living in the communities of Corciano, Deruta and Perugia*

Community	Subjects n	Blood lead level (μg/l) mean ± SD	range
Corciano	88	83 *(a, b)* ± 19	40-130
Perugia	116	96 *(a)* ± 40	40-340
Deruta	335	97 *(b)* ± 36	40-310

(a, b) $p < 0.05$ (Scheffé's test for multiple comparison)

Table 2. - Blood lead levels in children living in the three areas. Deruta children are divided into two groups based on the relatives' occupational lead exposure: Deruta I (not exposed) and Deruta II (exposed in ceramic plants or in workshops next to or in the houses)

Community	Subjects n	Blood lead level (µg/l) mean ± SD	range
Corciano	88	83 *(a,b)* ± 19	40-130
Perugia	116	96 *(a)* ± 40	40-340
Deruta I	199	90 *(c)* ± 30	40-230
Deruta II	136	107 *(b, c)* ± 41	40-310

(a, b, c) $p < 0.05$ (Scheffé's test for multiple comparison)

Table 3. - *Lead content in the ambient air in Corciano and in three different sites in Deruta (A, B, C)*

Community	Samples n	Lead (µg/m³) geometric mean ± SD
Corciano	21	0.11 *(a, b)* ± 0.02
Deruta A	22	0.17 ± 0.01
Deruta B	20	0.22 *(a)* ± 0.02
Deruta C	19	0.17 ± 0.02
Deruta A + B + C	61	0.19 *(b)* ± 0.02

(a) $p < 0.01$; *(b)* $p < 0.05$

ry plants (Deruta IIa) ($p < 0.05$) or in pottery workshops next to or in the houses (Deruta IIb) ($p < 0.01$). No difference was observed in house dust lead between Corciano and Deruta houses where no ceramic workers were living. Similar results were obtained regarding the concentration of lead in the dust collected in the streets in Corciano and Deruta. In fact, the geometric mean of lead concentration in the dust sampled in several streets in the center of Deruta was 10.6 mg/m² (SD = 2.0) whereas in the center of Corciano the geometric mean was 5.8 mg/m² (SD = 3.8). However, this difference was not statistically significant. The evaluation of lead concentration in tap water in Corciano and Deruta showed very low values (well below 5 µg/l) and no significant difference between the two areas.

In this study children living in an area with a high production of pottery have been demonstrated to have an increased lead absorption in comparison to children living in a rural area; although the difference is small it is statistically significant. The analysis of the factors commonly held responsible for an increased lead absorption in children of this age (3 to 12 years old) [12, 19, 22, 41] did not show any important difference among the three communities studied. In fact, all the children participating in the study had a similar social status; they lived in houses built of stones or bricks; the internal surfaces of the houses were new or renewed in the last twenty years, after the prohibition of lead paints for interiors in Italy. Therefore, most causes of pediatric lead poisoning in the USA [12, 19, 22] can be ruled out considering our study population. Lead content in tap water is capable of increasing lead absorption in populations living in old towns [27-28]. In several samples of tap water from Corciano and Deruta lead concentration has always been reported below 5 µg/l; this value is about 10 times lower than the upper limit established by the European Economic Community (EEC) (50 µg/l) [42] and much lower than the levels found by Sartor *et al.* in Belgium [28] and Moore *et al.* in Scotland [27], in areas where water lead was believed to be an important factor of increased blood lead level in the population.

Both pica and abnormal hand-mouth activity have been denied by parents of all the children admitted to the study. It is possible that the low incidence of these habits is related to the age of the children examined as both pica and hand-mouth activity are more common in younger children [12].

Lead derived from automotive gasoline emissions might be an important risk of pollution and lead exposure not only in big towns [43], but also in small communities [23]. Blood lead levels in children living in the town of Perugia are slightly, though significantly, higher than in children living in Corciano (90 µg/l *vs* 83 µg/l). In the urban area of Perugia, where all the children who have been studied live, the traffic is much heavier than in Corciano, a small town of 12,500 inhabitants, far from highways, and this can explain the difference between children's blood lead levels in Perugia and Corciano. The children who live in Deruta and whose family members are not exposed to lead (Deruta I) have blood lead levels slightly, but not significantly, higher than those in Corciano (90 and 83 µg/l, respectively). These data suggest that if there is environmental lead pollution in Deruta, caused by many small ceramic plants in the urban center, it is only of a moderate degree and not enough to clearly and significantly influence the blood lead levels of the resident children. This has been demonstrated by the environmental study: the lead concentrations in street dust in Deruta and house dust in the Deruta I group are slightly, but not significantly, higher than those in Corciano; the concentration of the metal in the air in Deruta (0.19 µg/m³) is well below the referred italian limit (2 µg/m³), although significantly higher than in Corciano (0.11 µg/m³). The higher blood lead levels in children of Deruta II group, in comparison to Deruta I children, can be explained taking into consideration that the former group has an additional source of lead, represented by their parents or cohabitants occupationally exposed to the element; they, in fact, can carry lead at home by hair, skin and clothing as already shown by Baker *et al.* [15] and Dolcourt *et al.* [44]. This is supported in our study by the results of lead concentration in house dust that show higher values in the houses of children having parents working in ceramic plants (Deruta IIa) or in workshops

Table 4. - *Lead content in house dust in Corciano and Deruta. Deruta houses are divided into three groups based on the relatives' occupational lead exposure: Deruta I (not exposed), Deruta IIa (exposed in ceramic plants), Deruta IIb (exposed in workshops next to or in the houses)*

Community	Rooms (*) (houses) n	Lead (μg/m²) geometric mean ± SD		range	median
Corciano	10 (4)	0.8 *(a, b, c)*	± 3.8	0.1-3.6	1.1
Deruta I	9 (4)	1.8	± 3.6	0.2-15.5	1.3
" IIa	17 (8)	2.7 *(c)*	± 2.1	0.6-8.0	3.2
" IIb	10 (5)	4.7 *(b)*	± 1.7	2.0-8.3	5.8
Deruta I + IIa + IIb	36 (17)	2.8 *(a)*	± 2.5	0.2-15.5	3.2

(a, b) $p < 0.01$; *(c)* $p < 0.05$
(*) = number of rooms sampled for dust; the number of houses is in brackets

next to or inside the houses (Deruta IIb). Moreover, the permanence of children in the workshops where glazing and decoration of pottery is performed, can be another important additional source of lead absorption.

In Table 5 mean blood lead levels of primary school children from Corciano and Deruta are compared to the values obtained in the 1978 study [39]. In the 8 year period a clear reduction of blood lead levels is evident, both in Corciano (- 53.5%) and in Deruta (- 61.9%) children. The evaluation of the gasoline usage in Umbria, in the period 1978-1985, did not show any significant variation. However, the amount of lead as anti-knock agent has been estimated from us to have been reduced of more than 30% in the same period (data kindly provided from AGIP Company), as a consequence of a law decree.

Therefore, the reduction in blood lead levels of children examined by us might be at least partially explained by the reduction of environmental pollution. This is in agreement with observations in other countries [32-35].

Adverse biological effects of low lead exposure

Lead is a non-essential element that has no biological value, and is, in fact, highly toxic. In 1965 Patterson [2] examined environmental contamination of lead from natural mobilization and absorption from food, water and air by humans. He estimated that 2 mg/kg body weight could be considered the "natural" amount of lead (in humans not exposed to the environmental redistribution of lead, caused by human activities) to be found in the body, and 2 μg/l the natural concentration in blood. Subsequent studies have shown that the concentrations of lead in compact bone (an organ of elective deposit of the metal) in the American and English populations is presently 500 times higher than that of the Peruvians who lived 1600 years ago [45]. Furthermore, the levels of lead are much lower in populations who live in areas far from modern civilization [46].

Although it is not possible to experimentally establish at what level the "natural" biological interaction between lead and the living organism occurs, there is much evidence which indicates that very low levels of lead, such as those that can be found in the general population, can produce adverse effects, especially in infancy. The most widely known adverse biological effect of lead is definitely on the synthesis of heme. In 1970 Hernberg and Nikkanen [47] demonstrated that at blood lead levels found in the general population there is a reduction in the activity of the erythrocyte enzyme δ-aminolevulinic acid dehydratase (AlaD). They showed that the inhibition of the enzyme was directly proportional to the blood lead concentration and that, in the samples examined, there were no blood lead levels that did not cause an inhibition. Subsequent observations confirmed the increased inhibition of the enzyme to higher exposure to lead, the lack of an apparent threshold and a secondary exponential increase of urinary excretion of δ-aminolevulinic acid [48-49]. Fifty percent of inhibition of the enzyme is observed at blood lead levels of 167 μg/l and ninety percent inhibition is evident at levels of 555 μg/l. Furthermore, a significant increase of the AlaD activity is induced by chelation therapy [50]. Lead interferes with the biosynthesis of heme also at other levels, in particular on the incorporation of iron into the complete protoporphyrin molecule. This last stage of heme synthesis takes place in the mitochondria and is catalyzed by the enzyme ferrochelatase located in the inner cristae. An increase in the erythrocyte porphyrines (EP), an expression of a reduced utilization of this substrate for heme synthesis, is observed at low blood lead levels. Piomelli *et al.* [51] have used appropriate techniques to evaluate the existence of threshold levels for this effect in a wide population of urban children. They obtained clear indications that an increase of EP in children occurred at blood lead levels between 150 and 180 μg/l with a mean estimated level of 165 μg/l. This effect remained more or less unvaried even when the other parameters capable of increasing the EP levels were considered, such as a defi-

Table 5. - *Blood lead levels in primary school children living in Corciano and Deruta, recorded in 1978 and 1986*

Community		1978 Subjects n	1978 Blood lead level (µg/l) mean ± SD	1986 Subjects n	1986 Blood lead level (µg/l) mean ± SD
Corciano	Males	64	189 ± 37	26	91 ± 21
	Females	45	185 ± 29	21	82 ± 21
Deruta	Males	106	253 ± 77	136	101 ± 38
	Females	70	238 ± 69	130	94 ± 32

ciency of iron, in children younger than 2 years of age. Similar effects on the synthesis of heme have also been demonstrated by Rogan *et al.* [52], even though this study seems to point out a different individual sensitivity to the action of lead on the biosynthesis of heme. It is obviously important to note that although the damage to the mytochondrial function has been shown in erythrocytes, the action of lead on the synthesis of heme does not only occur in bone marrow, but in all tissues in which heme is the prosthetic group of the cytochrome system [50-51].

An important subclinical effect of lead in children is that it occurs at the cortical level of the kidney and is correlated to calcium metabolism. Some studies [53, 54] indicate that the ions of the metal reduce the transformation of the 25-hydroxyvitamin D (25-OHD) in 1,25-dihydroxyvitamin D [1,25-(OH)2D], the biologically active form of vitamin D, which stimulates the intestinal absorption of calcium, phosphorus and lead also. The kidney is recognized as being an important target organ for lead at high concentrations. However, among children with blood lead levels between 120 and 590 µg/l a significant negative association with serum 1,25-$(OH)_2D$ occurs [53], even though neither precise dose-effect curve nor a threshold level for this effect has been established.

It is still not sufficiently clear whether there is a correlation between exposure to lead and children's body growth. Impaired growth in children with increased blood lead levels is generally attributed to malnutrition or nutritional deficiences. When the influence of blood lead levels in the range of 50 to 350 µg/l on height, weight and chest circumference was examined [55] a significant negative correlation was found. This was independent from other considered variables that influenced growth such as sex, race, total dietary proteins or calories, hematocrit and transferrin saturation levels, suggesting the possibility of a direct biologic effect of low-level lead exposure on the growth of children [55]. General mechanisms might be mentioned to explain the interference of low blood lead levels with growth; for example the interaction of lead with reactions mediated by calcium as a second messenger [56-58], the decrease in heme-dependent enzymes [54, 59, 60], the possible inhibition of dopaminergic and adrenergic receptors in the hypothalamus [61-65], leading to neuroendocrine dysfunctions [66].

A very critical issue is represented by the effects of low lead levels in the fetus. The hypothesis that lead may cause intrauterine growth retardation [67-69], obstetric complications [67] or congenital anomalies [70] has not found convincing support in human studies. Only minor neonatal anomalies [71] have been reported in one study, but these have not been confirmed [72].

Another source of considerable debate in the last ten years has been the question whether or not blood lead levels considered safe are able to cause alterations in the nervous system. In children a negative relationship has been observed between blood lead levels and maximal motor nerve conduction velocity (MMNCV); Feldman *et al.* [73] and Landrigan *et al.* [74] demonstrated slowed nerve conduction in the absence of clinically detectable neuropathy; the relationship is not influenced by age, sex, residence or economic factors but it becomes negligible at blood lead levels lower than 200 µg/l [75]. The evidence of a possible threshold for this effect might be linked to the studied parameter (i.e. MMNCV) that is not well suited for detecting minor abnormalities in the peripheral nervous system (PNS). The central nervous system (CNS) has been demonstrated to be more vulnerable to lead than the PNS is [76]. Blood lead levels of 150 µg/l and below have been associated with impairment in early cognitive development, changes in cortical activity during sensory conditioning, alterations in brainstem auditory evoked potentials and impaired neurobehavioral function [77-81].

The last issue deserves a great deal of attention and consideration as pointed out by many recently performed studies. In fact, neurotoxic properties of lead at high dose are dramatic and well known, but symptoms of milder intoxications are not patent and a neuropsychologic impairment might be hard to discover. Several methodological difficulties have been shown as conditioning the frequent discrepancies observed in the results of different studies; among them inadequate markers of exposure to lead, selection bias, insufficient identification and handling of confounding variables, insufficient measures of performance [41]. An attempt to overcome the divergencies of previous studies, adopting a presumably more correct methodology, has been made by Needleman *et al.* [41]. They assumed dentine lead levels as a parameter for measuring protracted exposure to the metal and found that, in the USA, urban children with higher dentine lead levels obtained a lower score in the execution of tests evaluating intelligence, verbal, auditory or speech processing, attention and classroom behaviour. Cross sectional studies subsequently performed in Europe were not able to demonstrate a significant association between moderate elevation in body lead burden and deficits in IQ (intelligence quotient) [82-85], expecially when socio-economical factors were considered in the analysis [86-87]. Pocock *et al.* [87], in a recent evaluation of the results of a large cross-sectional survey of lead exposure and children's intelligence, found that parental IQ was the most prominent influence on child IQ; also other socio-economic factors had some importance (i.e family size, social class and quality of marital relationships). On the contrary, the influence of tooth lead concentrations on IQ was negligible once the other factors were taken into account. In 1987 Fulton *et al.* [88] examined a large sample of children living in Edinburgh, an area having lead-rich water supply and a high number of houses with lead plumbing. Children were 6 to 9 years old and had a mean blood-lead value of 104 µg/l; a significant relationship was shown between tests of ability and attainment and blood lead, even though the effect of lead was small in comparison to other variables. In this study a dose-response relationship was found with no evidence of a threshold.

However, the cross-sectional approach seemed to have low power besides several methodological difficulties [86, 89]; thus prospective studies were undertaken with the aim of obtaining a better evaluation of lead exposure since early stages of life and various measurements of children's development over subsequent years [77]. In Boston Bellinger *et al.* [77] found an inverse relationship between lead concentration in umbilical-cord blood, expecially in the range of 60 to 210 µg/l, and cognitive development assessed at 6, 12 and 24 months of age. At no age were scores significantly related to postnatal blood lead levels. An inverse relationship between both prenatal and neonatal blood lead levels (always lower than 300 µg/l) and performance on the Bayley Mental Developmental Index has also been described by Dietrich in Cincinnati area [90]. More recently, in the Port Pirie Cohort Study [89], the effect of environmental lead exposure on children's abilities at the age of four years has been evaluated. Prenatal blood samples have been obtained from the mothers at specified times during pregnancy and from each child at delivery (umbilical-cord blood) and at ages of 6, 15, 24 months and annually thereafter. In this group of children there was an inverse relation between the blood lead concentration in the obtained samples and the measures of cognitive functioning at four years. The integrated postnatal average blood lead concentration was 189 µg/l. This parameter of cumulative burden of body lead demonstrated the strong inverse relationship with the General Cognitive Index, which evaluates the age-specific cognitive functioning. This finding suggests that the adverse effect of exposure to lead on mental development is cumulative during early childhood. Moreover, no indication has been obtained of the existence of a clear threshold below which an adverse effect on mental development does not occur.

Conclusions

Even though lead has been utilized by man for many centuries and might have contributed to events that changed the course of history, such as the decline of the Roman Empire [91], it is still a central topic in discussions on environmental and occupational health. In the last decades the possibility of exploring the functions of biologic systems by very sophisticated and sensitive methods has allowed an impressive and progressive lowering of the safety limits of exposure. For the protection of children health limits of 600 µg/l of blood lead levels were considered safe in the '60s [92]; subsequently new limits have been established at 400 [93], 290 [94, 95] and 240 µg/l [17, 30].

However, many studies performed in different countries suggest that the adverse biologic effects in children may be demonstrated at lower absorption levels. In fact, besides the better known action on heme synthesis, the kidney, peripheral nervous system and central nervous system are also clearly impaired at blood lead levels between 150 and 300 µg/l. More importantly, for some of the CNS effects, a dose-dependent relationship has been found but not a threshold.

Taking into account that lead can cause very serious effects on the children's health, on the family and on the society, a series of recommendations are periodically formulated by different institutions.

The American Academy of Pediatrics Committee on the Environmental Hazards [17] based its suggestions on the knowledge that a) exposure to lead is widespread; b) lead causes serious impairment in children at relatively low levels of exposure; and c) the neuropsychologic effects are largely irreversible. The Academy recommends using erythrocyte protoporphyrin test to screen preschool children for lead toxicity and subclinical iron deficiency, starting between 9 and 15 months of age and continuing up to 6 years.

Our study confirms that also in Italy there are areas at greater risk of lead absorption for children, even though a reduction of blood lead levels has been observed over the last years, as documented in other countries. The lack of adequate information on the amount of lead absorption which does not produce adverse health effects should urge researchers and Health Authorities to extend the survey with the purpose of identifying and eliminating the sources of risk.

In fact, an abatement of environmental sources of lead is judged essential, together with the identification and correction of all predisposing factors for lead poisoning. Finally, it is important to educate the population, particularly the parents of children in the higher risk groups.

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