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Quantities of Lead Producing Health Effects in Humans: Sources and Bioavailability

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Levels of lead ingestion and inhalation producing increased body burden of lead and clinical toxicity in adults and children are compared with usual levels of exposure. The magnitude of lead exposure from air, water, and food is estimated. Sources of high level exposure to lead are described; urban street dirt, house dust, and paint are particularly common sources of high concentrations of lead. The bioavailability of different lead compounds is reviewed as well as factors affecting susceptibility to lead.

Introduction

In the United States the majority of nonindustrial cases of lead intoxication occur in children between the ages of one and six years, with the highest incidence between two and three years. Ingestion of lead-containing paint is considered to be the most frequent cause of severe lead intoxication among children. This may indeed be the etiology of the most severe poisoning cases; however, other sources of lead have assumed increasing importance. Recent clinical and experimental evidence has been gathered which indicates that important adverse health effects occur at levels of lead exposure that produce blood lead concentrations considered harmless in earlier years.

A number of cases of lead poisoning also occur in adults; many of these either are the result of occupational exposure to lead or are connected with consumption of illicit liquor. Contamination of foods with lead from ceramic ware has produced fatal poisoning in children and adults.

The World Health Organization has established tolerable levels of intake of lead for adults (*1*). These levels include lead from all sources.

Currently, no finalized guidelines exist on permissible levels of lead exposure for children which consider the metabolic differences between children and adults.

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Sources of Lead

Usual Exposure

Air. Concentrations of lead in air vary widely. The range of concentrations of lead in air to which humans are exposed either among the general population or occupationally have been described in such documents as the National Academy of Sciences' publication (*2*). Quantities of lead absorbed via the lungs by humans depend on the concentrations of lead in the different environments through which a person passes in the course of a day, the volume of air respired per day, distribution of sizes of lead-containing particles, and physiological factors of an individual that affect the percentage of inhaled lead that is transferred across the alveolar membrane.

Although many measurements of atmospheric lead have been made, information of this type generally does not take into account the different environments a person enters during the course of the day. Estimates on the amount of air inhaled are reported (*3*) and range from approximately 4 m^3/day in the 1-year-old child to approximately 20 to 25 m^3/day in the adult. Estimates of the influence of particle size, distribution of particle size and individual physiological variables on the absorption of lead are described in the general literature (*2, 4*). Relatively little appears to be known about individual physiological differences or the reasons for

these differences. For example, it is not even known whether children retain a higher percentage of inhaled lead than adults do, as is the case with ingested lead.

Several studies have been carried out of the magnitude of change in blood lead of adults caused by changes in concentration of lead in inhaled air. Azar et al. (*5*) report that each 1 μg of Pb/m^3 of air contributes 0.3 μg Pb/100 g of blood at air Pb concentrations of 0.2 to 9 μg/m^3. Under experimental conditions Griffins et al. (*6*) calculated with 1 μg Pb/m^3 of air contributed 1.4 to 2.0 μg Pb/100 g of whole blood at air lead concentrations of 3.2 and 10.9 μg/m^3 of air. Recently Chamberlain et al. (*7*) have calculated from experimental results that 1 μg Pb/m^3 air contributes 1.2 μg Pb/100 g of blood. These results agree closely with the conclusions of a World Health Organization task force on the basis of analysis of occupational data that 1 μg Pb/m^3 of air contributes about 1 μg Pb/100 g of blood (*8*). Overall, it appears that 1 μg Pb/m^3 of air will increase the blood lead concentration of adults by approximately 1 μg Pb/dl whole blood when air Pb concentrations range from 1 to 5 μg/m^3. Such a relationship has not been defined for children.

Water. The Public Health Service standard of lead in drinking water in the United States is 50 μg Pb/l. water (*9*). Drinking water generally contains much less than this quantity; most water supplies contain less than 10 μg Pb/l. In certain geographic locations lead piping is still present in water distribution systems, and when lead carries water of low pH or certain organic content the lead concentrations of the water supply may be increased substantially. Although this type of pipe is of limited distribution today in the United States, it does occur, as shown in Boston by the studies of Greathouse, Craum, and Worth (*10*). In the Beacon Hill section of Boston, the tap water exceeded the Public Health Service standard of 0.05 mg/l. for lead in drinking water in 65% of the homes. Studies on health effects of lead from drinking water are reported from Vervier, Belgium (*11*) and Edinburgh, Scotland (*12*). Frequently, persons exposed to lead via drinking water are unaware of the problem.

Under usual circumstances water contains less than 10 μg Pb/l. The amount of water consumed varies according to age, season of the year, and amount of beverages consumed other than water. Estimates of water intake have ranged from 300 ml/day for children to as much as 2 liters/day for adults (*13*). Unless the lead concentration of the water is above the PHS Drinking Water Standard, even persons consuming large amounts of water are exposed to relatively little lead from this source.

Food. Tepper reported that the average adult diet contains approximately 100 to 140 μg lead/day (*14*). Recent reports on dietary lead content (*15*) indicate that the lead content of the diet of young adults generally averages 150–250 μg/day. Several recent reports on dietary lead intake for infants and young children indicate that average levels of ingestion usually are between 75 and 120 μg Pb/day. Kolbye et al. (*15*) calculated average dietary lead intake to be 90–120 μg Pb/day for 6-month-old children and 75 μg Pb/day for 2-year-old children. These 1974 estimates were based on average food intake determined by dietary survey data and average concentrations of lead in foods. In a study of food samples duplicating 24-hr food intake that were collected during an epidemiological survey of 6 to 47-month-old children in 1975, Mahaffey reported dietary Pb intake to range from 12 to 505 μg Pb/day, with a mean intake of 110 μg/day and a median intake of 76 μg/day. In 1976, a similar study indicated a range of 11 to 719 μg Pb/day with a mean intake of 115 μg/day and a median intake of 95 μg/day. Lead intake for the highest decile was 316 μg Pb/day (*13*).

In summary, at normal levels of lead exposure, food constitutes the major source of lead as compared to air and water. It is important to note that this distribution can change markedly if any of these sources are contaminated by high concentrations of lead. Average intake of lead from air, food, and water appears to be below quantities that are thought to produce adverse health effects. Currently our estimates of lead intake that occurs when either air, food or water is contaminated with lead or is consumed in large quantities are imprecise. Little is known of daily variation in intake.

Unusual Lead Exposure

Screening programs such as those conducted by the Center for Disease Control and state and community health departments report elevated blood lead concentrations among young children. Sources of high levels of lead exposure include paint, street dust or dirt and other sources such as putty or plaster. Existing case histories for individual children cite many varied sources of lead exposure. The relative importance of these sources for populations is yet to be defined. The presence of normal mouthing activity or of pica is required for certain of these sources of potential exposure to reach the child. Both mouthing of objects and pica, i.e., ingestion of nonfood substances, are common in children. Barltrop (*16*) reported that in a sample of children 12 to 72 months of age, 78% of the children had mouthed objects and 35% had ingested them. The

prevalence decreased with age, until at 4 to 5 years, 33% of children mouthed objects while 6% had pica. Other estimates suggest that approximately one half of all children 1 to 3 years old have pica (*17*). Lead-containing paint has been the cause of numerous cases of lead poisoning; this relationship is well documented (*18–23*). Many older paints, especially those made and used in the years before World War II, contained very high amounts of lead, often substantially in excess of 1%.

Over a number of years, levels of lead in paint have been reduced. A 1974 marketplace survey revealed that 70.8% of oil-based paints and 96.1% of water-based paints contained less than 0.06% lead (*2*). Recently, it has been recommended by the Committee on Toxicology of the Assembly of Life Sciences of the National Academy of Sciences that a maximum of 0.06% lead be permitted in paint. Changes in the lead content of paint sold in recent years and in the future will not remove the problem of lead-based paint in older housing. However, the lead content of paint has been reduced, and the trend for the future is one of reduced exposure to lead from paint.

Dust and certain soils contain high concentrations of lead. Numerous reports of several thousand parts per million of lead in dirt and dust have been published (*24*). Lepow et al. (*25*) report that urban household dust from a group of homes in Hartford, Connecticut, contained 11,000 ppm lead. Martin (*26*) has reported up to 50,000 ppm of Pb in environmental dust and soil near a lead works.

Several efforts have been made to investigate the quantities of lead that may be ingested via pica. The best clinical estimates suggest that a child with pica may eat 1 to 3 g of paint per week (*2*); however, there is no reason to assume that this is the maximal amount ingested (*17*). Estimates on amounts of soil or dirt consumed from pica would be purely speculative. If dirt or soil contained 5000 ppm Pb, consumption of slightly over 1 g of dirt or soil per week for several months would result in a level of lead ingestion that is consistent with development of clinical lead poisoning in a young child.

Transfer of lead to the hands of the child from dirt, dust, or soil has been investigated. Sayre et al. (*27*) report a clear increase in the amount of lead on children's hands with the amount of lead present in household dust. If dirt or dust in the child's environment contains high concentrations of lead, more lead is present on the hands or on objects that are handled and is available for ingestion via normal mouthing activities. Barltrop (*28*) has noted that the critical issues are how much lead is transferred to the child's mouth, where it comes from, and how it compares to the magnitude of other sources. Lepow et al. (*25*) found that mean lead concentrations of 2400 ppm could be removed from the hands of young children living in environments where outdoor dirt averaged 1200 ppm and household dust had a mean lead concentration of 11,000 ppm. Cleaning children's hands removed approximately 25 to 30 μg of lead per cleaning under conditions of the study. The actual quantity of lead ingested by the child from dust and dirt was not documented. However, at the lead concentrations of dust and soil present in these environments ingestion of only 100 mg of dust or 1 g of soil daily for several months would produce a lead intake consistent with the development of clinical lead poisoning. The children who were the subjects of this investigation had elevated blood lead concentrations (40 to 120 μg/dl) for a period of 6 to 24 months.

A number of additional sources of lead exposure have ben reported, ranging from inhalation of lead released from burning to paper logs in a fireplace (*29*) to ingestion of lead from foods contaminated by lead released from silver-plated holloware (*30*). Additional sources have included: colored newspaper (*31*), curtain weights (*32*), and lead-soldered electric water kettles (*33*). Certain pieces of ceramic dinnerware can release substantial quantities of lead if acidic food is stored in them for extended periods of time. Cases of fatal (*34*) and nonfatal (*35*) lead poisoning have been reported from this source. The number of persons affected by such products is thought to be much more limited than the number of persons exposed to lead from paint, dust, and soil. The more unusual sources arise from an unintended use of a product or from accidental contamination of products following changes in manufacture of the product or ingredients used in the product. Certain of these products, such as ceramic ware, are subject to regulations limiting the magnitude of lead exposure. In this case, adequate control over ceramic ware is the major problem, because of the large variety of individual products and limited resources for inspection. Sources of lead exposure such as colored newspapers have only recently been identified. As these sources of lead become known, they may become subject to regulation by agencies such as the Food and Drug Administration or the Consumer Product Safety Commission.

Lead Exposure in Adults

Usual Exposure

Several estimates have been made of common levels of lead exposure. Because gastrointestinal absorption of lead by adult subjects is only about 5–10%, fecal excretion provides a rough estimate of

intake. Kehoe (*36*) reported "normal" mean 24-hr fecal excretions of 230 ± 288 μg (S.D.) in a group of 453 subjects and 398 ± 310 μg (S.D.) in 102 others. In the former group, the majority of persons had fecal lead excretions of less than 200 μg/day. Blood lead concentrations were not reported. The individuals were active adults, employed under conditions known to result in a negligible degree of exposure to and absorption of lead. The latter group was essentially similar. The difference in mean excretions was considered to reflect both local and individual dietary habits and the smaller sample size of the second group (*36*). Estimates on normal sources of lead exposure are discussed in a previous section. Tepper reported that the average adult diet contains approximately 100–140 μg of lead per day (*14*). Recent reports on dietary lead content (*15*) indicate that the lead content of the diet of young adults generally averages 150–250 μg/day.

Ingestion of Lead at Elevated Levels in Adults

Kehoe (*36*) performed balance studies in four young adult male volunteers. The period of study varied from several months to nine years. These men ingested lead as lead acetate or lead chloride along with their meals during the test period, and the lead was added in quantities of 0.3, 1.0, 2.0, and 3.0 mg per day above normal dietary lead intake which was about 300 μg per day.

Intake of a total of 0.6 mg lead/day for one year resulted in a barely detectable increase in the lead content of urine and no demonstrable increase in blood lead concentration. The total 1.3 mg dose of lead/day resulted in a progressive increase in urinary excretion of lead and in the lead content of blood and other tissues. Persons ingesting 2.3 or 3.3 mg/day showed an increase in blood lead concentration which, if continued, would rise above 80 μg/100 ml, a level that is generally believed to be hazardous. Kehoe (*36*) also reported accidental exposure to two young adults who ingested between 5 and 10 mg of lead/day for one month. This level and duration of lead exposure produced symptoms of acute lead intoxication.

In the course of the balance studies, absorption of lead from the diet was found to vary between 5 and 10% for the young adult male subjects. Similar results were reported by Hursh and Suomela (*37*), using short-lived radioactive lead. Later workers, using stable isotopes of lead, determined lead absorption by adult males to be 6–14% of either lead nitrate or food lead when the lead was ingested with the meal. Under fasting conditions, gastrointestinal lead absorption can be as high as 70% (*38*).

In 1974, Stuik (*39*) reported the results of lead administration to adult (18–26 yr) volunteers of both sexes. Groups of five subjects received either 20 or 30 μg Pb orally/kg body weight/day for 3 weeks, except on weekends. The lead was given in a glycerin capsule after a meal. The body weights of the individuals were not reported. The responses and sequence of changes were as follows: at first, within 3 days, blood lead increased and erythrocyte δ-aminolevulinic acid dehydrase decreased. In females, erythrocyte protoporphyrin IX started to increase after about 2 weeks, up to two times the values before exposure. In males ingesting 20 μg Pb/kg body weight, these changes were not observed, however. Males ingesting 30 μg Pb/kg body weight/day showed a small increase in erythrocyte protoporphyrin IX. Urinary δ-aminolevulinic acid increased transiently, only in the first week, in males at this dose.

Since the body weight of only one individual was given (125 kg), it is not possible to know the total dose of lead to the subjects. If a "reference man" is assumed to be 70 kg, the total dose at 20 μg Pb/kg body weight is 1.40 mg/day and, for a 54 kg "reference woman," 1.08 mg/day. At these levels of intake, blood lead concentrations rapidly increased in 17–22 days, from 20.6 to 40.9 μg/100 ml in males and from 12.7 to 30.4 μg/100 ml in females. The blood lead concentrations then tended to become constant. The subjects were treated with EDTA to remove accumulated lead.

At the higher dose, 30 μg Pb/kg body weight/day, the mean blood lead concentration rose to 46.2 μg/100 ml. It is not clear if these were the same volunteers of the first study. Blood lead in the female subjects reached 41.3 μg/100 ml, which is higher than the 30.4 μg Pb/100 ml produced by administration of lead at the same dose in the first experiment. These differences may be due to individual differences if the subjects differed from the first experiment, or to changes in variables such as nutrient content of the diet, which is known to affect the percentage of lead absorbed. These results suggest that some differences exist between males and females with regard to tolerance to lead. Females develop a significantly higher level of erythrocyte protoporphyrin IX than males at the same level of lead exposure. This study established that ingestion of approximately 1.0 and 1.5 mg of lead/day, for as short a time as 21 days, will result in significant increases in blood lead concentration and interference with heme synthesis (*39*).

Inhalation of Lead by Adults

In adults, approximately 40% of inhaled lead is absorbed across the alveolar membrane or is ab-

sorbed by the gastrointestinal tract after being removed by ciliary action from the respiratory tract and swallowed (*2*). The amount retained will vary with particle size. The 40% figure is based on a "normal" mixture of particles occurring in urban air. Recently, Chamberlain et al. (*7*) investigated the retention of ^{203}Pb by adults following inhalation. The source was exhaust from a combustion engine in which the fuel contained ^{203}Pb-tetraethyllead. Of the inhaled lead, 35% was retained in the lungs, and the lead was cleared from the lungs with a half-life of 6 hr. About half of the inhaled lead was present in the blood 50 hr after inhalation and about half of the ^{203}Pb was deposited in bone and in other tissues. From 72 hr on, the amount of ^{203}Pb in blood declined with a mean biologic half-life of 16 days. The investigators calculated that continuous exposure (24 hr/day) to a concentration of 1 μg Pb/mm^3 of air for a period of months would result in an increase of about 1 μg Pb/100 ml of whole blood.

Lead Exposure in Children

Lead Retention in Children

Experiments with children, similar to those performed in adults by Kehoe, have not been conducted. Closely controlled studies that provide information about the level of blood lead that accompanies a particular level of lead intake do not exist. Zielhuis' review (*40, 41*) relating blood lead concentration to hematologic and functional changes discusses mainly adults rather than children. The preponderance of clinical observations suggest that children develop symptoms at lower blood lead concentrations than adults. It is also highly probable that children develop a higher blood lead concentration at equal levels of exposure as compared to adults because of their greater rate of absorption and smaller body size.

Absorption of dietary lead by children has been reported (*42*) to be substantially higher than by adults. The children in this study were three weeks to eight years of age. A mean value of 50% net absorption and 18% retention of dietary lead occurred. Ziegler et al. (*43*) conducted metabolic balance studies in young children from 2 to 25 months of age. Levels of lead ingestion higher than the level usual in the diet were not investigated. A lead intake of less than 50 μg/day (based on individual balance data) appears to be accompanied by negative lead balance. Interpretation of the data at these levels is difficult and may be complicated by sources of lead in addition to food, water, and air, e.g., dust and soil. For children, the actual percentage retention of inhaled lead is not known. Currently, as in the past, when lead exposure from air is calculated for children, adjustment is made for the smaller respiratory volume of children, but the same percentage retention is used as that determined experimentally for adults.

Estimates of Lead Exposure for Normal Children

Chisolm and Harrison (*44*) determined that mean fecal lead excretion of children aged 12 to 35 months with no known undue exposure to lead is 132 μg/day. Barltrop and Killala (*45*), in a study of children 2 to 3 years of age and with no unusual exposure to lead, reported a mean fecal excretion of 130 μg/day with an upper normal limit of 180 μg. If one assumes that children absorb 40% of ingested lead, a fecal lead excretion of 130 μg/day represents an average intake of 220 μg of lead per day from all sources. An average intake of dietary lead of 80–100 μg is suggested by the studies of Mahaffey (*13*) and Kolbye et al. (*15*).

The Food and Drug Administration, under contract with the Comprehensive Health Care Clinics of Children's Hospital, Washington, D. C., determined dietary lead intake in self-selected diets of children 1 to 4 years old (*13*). The surveys were conducted in 1973–1974 and 1974–1975. In both surveys, the children selected were free of organic disease and were grouped as having a blood lead concentration of < 30 or > 40 μg Pb/100 ml of whole blood. The groups were matched for age, sex, and other demographic factors. Average dietary lead intake was 105 μg per day in 1973–1974 and somewhat less, 80 μg/day, in 1974–1975. In neither survey was there a significant difference between the dietary lead intake of children with normal or elevated blood lead concentrations.

From available information on ingestion of lead, it appears that many 2- to 3-year-old children will tolerate an oral lead intake of up to 200 μg/day without an elevation of blood lead to > 40 μg Pb/100 ml whole blood. Chisolm stated (*14*) that as daily ingestion of lead is increased from 300 to 650 μg/day there is increased urinary excretion of δ-aminolevulinic acid, an adverse metabolic effect, i.e., interference with porphyrin metabolism, the formation of heme. This occurs as the blood lead concentrations rise above 40 μg/100 ml of whole blood.

A joint FAO/WHO Committee (*1*) established a provisional tolerable *weekly* intake of lead for adults of 3 mg but did not suggest a value for infants and young children. A Department of Health, Education, and Welfare-appointed *ad hoc* committee (experts in pediatric lead toxicity) recommended (*14*) that 300 μg of inorganic lead/day be the permissible

amount from all sources for 1- to 3-year-old children. Mahaffey et al. (*46*) estimated that young children are exposed to approximately 100 μg of lead/day from air, food, and water, but it is important to note that exposure for a particular child, on any given day, may be from 20 to 500% of this.

Although dietary intake of about 200 to 300 μg of lead/day appears to be tolerated by 2- to 3-year-old children, the acceptability of these levels for young children and for infants of one year or less is not well established. Infants of less than one year are smaller in body size and have higher metabolic rates than 2- to 3-year-olds. These factors produce a proportionately higher exposure to lead from air, water, and food. In addition, calculations of tolerable lead exposure in proportion to body size may not be totally adequate to establish tolerable lead intakes for infants, as there are differences in maturation of the central nervous system and young infants may absorb higher percentages of dietary lead than do 2-year-olds.

Estimates of Lead Exposure in Lead Poisoned Children

Chisolm and Harrison (*44*) determined the 24-hr fecal excretion of lead by children under 6 years of age. The children were grouped on the basis of having blood lead concentrations of < 60 μg/100 ml of whole blood, or > 60 μg Pb/100 ml with or without symptoms of lead intoxication such as: anemia resistant to iron therapy, severe constipation, anorexia, hyperirritability, bizarre behavior patterns, intermittent vomiting, accompanied by mild or severe encephalopathy.

Children who were found to be asymptomatic with blood lead concentrations greater than 60 μg/100 ml had roentgenographic evidence of lead storage in bone and increased coproporphyrin excretion in the urine. The children with symptomatic lead poisoning excreted 5 to 104 mg of lead/day, and the median value was 27 mg/day. Children with evidence of an elevated body burden of lead but without overt lead toxicity excreted between 116 μg and 9.6 mg/day with a median value of 1.1 mg/day. Those children with blood lead concentrations less than 60 μg/100 ml of whole blood excreted between 12 and 175 μg/day. Chisolm and Harrison (*44*) estimated that 5 to 6 months duration of exposures associated with these fecal lead excretions were required to produce these blood lead levels with or without the symptoms.

Barltrop and Killala (*45*) reported fecal lead content of normal children and children with evidence of clinical lead toxicity from paint ingestion. Lead excretion was reported in mg per single fecal specimen which was collected upon admission to the hospital or clinic. Normal children excreted a mean of 130 μg per specimen while the children with clinical lead poisoning excreted between 570 μg and 1.9 mg per specimen.

On the basis of these data, it has been concluded that absorption of 1 to 2 mg of lead daily for 5–6 months might cause symptomatic poisoning in 1- to 2 year-old children (*47*) or might cause an elevation of body burden of lead and a derangement of porphyrin metabolism (*14*). Subsequent to these estimates of quantities of lead needed to produce symptomatic lead toxicity in children, three additional investigations on lead exposure in children have been reported (*48–50*). Ter Haar and Aronow (*48*) reported fecal lead excretion in micrograms Pb/gram dry weight of fecal material per day for 1- to 3-year-olds. Ten control children from suburban Detroit with no known exposure to an excess of lead excreted an average of 4 μg (range 2–7 μg)/g dry weight per day, with a daily average of 15 g dry weight of fecal material. These values correspond to an average fecal lead excretion of about 60 μg Pb/day. Blood lead values for the control children were not reported in this publication. Eight children who had been hospitalized with the suspicion of elevated body burdens of lead excreted averages of 4, 7, 18, 19, 20, 40, 49, and 1640 μg/g dry weight/day. For these children an average excretion is not very meaningful as two of them excreted lead in the control range, while one child excreted in excess of 1640 μg/g dry weight/day. The total weight of fecal material excreted by the lead-exposed children was not reported. However, if daily fecal excretion of 15 g dry weight is assumed [however, see Hammond (*50*)], the middle four concentrations correspond to an excretion of 270, 285, 300, and 600 μg Pb/day.

Thirty normal children (*49*) from homes in suburban Detroit, where lead poisoning was not a problem, excreted a mean of 79 μg Pb/g dry weight/day with a range of 22–174 and a median of 75 μg/g dry weight/day. Children thought to be exposed to lead excreted an average of 1781 μg Pb/g dry weight/day with a range of 8–29,030 and a median value of 218 μg/g dry weight/day.

Hammond (*50*) performed repeated determinations of fecal lead excretion by children having whole blood lead concentrations in excess of 40 μg/100 ml. He found that fecal lead excretion above "background" levels is highly variable, probably due to the fact that the pica habit that produces highly elevated fecal lead concentration is sporadic. He indicated that "by procuring several stool samples, a low lead sample is readily found in almost any child, irrespective of its blood lead concentra-

tion." However, the great majority of the children investigated by Hammond having blood concentrations of > 40 μg Pb/100 ml whole blood had fecal excretions of > 80 μg Pb/g dry weight/day with an average total dry weight of 6 g. The dry weight and lead content of fecal specimens in these studies were highly variable since constipation can occur in children with elevated body burdens of lead. Because of this variability, it is extremely difficult to estimate the quantities of lead ingested by children exposed to large amounts of lead on the basis of a single 24-hr stool specimen. It is not known if the absorption of lead varies with rate of passage of fecal material through the gastrointestinal tract. Background levels for children not exposed to elevated amounts of lead appear to be more constant.

Other Parameters Affecting Lead Toxicity

Form of Lead

Organic lead compounds such as tetraethyllead or tetramethyllead are highly toxic compared to inorganic lead compounds. Lead values on autopsy following tetraethyllead or other organic lead poisoning are sparse. However, the partitioning of lead in the tissues in tetraethyl lead poisoning occurs as one would expect. Tetraethyllead is lipid-soluble, readily diffusible, and is rapidly accumulated in nonosseous tissues, particularly the brain. The onset of symptoms is rapid; there is little time for lead to accumulate in bone before the symptoms of toxicity occur. This difference in partitioning of lead between persons dying of organic lead intoxication and those with chronic inorganic lead poisoning emphasizes the importance of the concentration of lead in a target organ rather than the total body burden of lead.

Data on the relative toxicity of different forms of inorganic lead show a much less clear-cut picture. Several points do stand out: (1) The solubility of the compounds in acidic or basic solutions is not, in itself, predictive of bioavailability. (2) Size is important. Lead absorption is greater from lead as small particles than from the same dose as large particles. However, when large pieces of lead are ingested, such as lead shot or a lead curtain weight, they may lodge in the gastrointestinal tract, slowly dissolve, and cause severe lead poisoning.

Part of the difficulty in interpreting data on bioavailability of different lead compounds is attributed to the variety of assay systems utilized. In long-term studies, the results have been reported from a number of species including ruminants and birds. The gastrointestinal systems of these species are markedly different from that of the human. Considerable data have been obtained from studies in which the lead compounds were fed for 48 hr (*51, 52*). Although these studies were well controlled, their short duration provides information on only some aspects of lead absorption. Under circumstances where a difference in absorption may be due to physiological adaptation and not to the physical form of a compound, 48-hr studies are unlikely to detect these changes. For example, studies in animals have shown that iron deficiency enhances lead retention several fold (*53*); however, this effect is not detectable in the short-term assay (D. Barltrop, personal communication). Barltrop (*24*) reported that lead chromate, lead sulfide, and lead molybdate produced lower blood, kidney, and femur lead concentrations than did lead acetate, while lead oxalate and basic lead carbonate produced higher tissue concentrations of the lead. In these studies, the rats were fed diets containing the various compounds at equivalent lead levels for 48 hr. Elemental lead having a particle size of 180 to 250 μm was taken up only one-fifth as well as lead acetate. However, when particle size of the elemental lead was reduced to < 180 μm, the tissue lead concentrations were approximately twice those with the larger particles. While considering particle size of importance, Barltrop (*24*) noted that it is not possible to predict particle size of added lead compounds after incorporation into the diet, or to predict the physical behavior of the particles in the lumen of the gastrointestinal tract.

Allcroft (*54*) reported that 200 to 400 mg of lead/kg body weight, ingested in any one day as either the acetate, basic carbonate, or oxide, caused death of calves up to 4 months old. The apparent absorption of lead in sheep was reported (*55*) to be similar, whether the lead was given as the acetate, nitrate, or as naturally contaminated hay. However, because both the cattle and sheep are ruminants and have far different gastrointestinal systems than humans, these results are not necessarily predictive for human absorption of the compounds. Interestingly, Buck (*56*) observed that lead in greases and oils is more toxic than elemental lead or lead salts. These differences could be due to the nature of the vehicle. Barltrop (*24*) reported that increasing the amount of corn oil in the diet of rats increased their absorption of lead.

In 10-week studies, Ku et al. (*57*) found that for both young and mature rats, ingestion of either lead acetate or a complex of lead with a phospholipid resulted in similar concentrations of lead in the femur, kidney, liver, and brain.

Several studies compared the bioavailability of lead as it occurs in natural foods with that of lead

acetate. Equal concentrations of tissue lead were obtained in rats (*58*) and quail (*59*) fed oysters containing high concentrations of lead or an equivalent amount of lead as lead acetate either with or without the oysters. In both of these experiments the trace metal contents of the diets were found to be constant in the diets. Rabinowitz et al. (*60*) found that blood lead concentration in humans was the same, whether lead was that of the food or lead nitrate, when the total lead intake remained the same.

Presence of Other Components in the Diet

In general, effects produced by nutritional factors cannot be separated with certainty into a component that affects absorption of lead in the gastrointestinal tract from one that alters the metabolic capacity of the animal or human.

Garber and Wei (*61*) investigated gastrointestinal absorption of lead in adult mice after oral ^{210}Pb acetate. They found that over a 1000-fold range of dose, the percent absorption of lead did not vary when food was withheld. Food in the gastrointestinal tract reduced the absorption of trace amounts of lead (0.02%) but did not affect the absorption of 2 or 20 mg Pb/kg body weight. The three chelating agents, ethylenediaminetetraacetic acid (EDTA), diethylenetetraminepentaacetic acid (DPTA), and nitrilotriacetic acid (NTA), had variable influences. Neither EDTA nor DPTA altered lead absorption but NTA increased lead absorption. In longer-term studies in rats (7 weeks) Mahaffey and Goyer (*62*) did not observe an increase of tissue lead when NTA was fed with the lead.

Regarding natural food components, Garber and Wei (*61*) reported that lead absorption was increased by the chelating agent sodium citrate and by orange juice, which contains citric acid. Administering sodium citrate with HCl at a concentration similar to the acidity of the orange juice did not change the absorption of the lead.

For some time, milk has been considered to be an antidote for lead in cases of industrial poisoning. Data in experimental animals appear to be contradictory. Kello and Kostial (*63*) gave 6-week-old rats a single oral or intraperitoneal dose of ^{203}Pb in trace amounts and reported large increases in lead retention when the diet contained several types of milk as compared to rat chow. However, Garber and Wei (*61*) gave ^{210}Pb orally with larger amounts of lead as carrier to 6-week-old mice and found no effect of the milk on absorption.

It is not known whether the reported differences in the effect of milk on lead absorption are due to species variability, the dose of lead administered or other experimental variables. There is little doubt that diets supplying adequate amounts of milk can influence susceptibility to lead toxicity by providing an adequate supply of calcium and phosphorus. Less than adequate intakes of these nutrients are known to increase susceptibility to lead toxicity in humans and experimental animals. Barltrop and Khoo (*52*), while they did not test milk itself, tested several milk components for an effect on lead absorption in rats. They found that the high fat and protein content of milk might be expected to increase lead absorption, but that this effect would be counteracted by the high mineral content of milk.

Other foods have been proposed for the prevention of lead poisoning. Several of these contain complex, relatively nondigestible carbohydrates. Carr et al. (*64*) reported that in 7- to 8-week-old rats, when the standard laboratory diet contained 10% alginate, lead absorption was reduced. Kostial et al. (*65*) reported that alginates reduced lead uptake from the gastrointestinal tract of newborn rats. However, in three human volunteers, additions of alginate to the diet did not affect lead absorption (*66*). Koshcheev et al. (*67*) suggested that a generous supply of carrots and cabbage in the diet of workmen increased lead excretion and reduced urinary coproporphyrin III. The pectin and ascorbic acid contents of these products were considered to be the effective agents.

The overall ability of individual dietary components to increase or decrease lead absorption has not been established in humans. Studies to demonstrate these effects should ideally be conducted in humans over a relatively long period of time, since the effect of foods would have a greater influence over a prolonged time rather than as short-term therapeutic measures. Alternatively, animal testing would need to be done in a species such as the miniature pig, in which the gastrointestinal physiology is similar to that of humans.

Metabolic Condition of the Subject

There is a marked difference in lead absorption between children and adults. Details of the research defining these differences have been described above. Overall, young children absorb 3 to 10 times the amount of lead that adults do. Diets low in several nutrients appear to result in higher body burdens of lead at fixed levels of lead intake. For example, diets deficient in calcium and/or phosphorus result in higher tissue concentrations of lead at equivalent levels of lead intake. These effects of calcium and phosphorus have been reported for a number of animal species. Increased susceptibility to lead toxicity is not a direct function of level of

calcium intake. When dietary calcium intake is below the physiological requirement for calcium, retention of lead increases (*68*). Addition of high levels of calcium does not result in reduced retention of lead compared to retention occurring at normal levels of calcium intake (*13, 69*). On the basis of these observations, it is likely that a portion of the increased retention of lead is due to metabolic changes produced by calcium deficiency rather than simply the physical presence of calcium in the gastrointestinal tract. Increased absorption of lead has also been observed in balance studies with human infants receiving diets composed of normal infant foods. Slight reductions in dietary calcium content resulted in increased absorption of the lead present in these normal diets (*43*). Effects of calcium at higher levels of lead ingestion are not known. Epidemiological studies with young children have shown that children with elevated blood lead concentrations consumed diets that were significantly lower in calcium and phosphorus than those of children with normal levels of blood lead (*46*).

Diets which are low in iron increase retention of lead. Rats on diets deficient in iron showed a two- to threefold increase in tissue lead retention (*53*). The degree of iron deficiency was not extreme, as animals from this experiment showed only a modest decrease in hemoglobin concentration. Dietary deficiences of iron commonly occur in the population groups in which lead poisoning is most frequent. Levander and co-workers (*70*) reported that weight gain and hematocrit were significantly lower in animals which were both vitamin E-deficient and fed lead than in animals which were either only vitamin E-deficient or only fed lead. Tissue lead concentrations were not reported in this publication. Sobel et al. (*71*) reported that lead absorption as demonstrated by tissue lead concentrations is greater in rats receiving diets to which vitamin D was added than in rats receiving vitamin D-deficient diets.

Deficiences of nutrients do not always increase lead absorption. For example, neither low nor highly elevated intake of abscorbic acid appreciably influenced tissue retention of lead (*72*).

Factors other than minerals and vitamins have been found to influence lead absorption. Barltrop and Khoo (*52*) reported that increasing the fat content of the diet resulted in a higher absorption of a dose of lead. The protein content of the diet is also a factor in determining susceptibility to lead toxicity. Baernstein and Grant (*73*) found that rats fed lead chloride showed lower mortality and a diminished weight loss when the protein level of the diet was increased from 6 to 13 and 20%. Gontzea and coworkers (*74*) observed that doubling the protein content of the rat's diet from 9 to 18% decreased susceptibility to lead toxicity as judged by lead content of liver, kidney, and blood. Der et al. (*75*) observed that rats fed 4% protein diets had higher blood lead concentrations than animals fed 20% protein diets when lead was injected subcutaneously. These data are difficult to interpret, because both groups of rats were injected with 100 μg of lead acetate daily for 40 days. Rats receiving diets containing 4% protein were severely growth-retarded. Although equal quantities were injected, the dose per unit body weight was markedly different.

The pathologic effects of lead are more closely related to the concentration of lead in critical tissues such as brain and kidney than to total body burden of lead. A number of metabolic factors in the subject act to determine the amount of lead absorbed and the partitioning of lead between tissues, such as brain and kidney, and storage in a relatively nondiffusible matrix, such as bone.

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