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An Assessment of the Hazards of Lead in Food

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Exposure to lead (Pb) continues to be a source of concern for the U.S. Food and Drug Administration and other federal regulatory agencies. Blood lead levels as low as 10 μg Pb/dl have been associated with impaired neurobehavioral development in children and infants. Because of exposure to the fetus, blood lead levels of 10 μg Pb/dl are also of concern in pregnant women. Blood lead levels of 30 μg Pb/dl have been associated with elevated blood pressure and other adverse effects in adults. The dietary exposure that results in these blood levels of concern were estimated to be 60 μg Pb/day for children age 6 years or younger, 150 μg Pb/day for children age 7 years or older, 250 μg Pb/day for pregnant women, and 750 μg Pb/day for adults. A provisional tolerable total dietary intake was derived by applying a factor of 10 to obtain an exposure level that would include some margin of safety.

INTRODUCTION

The concern within federal regulatory agencies that led to the ban or restriction on the use of lead in gasoline and paint in the early 1970s has continued because of observations of adverse effects at decreasing levels of lead exposure. Only 5 years ago the main source of exposure to lead for most individuals was considered to be the diet (U.S. EPA, 1986). However, the effort made by the U.S. Food and Drug Administration (FDA) to reduce dietary exposure to lead, largely through the reduction in the use of lead solder in cans (Bolger *et al.,* 1991), has made diet a minor contributor to the total lead exposure of most of the population. Nonetheless, dietary lead is a major source of lead exposure for some individuals and a contributor to an overall lead exposure problem among the entire population. Therefore, the FDA is continuing its efforts to limit exposure to lead.

Adverse Health Effects of Lead

Lead is known to affect a number of different biochemical and physiological processes, cell types, tissues, and organ systems. The primary targets for the toxicity of lead include the red blood cells and their stem cells, the central and peripheral nervous

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system, and the kidneys. During the past decade, levels of exposure to lead that were once thought not to pose a hazard have since been shown to elicit deleterious effects. In addition, lead may affect the neurobehavioral development of newborns, infants, and children exposed to lead either *in utero* or postnatally. Other effects noted at low exposure levels include effects on heme biosynthesis and vitamin D metabolism.

The index of lead exposure most frequently cited is that of blood lead, which is used as a co-index for acute exposure to lead along with blood erythrocyte protoporphyrin levels. Lead levels in teeth and bone have also been used and may be more indicative of cumulative exposure. However, because of the much greater ease in obtaining and analyzing blood specimens, most studies involving large sample groups have relied on blood lead as a sole measure of exposure.

Children, infants, and fetuses. Fetuses, infants, and children are at particularly high risk. Studies on the effect of lead in children with blood lead levels in the range of 5–20 μg/dl have demonstrated a highly statistically significant correlation between blood lead level and performance in tests designed to measure cognitive function (Bellinger *et al.*, 1986a, 1986b; Needleman and Gatsonis, 1990; Winneke *et al.*, 1990). None of the available studies contain evidence of a threshold for the adverse effects of lead. They do indicate that a blood lead level as low as 10 μg/dl may be considered to be an effect level.

Because of the sensitivity of the fetus, particularly during the development of the nervous system, pregnant women as well as nonpregnant women of child-bearing age are of the greatest concern among the adult population. Umbilical cord levels as low as 10 μg Pb/dl in the fetus have been reported to adversely affect neurobehavioral development (Bellinger *et al.*, 1987). Although cord blood levels tend to be, on the average, about 20% lower than maternal blood levels (U.S. EPA, 1989), there is no clear evidence that the placenta represents a significant barrier to lead. Therefore, 10 μg Pb/dl may be considered to be an effect level for pregnant women as well.

Adults. Levels of 30 μg Pb/dl have been repeatedly associated with peripheral nerve dysfunction, red blood cell protoporphyrin elevation, and elevated blood pressure in adults (U.S. EPA, 1986; WHO, 1987). Higher blood lead levels (50–100 μg Pb/dl) have been associated with adverse effects on central nervous system function, chronic renal failure, reproductive dysfunction in males and females, and anemia. Several studies have found correlations between elevated blood pressure and blood lead levels below 30 μg/dl (Pirkle *et al.*, 1985; Weiss *et al.*, 1986; Sharp *et al.*, 1989). However, in a large study of adult males, a relationship between blood lead and hypertension could be observed only at levels of 37 μg Pb/dl or higher (Pocock *et al.*, 1984). The higher incidence of hypertensive disease in workers with occupational exposure to lead (Selevan *et al.*, 1985) and of elevated blood pressure in laboratory animals exposed to lead (Victery, 1988) indicates that hypertension results from high blood lead levels, rather than the converse. Thus, the weight of the evidence indicates that a blood lead level of 30 μg/dl in adults results in a significant elevation in blood pressure that may be expected to increase the incidence of hypertension-related diseases such as stroke and heart disease.

Lead Ingestion and Blood Lead Levels

Infants, young children, and adults. The relationship between lead ingestion and blood lead levels in children and adults has been estimated to be 0.16 and 0.04 μg

Pb/dl blood per microgram of lead ingested per day, respectively (U.S. EPA, 1986). These conversion factors are appropriate for predicted blood levels at relatively low levels of ingestion that result in blood levels of up to 10 μg Pb/dl in children and 30 μg Pb/dl in adults. Higher exposures result in considerably lower proportional increments in blood lead concentration (U.S. EPA, 1989). However, because the primary concern about lead exposure from foods involves relatively low exposures, the conversion factors for low-level exposures are appropriate for limiting dietary intake of lead. These values, which relate dietary exposure to lead with internal blood levels, are empirically derived and do not consider variation in lead absorption due to sex or diet (Mahaffey, 1985). We used these conversion factors to derive dietary effect levels for children, pregnant women, and adults (Table 1).

Older children. The 0.16 factor used to calculate blood lead from daily intake for children and most of the other data relating lead intake to blood lead levels have been derived from studies on infants. However, because of changes in body weight and other pharmacokinetic parameters, the quantitative relationship between lead intake and blood lead levels may be expected to change with age, with the appropriate conversion factor eventually decreasing to 0.04 for adults. We predicted the dietary intakes that will result in a blood lead level of 10 μg/dl by using two different estimates for the rate of absorption (Table 2). For the first estimate, we assume that a rate of 48% absorption from the gastrointestinal tract, which is an average value from studies in infants, is also applicable to older children. For the second estimate, we assume that there is a graded decrease in absorption with age in which the rate of absorption is prorated on the basis of growth rate to account for the decrease to an average of 11% absorption for adults. These estimates were attained by using values generated by a pharmacokinetic model developed under contract to the EPA (Harley and Kneip, 1985; U.S. EPA, 1989).

The dietary intake values predicted by using a 48% absorption rate for people of all ages is close to the 60 μg/day value obtained with the 0.16 conversion factor, with a slightly lower value predicted for children ages 2–7 years and a slightly higher value for infants and children age 8+ years. Even if adjustments are made for changes in the rate of absorption that may be expected with development, a dietary lead intake of 60 μg/day may still reasonably be considered as an effect level for children ages 0–6 years. For older children, however, the available data indicate that a much larger ingestion rate (150–200 μg Pb/day) would be required to produce the same blood level. However, there are no empirical data to verify this prediction.

Pregnant women and fetal exposure. A number of physiological changes occur during pregnancy. Because lead is known to be distributed, at least in part, through the same

TABLE 1

EMPIRICALLY DERIVED DIETARY EFFECT LEVELS

Population	Blood lead effect level (μg Pb/dl)	Conversion factor	Derived dietary effect level (μg Pb/day)
Children	10	0.16	60
Pregnant women	10	0.04	250
Adults	30	0.04	750

TABLE 2

PREDICTED DIETARY INTAKES THAT RESULT IN 10 μg Pb/dl IN BLOOD OF CHILDREN AT VARIOUS AGES

	Dietary intake[a,b]		
Age (years)	No growth[c]	Growth	Empirical
1	71 (48)	71 (48)	60
2	48 (48)	48 (48)	—
3	52 (48)	71 (35)	—
4	52 (48)	71 (35)	—
5	54 (48)	74 (35)	—
6	54 (48)	74 (35)	—
7	58 (48)	133 (21)	—
8	77 (48)	176 (21)	—
9	94 (48)	214 (21)	—
10	79 (48)	181 (21)	—
Adult	— (11)	— (11)	250

[a] All dietary intake values are in μg/day. The absorption percentages used to calculate the intakes are given in parentheses. Dietary intake values are calculated from model-generated uptake values using the following equation: intake = uptake ÷ percentage absorption.

[b] The uptake (μg/day) is based on the Harley and Kneip (1985) pharmacokinetic model and reflects the amount of lead absorbed daily from the gastrointestinal tract, where uptake = intake × percentage absorption. The values estimated for children ages 1–10 years were 34, 23, 25, 25, 26, 25, 25, 28, 37, 45, and 38, respectively. The following is an example of the calculated intake for children age 1 year: 34 μg/day ÷ 0.48 = 71 μg/day.

[c] The "No growth" dietary intake value is calculated from the uptake value and assumes that the rate of lead absorption in older children is identical to the rate (48%) measured in infants. The "Growth" dietary intake value assumes that the absorption rate gradually decreases at a rate proportional to body weight until it reaches the adult value (11%). The empirical values are based on correlated measurements of dietary intakes and blood values in infants and adults. Empirical values are not available for children older than infants.

mechanisms that govern the distribution of calcium, the gestational changes that affect calcium may also be expected to affect lead. For instance, the fractional absorption of calcium from the gastrointestinal (GI) tract has been reported to increase by about 70% during pregnancy (Heaney and Skilman, 1971). Some, but not all, studies also indicate that the mobilization of calcium from bone increases during pregnancy. This increase may be due to a pregnancy-induced calcium deficiency. The same mechanism may also produce a higher blood lead level even with a constant lead uptake (Pitkin, 1985). Empirical evidence, however, indicates that blood lead levels in pregnant women are not significantly different from those of nonpregnant women and do not change appreciably during pregnancy (Gershanik *et al.*, 1974; Alexander and Delves, 1981). Thus, the physiological changes that occur during pregnancy do not seem to result in a net increase in maternal blood lead levels. One possible explanation is that any increases in calcium and lead uptake from bone or the GI tract are compensated by uptake by fetal tissues (e.g., bone stores). Therefore, the conversion factor derived from normal adults (0.04) may also be suitable for pregnant women for the purpose of limiting fetal exposure to lead.

Women of childbearing age and fetal exposure. Although no compelling evidence indicates that the mobilization of calcium, and therefore lead, from bone increases

during pregnancy (Pitkin, 1985), some release is normal. Under steady-state conditions, the release of lead from bone and soft tissue will be equal to the rate of uptake to these compartments from blood. The half-lives for the dissemination of lead from internal stores (40 days for soft tissue, several years for bone) are long enough that the release of lead from internal stores during at least the first 2 months following cessation of intake from a contaminated source will reflect prior exposure rather than current exposure.

Data concerning the distribution of lead to and from bone during pregnancy are not available. Using data obtained from adult males, Rabinowitz *et al.* (1976) estimated that the amount of lead released from bone and soft tissue under steady-state conditions is equal to about 20% of the daily lead uptake. If these values are assumed also to apply to women both before and during pregnancy, a steady-state blood lead level of 50 μg Pb/dl (10 μg Pb/dl ÷ 20%) would need to be maintained to produce bone lead levels that result in the release of enough lead to produce a blood lead level of 10 μg Pb/dl after exposure is terminated. For a hypothetical single-source pregestational lead exposure that is terminated on the onset of pregnancy, a daily intake of 1250 μg/day (50 μg Pb/dl ÷ 0.04 μg Pb/dl per μg/day) would be necessary to generate the fetal effect level. Because this is higher than the effect level for adults (750 μg Pb/day), a limit of lead intake that will protect the woman herself will also protect a developing fetus in a subsequent pregnancy. Therefore, nonpregnant women of child-bearing age may be considered along with other adults for the purpose of limiting lead intake.

Lactating women and infant exposure. Although there has been some concern that high lead exposure may occur through breast feeding, the available evidence indicates that lead levels in human milk are not significantly higher than those encountered in infant formula (Ryu *et al.*, 1983) and that blood lead levels in nursing infants are somewhat less than maternal blood lead levels (Wolff, 1983). Rockway *et al.* (1984) found mean lead levels <3 ng/ml in breast milk in a population with a mean maternal blood level >11 μg/dl. Furthermore, there was no significant correlation between maternal blood and milk lead concentrations. We therefore conclude that there is no evidence to suggest that exposure to lead through nursing is a more significant route of exposure to maternal lead than when transfer occurs across the placenta. However, in the absence of data concerning the effects of high maternal lead intakes on nursing infants, a conservative approach would dictate that a standard set for pregnant women should also apply while the mother is nursing.

Provisional Tolerable Total Intake Levels for Lead

Provisional tolerable total intake levels for lead are presented in Table 3. These values were obtained by dividing the dietary effect levels identified above by a safety or uncertainty factor of 10. Because their derivation is based on the relationship between lead ingestion and blood lead level, these levels are applicable to dietary exposure only. The levels are provisional because safe levels of lead exposure have not been identified.

Based on the Food and Drug Administration's Total Diet Study, current dietary intakes of lead in various age groups have been estimated to range from 5 to 11 μg Pb/day (Bolger *et al.*, 1991). Other sources of exposure, particularly from soil and

TABLE 3

PROVISIONAL TOLERABLE TOTAL INTAKES OF LEAD FOR VARIOUS POPULATION GROUPS

Population	Effect level		Proposed provisional tolerable total intake level (μg Pb/day)
	Blood (μg Pb/day)	Diet (μg Pb/day)	
Young children (0–6 years)	10	60	6
Older children (7+ years)	10	150	15
Pregnant and lactating women	10	250	25
Adults	30	750	75

dust ingestion, contributions from housewares, and dietary sources not included in the Total Diet Study will add to this dietary exposure. Consequently, these provisional tolerable total intake levels for exposure (Table 3) are presently exceeded by most children and a significant portion of the adult population. Single sources of lead which may by themselves exceed a level of 75 μg/day in some adults include dust, drinking water, ceramicware, or wine (U.S. EPA, 1986, 1989). Whether the provisional tolerable total intakes are attainable or not, they represent levels at which some margin of safety would be reached.

A risk assessment must consider both toxicity and exposure. The main focus of this discussion pertains only to the hazards of lead without consideration of exposure. However, even without the contribution from the diet, lead exposure from dust may be expected to exceed the level of concern in a significant fraction of the population, particularly in young children (U.S. EPA, 1989). Any decision to limit exposure to lead from a particular source must consider the addition of that particular source to exposure from other nondietary and dietary sources. The provisional tolerable total intake levels do not account for exposures to lead that may be expected to occur from other sources. Therefore, these numbers will need to be adjusted downward to allow for other anticipated exposures to lead. Table 4 provides examples of levels that might be selected for an individual dietary source.

TABLE 4

EXEMPLARY ADJUSTED DIETARY LEAD INTAKES (μg/Day)[a]

	Provisional tolerable total dietary intake			
	10%	25%	50%	100%
Young children (0–6 years)	0.6	1.5	3	6
Older children (7+ years)	1.5	3.75	7.5	15
Pregnant and lactating women	2.5	6.25	12.5	25
Adults	7.5	18.75	37.5	75

[a] Lead intake at which various percentages of the provisional tolerable total dietary intake are equal in children, pregnant women, and adults.

CONCLUSIONS

For protection of young children from the toxic effects of lead, a Provisional Tolerable Total Dietary Intake of 6 μg/day was derived. For the protection of a fetus from the deleterious effects of lead, it was calculated that maternal consumption should be below 25 μg/day. Available information indicates that a daily intake of 75 μg/day may be considered tolerable for adults. The acceptable contribution of an individual dietary source to the total exposure must take into account the lead exposure that will occur from other dietary and nondietary sources.

The current best estimate of dietary intake of lead by children and adults is 5–11 μg/day. Additional exposure may be expected from dust, air, and housewares. Dietary exposure to lead continues to be a problem, particularly for children. Further efforts by the FDA to reduce dietary exposure to lead are justified.

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