Gastro-Intestinal Absorption of Lead in Children and Adults: Overview of Biological and Biophysico-Chemical Aspects

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Abstract

Intake and uptake of lead in the general population is mainly via the gastro-intestinal (GI) tract. Those biological and biophysico-chemical factors operating in the GI tract are the main determinants of Pb bioavailability. They include sites of Pb uptake, the physiology of uptake/transport to blood, the stage of development, interactions of Pb with nutrients, and GI biochemical transformations of ingested material. Lead uptake occurs as ion or complex, from micelles and perhaps by pinocytosis in the infant. Uptake is mainly via the duodenum but other sites can participate, e.g. ileum (pinocytosis) and colon. Transport to blood is by active, carrier-mediated transport and passive diffusion. Uptake may include movement through intercellular tight junctions.

Lead uptake is affected by nutrients in the GI tract, operating synergistically or antagonistically. Iron and calcium interactions are most important and augment those also occurring in vivo in tissues.

Liberation of lead from diverse ingested media, e.g. food, paint, soil and dust, mining waste, is affected by their chemical/physical forms, hydrolytic and oxidative processes in gastric fluid and other GI sites. Such changes in vivo are poorly simulated by in vitro tests. The downward revision of blood lead (Pb–B) levels considered 'safe', to about 0.5 μmol L^{-1} (10 μg dL^{-1}) or lower, causes even sources of moderately bioavailable Pb to become important.

Introduction

The concept of biological availability as applied to the public health risks from environmental pollutants is a relatively simple one: potential human health risks associated with a substance are actualized when the substance in a bioactive form is deliverable or delivered to sites of toxic action. The specifics of the delivery are modulated by the many factors discussed in the symposium, including the nature of the lead-containing environmental matrix in sources and pathways.

In areas of nutrition and pharmacology/pharmacokinetics, assessment of a substance's bioavailability has often been the *sine qua non* of research effort and quantitative application. The volume of published work relating to the topic in these disciplines is considerable and growing. Bioavailability is also implicit in that dictum of toxicology which states that 'the dose makes the poison'. The environmental epidemiology of toxic metals and metalloids, by contrast, has often given less attention to circumstances of their form-specific bioavailability and/or bioactivity (*e.g.* Mushak, 1987a, 1985, 1983). This is due in part to the absence of information on form-specific bioactivity and in part to an assumption that the core element should confer uniform toxicity.

Various functional definitions of bioavailability have been put forward and these have as their basis entry into systemic circulation, delivery to sites of action or the extent of some effect.

A generic form of the definition by Firsov and Piotrovskii (1986), put forth for drugs, is useful:

"The biological availability is the fraction (nutrient, drug or human environmental toxicant) of substance entering the systemic circulation (extent of systemic absorption) and the rate at which entry occurs."

The bioavailability of environmental lead in human populations is defined by the biological aspects of lead uptake from body compartments, the biophysico-chemical behavior of different lead species in body compartments, interactive relationships of lead with other species in body compartments and toxicokinetics of lead in the human body. We are here concerned with intake/uptake of exogenous lead, but it should be kept in mind that release of lead from the body stores such as the skeleton produces bioavailable lead and exogenous lead exposure.

How does one determine lead bioavailability, particularly ingested lead, in human populations? Approaches include: (1) use of appropriate experimental animal models to simulate the behavior of lead species in humans; (2) validated multimedia toxicokinetic models using appropriate intake/uptake kinetic parameters; or (3) epidemiological approaches through biological monitoring, including methods of inferential statistics for identifying relationships of biological markers to lead sources or pathways.

Bioavailability of lead in the gastro-intestinal (GI) tract of humans and experimental animals is of particular interest, since

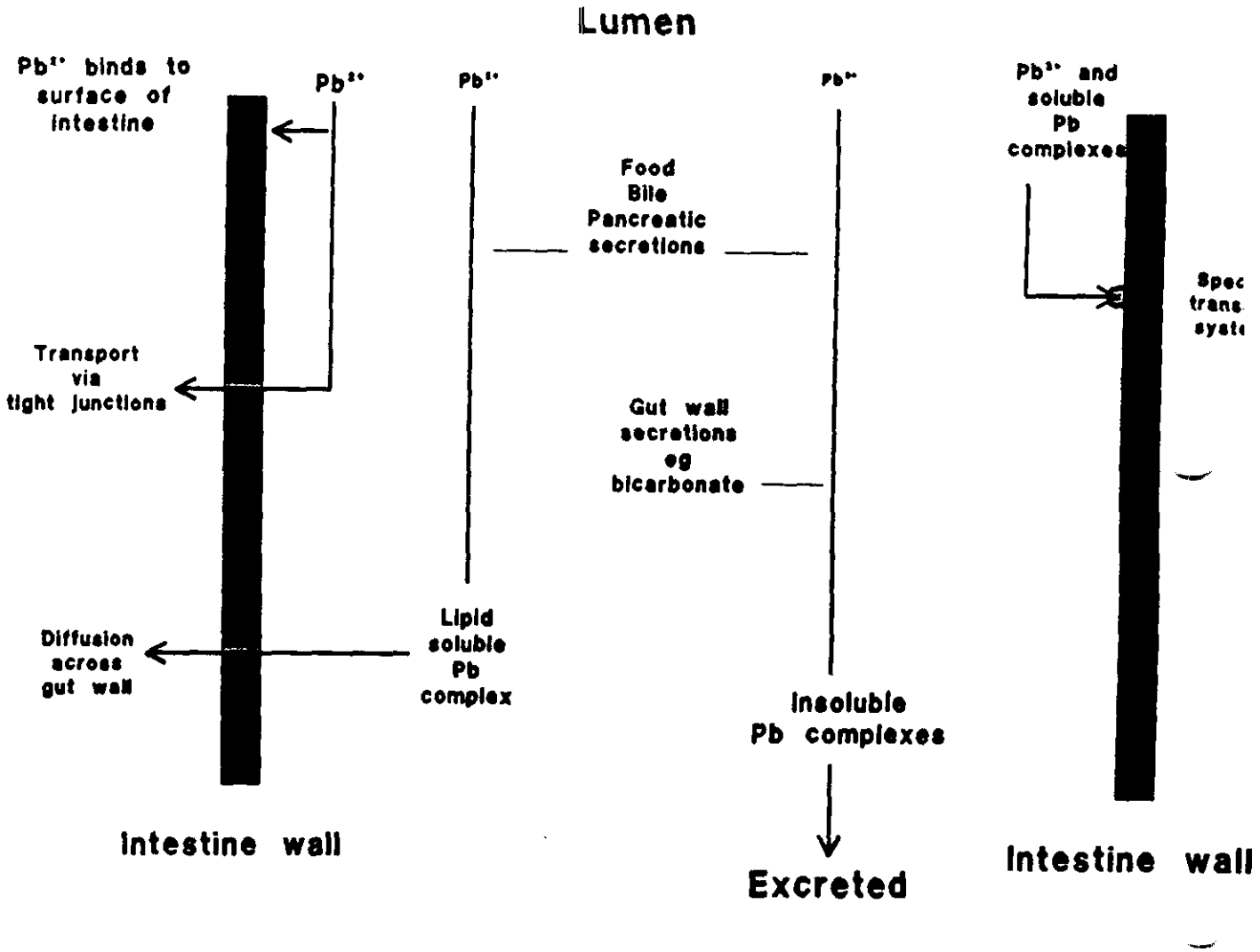

Figure 1 *Schematic diagram of intracellular/inter- cellular lead uptake by enterocytes in the human small intestine. Ions with a ++ charge within/between cells are either hydrated or interacting with ligand sites during diffusion.*

ingestion is the major route of lead exposure for most risk segments of the general population. The enteric bioavailability of lead in some ingested medium, in turn, is governed by various intrinsic (biological and biophysico-chemical) or extrinsic (level of source-specific exposure) factors which can operate separately or in combination.

Biological Determinants of Human GI Absorption of Lead

Biological determinants include: (1) interspecies differences, *e.g.* ruminant *vs* monogastric species such as humans; (2) the site of lead uptake in the GI tract; (3) the physiological and molecular processes underlying lead uptake and transport to the systemic circulation from the gut; and (4) the stage of physiological development, *e.g.* children *vs* adults and young/middle-aged adults *vs* the aged.

Interspecies differences in the GI absorption of lead

Interspecies differences in the enteric and metabolic handling of xenobiotics have principally been of interest in the area of organic chemical substances (Calabrese, 1984; Rall, 1969; Smyth, 1960), with particular reference to distinctions attributable to mixed function oxidase (MFO) transformations of various substances. Comparatively less has been forthcoming with regard to metals and metalloids (Calabrese, 1984). Some relevant comparisons have appeared for arsenic and selenium and certain forms of mercury (Mushak, 1985, 1983) but rather less for inorganic, divalent lead, the most environmentally significant chemical form (see, however, Scharding and Oehme, 1973 and relevant papers in these Proceedings).

Any effect of species on lead bioavailability would depend on differences in such parameters as GI tract anatomy and physiology, gastric processing of lead-bearing media, GI tract acidity and/or oxidation–reduction potential and the participation of biliary clearance. Existence of species-dependent differences, in turn, becomes a key consideration in the development of animal models of lead bioavailability in human populations. Specific

Table 1 *Studies of lead uptake sites in the mammalian GI tract.*

Species	Dosing details	Results	Reference
In vivo			
Male Wistar rats	*In situ* ligated intestinal loops injected w/Pb–203	Pb uptake primarily in duodenum	Conrad and Barton, 1978
Sprague-Dawley suckling rats: 10, 14 and 24 days old	GI intubation w/Pb–203 followed by segment radiography	Duodenum is site of PB uptake w/transport, transport, ileal uptake w/retention at 24 days	Henning and Leeper, 1984
Same: 9–16 days old	GI intubation w/Pb–203 as salt or in milk micelles	Pb salt absorbed in duodenum, Pb in micelles absorbed in ileum	Henning and Cooper, 1988
3–4 week-old White Leghorn chicks	Pb–203 injected into situ ligated intestinal loops, different diets	Label uptake in duodenum varied w/level of nutrients	Edelstein *et al.*, 1984
C56 Bl/6 Jax adult mice	Pb–203 given via open-ended duodenal loop perfusion	Duodenal uptake, variable with iron status	Flanagan *et al.*, 1979
Adult guinea pigs	PB–Oac in drinking water	Pb uptake in ileum and colon, similar tissue levels	Rizzi *et al.*, 1989
Adult guinea pigs	Dosing of isolated loops, colon and jejunum w/Pb solution	Jejunal uptake higher than for colon; other sites not tested	Hussein *et al.*, 1984
In vitro			
Adult Wistar rats	Everted duodenal sacs incubated w/Pb–210	Label uptake and transport, mucosal to serosal surfaces of duodenum	Barton, 1984

lead bioavailability in humans are presented elsewhere in these Proceedings.

There is little evidence to support any notion that ingested lead behaves differently in ruminants compared to monogastric animals, whatever the differences in gastric anatomy and physiology. For example, regurgitation and chewing of lead-containing material and a methanogenic, chemically reducing milieu in the ruminant GI tract might be expected to affect lead bioavailability differently than when simple passage of ingested lead through the monogastric stomach and intestines with an oxidative environment occurs.

On the other hand, there is extensive literature documenting that ruminants readily absorb lead from contaminated range feed/soil and experimentally-dosed diets (*e.g.* Allcroft, 1950; US EPA, 1986; Zmudzki *et al.*, 1986) and are at rather high risk for lead poisoning (Allcroft, 1951; Hammond and Aronson, 1964; Zmudzki *et al.*, 1986). This vulnerability possibly reflects soil ingestion during grazing. Furthermore, Stara (1971) has reported that the extent of GI uptake of elements such as cesium by the ruminant (80%) is not much lower than monogastrics (90%). These Proceedings discuss the topic elsewhere.

Sites of uptake of lead

The epithelial lining of the small intestine in humans and experimental animals is the principal anatomical an physiological locus of uptake and transport from the lume There also is evidence for the involvement of colon epithelium in experimental systems. The stomach separate plays a role in uptake via transformation(s) of lead-bearir media or form- specific lead to potentially more soluble otherwise mobile forms.

Uptake involves epithelial cells on the mucosal surfac the enterocytes. These specialized cells are structured wi finger- like projections, the microvilli (Figure 1). Su morphology provides an enormous surface for contact with a uptake of lead and other substances relative to cellular volur and time in the gut. Note in Figure 1 the intercellular junctio and associated intercellular lateral space, which also m participate in lead transport.

Various *in vivo* and *in vitro* studies have been done identify the site(s) of uptake and transport of lead, and the mc significant reports are summarized in Table 1. It is important keep in mind that these data were gathered typically by usi surgically and physiologically manipulated segments of the tract in experimental species. The full extent to which the manipulations introduce artifacts in the results is not known

In rats and other species, lead uptake and transp principally occurs in the duodenum in developing and matu animals (Henning and Cooper, 1988; Barton, 1984; Edelstein

Table 2 *Studies of lead uptake sites in the mammalian GI tract.*

Species	Dosing details	Results	Reference
In vivo			
Adult and suckling Sprague-Dawley rats	Oral intubation or drinking H_2O; Pb dose range of 1–100 mg kg^{-1}	Concentration-dependent uptake rates were observed, *i.e.* carrier transport and saturation kinetics	Aungst *et al.*, 1981
C56, Bl/6 Jax adult mice	Open-ended, *in-situ* perfusion, Pb–203 or Pb–210 + carrier	Uptake dependent on lumen Pb, *i.e.* saturation kinetics	Flanagan *et al.* 1979
White Leghorn chicks	*In vivo*, ligated duodenal loops, injected Pb–203 + carrier, 0.01–1.0 nM Pb	Concentration-dependent Pb uptake; saturation kinetics	Mykannen and Wasserman, 1981
Suckling Sprague-Dawley rats	*In vivo* intubation of Pb–203, as salt or in milk micelles, segmental analyses of intestinal tract	Pb in micelles absorbed only with retention in ileum, Pb salt absorbed in duodenum with transport	Henning and Cooper, 1988
In vitro			
Adult Wistar rats	Rat everted gut sacs with Pb–210 in bathing medium, active transport inhibitors	Duodenal sacs transported Pb, by active transport. Ileal and jejunal sacs did not transport Pb	Barton, 1984
Adult and juvenile Sprague-Dawley rats	Everted gut sacs with Pb ion at 0.5–48.3 μM, metabolic inhibitors	Non-linear Pb uptake *vs* dose, active transport dominant at all doses, with diffusion <20%	Aungst and Fung, 1981
Adult rats	Everted gut sacs with Pb ion. Cellular Pb localized by histochemical techniques	Pb appears localized between enterocytes, in 'tight junction' region	Coogan, 1982 Morton *et al.*, 1985

al., 1984; Henning and Leeper, 1984; Flanagan *et al.*, 1979; Conrad and Barton, 1978). In general, the more reliable *in vitro* data support *in vivo* results, *i.e.* uptake via duodenum (Barton, 1984). In other studies experimental artifacts, such as the use of medium cofactors that remove lead by precipitation, limit conclusions to be drawn about regional uptake in the small intestine (*e.g.* Blair *et al.*, 1979; Gruden and Stantic, 1975).

Hussein and coworkers (1984) have found that lumenal lead dosing of isolated loops of guinea-pig colon and jejunum yields significant lead uptake at both sites, but colonic uptake is less than that in jejunal epithelium. The relative amount of lead actually entering the bloodstream from transcolonic transport was not determined. However, Rizzi *et al.* (1989) reported that orally dosed guinea pigs showed tissue levels of lead in colonic tissue similar to those in ileum.

In theory, xenobiotic transport from the gut to the circulation can entail such processes as carrier-mediated transport, passive and facilitated diffusion, pore filtration, phagocytosis and pinocytosis (Calabrese, 1984). In the case of lead, a number of these mechanisms have been identified. Various studies of the kinetic nature of lead movement from the intestinal lumen to the bloodstream are presented in Table 2.

Transport of lead from duodenum to the blood stream appears to include significant intracellular uptake via a saturable active transport system that normally functions for metal nutrients, such as calcium and iron, with further uptake by passive diffusion being reported (*e.g.* Flanagan *et al.*, 1979; Barton *et al.*, 1978).

Evidence for carrier-mediated transport includes observation of energy requirement and identified carrier proteins (*e.g.* Henning and Cooper, 1988; Barton, 1984; Mykannen and Wasserman, 1981) and saturability of transport indexed as loss of tissue lead linear response above a certain level of oral dosing (Aungst and Fung, 1981; Flanagan *et al.*, 1979).

There is also evidence that paracellular uptake of lead via diffusion through 'tight junctions' will occur, based on rat everted sac techniques and histochemical staining. Epithelial tight junctions have a pore diameter of 10–16 Å, a negative charge density and high selectivity for cations (*e.g.* Morton *et al.*, 1985; Coogan, 1982).

Is this mode of uptake an artifact of experiment or is it in co-existence with intracellular transport *in vivo* but restricted to cationic (*vs* complexed) lead? The latter is the more likely, and supporting information from data on other ionic metals exists.

It is known that some uptake of iron, in low molecular

Table 3 *Relationship of age and development to GI absorption of lead.*

Study group	Study details	Results/comments	Reference
Humans			
8 children, aged 3 months to 8 years	11 lead balance studies	Mean extent of Pb uptake was 53%	Alexander *et al.*, 1973
12 infants, aged 2 weeks to 2 years (2 studies)	Two-part lead balance studies: *Part 1:* 51 studies with 9 children	42% absorption	Ziegler *et al.*, 1978
	Part 2: 38 studies with 6 children	42% absorption	
29 hospitalised children, aged 3 weeks to 14 years	Lead balance studies: 104 studies with 29 children	Showed highly variable uptake, 15 children in negative balance, w/ –40% uptake. Results limited by unknown Pb exposure and stresses of disease and injuries, *e.g.* bone fractures	Barltrop and Strehlow, 1978
Animals			
Sprague-Dawley suckling rats	Intubation of Pb–203 at varying doses as salt or in milk micelles	Ileal uptake of lead with retention is greater than elsewhere in gut	Henning and Cooper, 1988
Albino rats: 1–2 week-old sucklings; 6–8 week-old weanlings	GI administration of Pb–203 and measurement of label	1 week-old animals absorb 70% lead *vs* 23% in weaned rats	Kostial, 1987
Fisher–344 rats: adult (8 months) and old (16 months)	Oral Pb disposition at 0, 250, 500 ppm Pb in drinking water	Marked changes in bone and soft tissue Pb of old rats; Pb–B was similar	Cory-Schlecta, 1990a
Fisher–344 rats: young (21 days); adult (8 months) and old (16 months)	Oral Pb disposition at various doses: 0, 2 or 10 mg Pb kg^{-1} day^{-1}	Changes in old rat bone and excreted lead; no change in GI uptake	Cory-Schlecta, 1990b
Fisher–344 rats: adult (8 months) and old (16 months)	Oral Pb disposition at 50 ppm Pb in drinking water	Increases in Pb–B and soft tissue Pb in old rats; may reflect higher uptake	Cory-Schlecta *et al.*, 1989

weight forms, is through passive diffusion and occurs via tight junctions (Simpson *et al.*, 1989) while aluminum is normally transported via tight junctions (Provan and Yokel, 1988). Furthermore, aluminum uptake is markedly enhanced by citrate in animals and humans (Slanina *et al.*, 1986; Froment *et al.*, 1989a), while citrate imparts a similar enhancement of lead absorption (Spickett *et al.*, 1984). Froment *et al.* (1989b), using ruthenium red and Ussing chamber techniques, have shown conclusively that citrate functions in aluminum uptake by opening tight junctions for more facile aluminum passage.

Age and developmental determinants of GI lead absorption in humans and animals

It is now known that age and the stage of development in humans and experimental animals have an intrinsic effect upon body lead burdens. These closely linked factors potentiall operate through a variable combination of: (1) the extent c lead uptake in the GI tract; (2) the distribution of lead amon tissues and its retention; (3) the relative efficiency of excretic of absorbed lead.

In examining this body of data, it is important t understand the nature of the techniques for assessing the abo inter-related phenomena with respect to distinguishing amor higher uptake, higher retention and relatively lower extent excretion. One should also understand that higher uptake intestinal epithelium does not necessarily result in more le delivered to the blood. These distinctions have not always be comprehended by various investigators. We are main concerned here with age and development as a factor in mc lead uptake from the GI tract, and this topic has been review

Table 4 *Various nutrient relationships with lead in humans.*

Group	Study design	Results*	Reference
All nutrients			
Adult volunteers (n = 23)	Ingestion of Pb–203 label variably umed with meals	Minimal uptake of 61% Pb with fasting, 4% uptake with meals. Intermediate uptakes between these times	James *et al.*, 1985
Calcium			
Cluster sampling of 1–11 year-old children in NHANES II (n = 2926)	Statistical analyses of Ca in diet *vs* Pb	Dietary Ca inversely related to Pb–B. (p = 0.028)	Mahaffey *et al.*, 1986
Infants (see Table 3)	Statistical analyses of dietary Ca and Pb uptake in balance studies	Pb uptake inversely related to diet Ca; occurs even within Ca RDA guidelines	Ziegler *et al.*, 1978
Children 1–6 years old (n = 43)	Statistical analyses of dietary Ca and Pb–B	Ca intake and Pb–B were negatively correlated (r = 0.327: $p < 0.05$)	Johnson and Ti 1979
Adult volunteers (n = 8)	Pb–203 label uptake in Ca/P–variable diets	In fasting, 60% Pb uptake, with Ca + P giving 10% uptake	Heard and Chamberlain 1982
Iron			
Children 2–6 years old in NHANES II survey (n = 1677)	Statistical analyses of Pb *vs* EP as a function of Fe a function of Fe	Dose-effect curves for EP *vs* Pb–B showed slope depends on % transferrin saturation	Marcus and Schwartz, 1987
Children at high risk for Pb toxicity and Fe deficiency	Analyses of relationship of Pb–B to EP and Fe deficiency	Children with Pb–B >1.5 μmol L^{-1} and elevated EP had increased rate of Fe deficiency	Yip *et al.*, 1981

EP = erythrocyte protoporphyrin.
* 1 μmol L^{-1} Pb–B = 20 μg dL^{-1}.

(Musak, 1989; US ATSDR, 1988; Kostial, 1987; US EPA, 1986). Some of the relevant studies are presented in Table 3.

The main focus of this area has rightfully been on the growing child. Also, there may be a role played by the ageing GI tract in lead toxicokinetics. While the latter is only now being examined to any extent, the ageing of populations in developed countries, especially in the United States, and the problem of potentially mobilizable lead after life-long body accumulation requires much more attention to the matter. Available data are included in Table 3.

Young children, in those studies where reasonably stable exposure histories can be assumed to have existed (Ziegler *et al.*, 1978; Alexander *et al.*, 1973), have been shown to absorb (and also to retain) more ingested lead than do adults, 40–50% *vs* 10–15% in adults. The data of Barltrop and Strehlow (1978) are based on hospitalized children with fully unknown lead exposure histories and who have metabolic stresses of disease and trauma, *e.g.* bone fractures, and are not easily interpreted. Many studies comparing developing *vs* adult experimental animal models show the same phenomenon (Mushak, 1989; US ATSDR, 1988; Henning and Cooper, 1988; Kostial, 1987; US EPA, 1986), and animal models of bioavailability must take account of this.

What is the physiological basis for enhanced lead uptake in young (pre-school) children and suckling animals? While pre-school children are more apt to be at risk for nutrient deficiencies which can enhance lead uptake, as discussed below, the nature of the studies of Ziegler *et al.* (1978) and Alexander *et al.* (1973) would tend to minimize any nutritional factor. For example, Ziegler *et al.* used a middle-class infant cohort in which deficiencies were apt to be minimal, while Alexander *et al.* used a broad range of children, only some of whom were in the deficiency-risk group.

In the rat, many of the structural parts of the small intestine are matured at weaning, including villus and crypt density (Trehair, 1989). Furthermore, the well-known general phenomenon of pinocytosis in the suckling rat ileum (*e.g.* Williams and Beck, 1969) has also been identified as a significant factor in increasing suckling animal uptake of lead in the gut. This involves ileal pinocytosis of lead in milk micelles (Henning and Cooper, 1988). Once pinocytozed, such lead remains sequestered in the cell, and can be [illegible] as

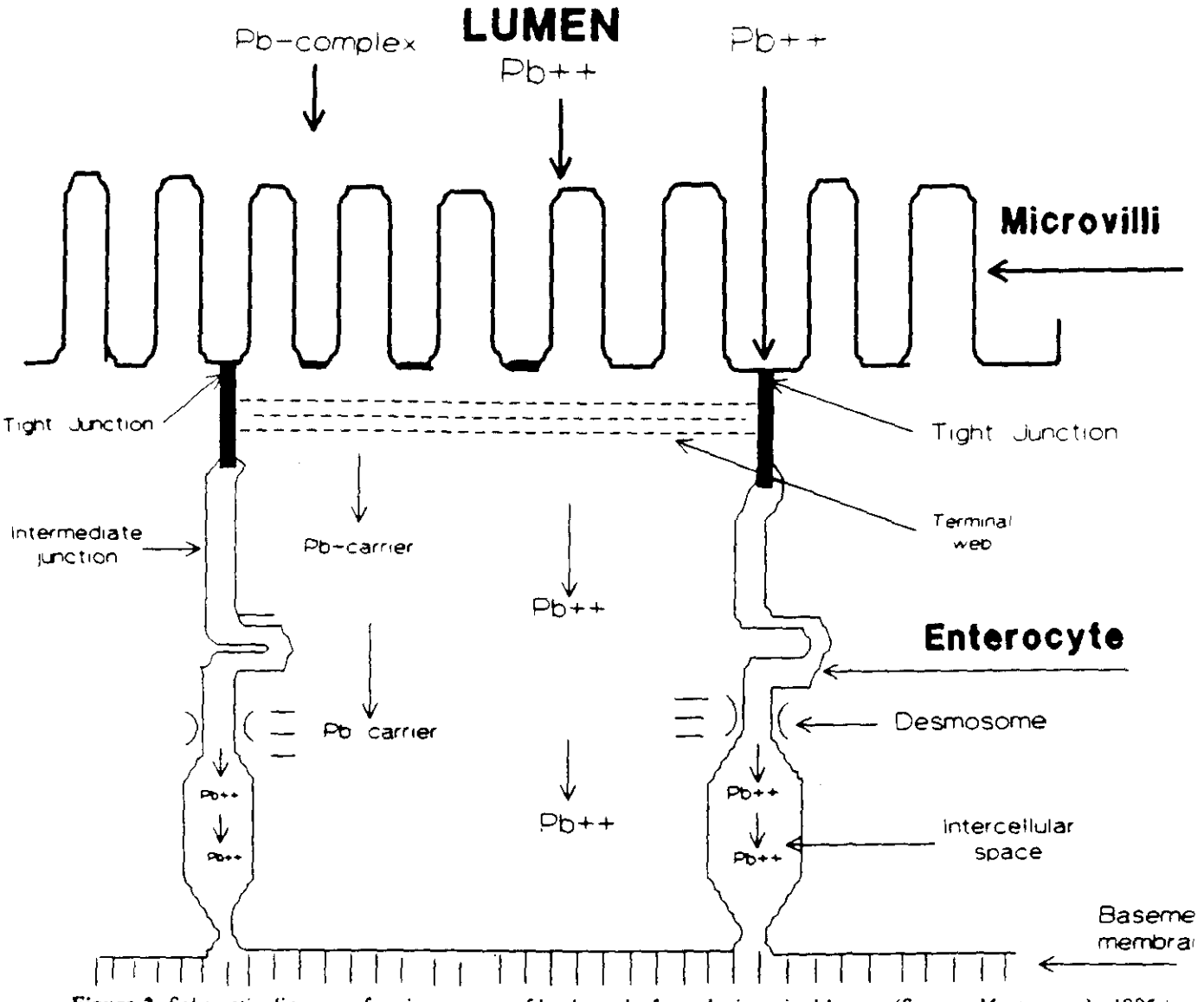

Figure 2 *Schematic diagram of various routes of lead uptake from the intestinal lumen. (Source: Morton* et al., *1985.)*

contributing to body retention without necessarily contributing to lead in blood. Epithelial desquamation then results in simple elimination. Consequently, such uptake does not translate to more lead entering the general circulation.

The level of ontogenic concordance in gut maturation between humans and animals in the neonate and suckling period is not high, inasmuch as the human newborn starts life with a more mature GI tract than the neonate rat (Henning, 1987). On the other hand, acid and pepsin production rates in children do not approximate adult levels until about two years of age (Christie, 1981; Deren, 1971), and some food proteins may be more readily taken up in infancy than later, suggesting a pinocytotic mechanism (Walker, 1985; Henning, 1987).

Limited information exists on changes in Pb uptake in the ageing mammalian GI tract. In human populations there appears to be a modest falloff of lead body burden owing to either metabolic or dietary changes (*e.g.* US EPA, 1986) after age 60. The post- menopausal female segment actually shows an increase, probably due to bone mineral changes and enhanced bone lead resorption (Silbergeld *et al.*, 1988). In the ageing rat, oral dosing at 50 ppm lead is associated with an elevated blood lead level compared to the younger adult, but this difference does not persist at higher dosings (Cory-Slechta *et al.*, 198 Cory-Slechta, 1990a). These studies suggest that ageing ma affect tissue lead distribution and lead excretion more than (uptake (Cory-Slechta, 1990a,b; Cory-Slechta *et al.*, 1989).

Interactive-relationships of lead in the GI tract

Lead absorption from the GI tract of humans and experimen animals is markedly affected by the presence or absences other bioactive agents in the gut, particularly certain classes nutrients (Mushak, 1987b; US EPA, 1986; Mahaffey, 198 Such interactions augment those which occur elsewhere wit the body and help to define overall lead toxicokinetics and le toxicity in humans.

An integrated expression of such interactive behaviour the full diet effect, as seen by the impact of meal scheduling lead uptake in the human gut. James *et al.* (1985), using hum volunteers ingesting labelled lead (Pb–203), found that whe meal was taken 12 hours before tracer lead ingestion, la retention was about 62%. A similar percentage was found wh meals were consumed seven hours after label ingestion on empty stomach. Shorter periods of label–meal separation g intermediate retentions, while the lowest retention, about

Table 5 *Toxicity risk in lead sulphide-based ethnic preparations.*

Preparation	Subjects	Outcome*	Reference
Surma	Case report	Severe Pb poisoning with encephalopathy	Warley *et al.*, 1968
Surma	Asian children (n = 37) using 'surma' *vs* Asian controls (n = 25)	Mean Pb–B = 1.7 μmol L^{-1} for 'surma' children *vs* 1.0 μmol L^{-1} for controls	Ali *et al.*, 1978
Surma	Asian children using 'surma' *vs* controls	Significantly elevated mean Pb–B over control Pb–B	Green *et al.*, 1979
Al kohl	Kuwaiti infants <6 months old (n = 4)	Acute Pb poisoning	Fernando *et al.*, 1981

* 1 μmol L^{-1} Pb–B = 20 μg dL^{-1}.

occurred with co-ingestion of meal and label. These results are in accord with a number of other studies showing the inverse link of lead uptake with levels of nutrients in the gut.

There are various categories of lead interactions applicable to GI behaviour of lead. While these can entail toxicant–toxicant interactions to some extent, attention has mainly been on lead–nutrient interactive behaviour. Interactions can be synergistic, additive or antagonistic, and in some important cases intrinsically antagonistic agents can appear to function extrinsically in a synergistic way due to their deficiencies during lead exposure, *e.g.* calcium–lead interactions.

There are many interactions with lead in the GI tract that have been described in the literature (see US EPA, 1986), but some have more obvious and recognized impacts on public health risk than others (Table 4). Two nutrients that figure prominently are calcium and iron. Phosphate and vitamin D metabolites are also important, but are not as fully characterized epidemiologically. Lead interactions with zinc, protein, fats, saccharides and natural chelators are known principally from studies in experimental animals.

A number of lead exposure populations have been studied in terms of calcium status and its effect on such measures as blood lead. This includes relevant data in the large and comprehensive Second National Health and Nutrition Examination Survey (NHANES II). Mahaffey *et al.* (1986) reported a statistically significant inverse association between dietary Ca intake and blood lead using data gathered in the NHANES II. This large analysis is consistent with balance study results of Ziegler *et al.* (1978) for infants and various investigations of the interactive relationship in high-risk children (Johnson and Tenuta, 1979; US ATSDR, 1988) and adult volunteers (Heard and Chamberlain 1982).

Numerous animal studies have described the quantitative and mechanistic aspects of Pb–Ca interactions in the mammalian gut, and these have been reviewed (US ATSDR, 1988; Mushak, 1987b; US EPA, 1986; Mahaffey, 1982). Mechanisms of interaction in the gut include a ternary interaction of Pb, Ca and phosphate (Heard and Chamberlain, 1982; Smith *et al.*, 1978) and competition of Pb–Ca for a carrier protein (Barton *et al.*, 1978), which would be an active, saturable transport process (see above). That the Pb–Ca interaction is a robust one can be seen in the study of Ziegler *et al.* (1978) where an inverse correlation of absorbed Pb and Ca intake was seen at intake levels of Ca within the range of recommended daily intake.

The large NHANES II database has also been analyzed in terms of Pb–Fe interactions in children at the ages of highest Fe deficiency. Iron status has been shown to be inversely related to blood lead, *i.e.* iron deficiency is associated with higher blood lead levels in this survey (Mahaffey and Annest, 1986; Marcus and Schwartz, 1987). Other reports showing this relationship and involving high-risk children have appeared (*e.g.* Yip *et al.*, 1981).

As with Ca, a number of animal models of the Fe–Pb interaction have been described in which Fe deficiency produces increased Pb uptake/retention. The Fe–Pb interaction is quite complex mechanistically, but it can be said that Fe deficiency stimulates iron absorption and this stimulation enhances Pb uptake via site binding at intestinal receptors for the nutrient (Morrison and Quarterman, 1987).

Are the lead–nutrient interactions metabolically reciprocal, *i.e.* do alterations in levels of enteric lead affect nutrient metabolisms in the same way as the reverse? At a simple glance, they might be expected to do so but they are not, and for a good reason. Lead is non-essential and xenobiotic, while elements such as iron, calcium, *etc.*, are essential nutrients under tight homeostatic control. It is reasonable that a xenobiotic agent can 'piggy-back' on one part of the overall homeostatic control pathway for nutrients, as in Pb binding to carrier proteins in nutrient deficiency. Fully reciprocal behavior would require that Pb effectively obliterate tight homeostatic control of nutrients, something which is highly unlikely at other than very high Pb exposures. Lead would, therefore, be less robust in affecting Ca or Fe uptake than the reverse.

This may explain why deficiencies in Ca and Fe enhance Pb uptake but the enhancement does not persist linearly with repletion or excess (*e.g.* Mahaffey-Six and Goyer, 1970; Morrison and Quarterman, 1987). Homeostatic control

nutrient is operative, whatever the level of Pb present. Furthermore, Pb can function to alter Ca metabolism in ways other than direct, reciprocal interaction. Fullmer and Rosen (1990) found that Pb affects Ca metabolism prior to calbindin D synthesis via the cholecalciferol system in experimental animals.

Overview of biological factors in GI uptake of lead

One can conclude that there are different mechanisms for GI uptake of lead in humans and experimental animals, and these are graphically summarized in Figure 2. As summarized by Morton *et al.* (1985), uptake of lead can include participation of the soluble, divalent Pb cation or various soluble complexes. Simultaneously, some sizeable fraction of divalent lead ion will be forming relatively insoluble, excretable lead complexes, *e.g.* hydroxide, bicarbonate or phosphate/mixed phosphate. Maturity of the GI tract and nutrient interactions affect these processes.

Uptake of lead ion by paracellular means, *i.e.* diffusion through 'tight junctions', has been shown in one study to be a major route under certain experimental conditions (see above). There is supporting evidence for this in other studies of elements and their interactions with 'tight junctions'.

Intracellular lead uptake is the route that has been studied and most accepted as the principal pathway in experimental systems. Such uptake is consistent with saturable, active transport as well as some passive diffusion. Diffusion most likely involves a neutral complex or other lipophilic form. Binding of lead ion to receptors in the enterocyte that serve for active transport of Fe and Ca would account for active transport. This dual mechanism of uptake appears to be one explanation of the non-linear nature of the relationship of lead dose in the GI tract and lead in blood or other biological marker.

Biochemical/Biophysical Factors in the GI Absorption of Lead

Some biophysico–chemical factors which affect the GI uptake of lead in human populations are of importance, and they include GI solubility, particle size and reactivity of the ingested lead- containing chemical matrix with reference to *in vivo* mobilization. These factors are not intrinsically biological but they operate within, and interact with, the biological uptake/intake compartments to affect bioavailability.

These factors take on added importance when one considers the chemically and physically diverse exposure media ingested by populations at risk: tap water, beverages, baby foods, adult diets in general, lead in urban dusts and soils arising from input from mobile emissions, paint and stationary sources, lead in communities impacted by lead production and use, *i.e.* secondary and primary lead smelter emissions and tailings from ore milling, lead battery plants, *etc.*

In vivo *bioavailability* versus in vitro *behavior*

One factor of concern in the GI handling of lead is the extent to which lead can be dissolved or otherwise mobilized with the ingestion of certain media, and movement to the stomach and small intestine. This especially applies to lead in those chemical forms considered to be inert by typical *in vitro* reactivity criteria. For example, it is important to keep a distinction between lead mobilization from media in the human stomach and simple solubility tests intended to simulate such complex activity. The latter are relatively crude simulations of events *in vivo*, given that the human stomach harbours significantly basal acidity, has a large capacity for sustained acid output in response to stimulation by acid-consuming ingested material, and may have, in its gastric fluid, substances other than just hydrochloric acid which can interact with the lead ion (see below)(Merki, 1988; Konturek, 1981; Davenport, 1977; Connell, 1974).

The resting pH of the gastric fluid in children is about 1 (Connell, 1974), while sustainable gastric acid output with stimulation can approach 150 mequiv L^{-1}, depending on such factors as the gastric oxyntic (parietal) cell mass (Konturek, 1981; Davenport, 1977). In addition to gastric HCl there are zymogens (trypsinogen, pepsinogen, renninogen), trypsin, pepsin, rennin and electrolytes (*e.g.* Davenport, 1977).

The complex interactions of the GI tract with lead can be illustrated in the *in vivo* behaviour of various chemical forms of lead. Lead sulphide, a chemical form of lead considered less bioavailable than the chloride, sulfate, or organic chelates, has a simple solubility product constant (Ksp) of 3.4×10^{-28} but is extensively solubilized by acidic gastric juice to lead chloride, $K\text{sp} = 10^{-4}$ (Healy *et al.*, 1982). Such reactivity towards gastric juice probably plays an important role in the reported bioavailability of this species, particularly when used in ethnic preparations such as the (conjunctival) eye cosmetic known as 'surma' in Asia and 'al kohl' in the Middle East. As noted in Table 5, the sulfide in such preparations has been documented as causing elevation of blood lead to toxic levels (*e.g.* Ali *et al.* 1978; Green *et al.*, 1979) and overt lead intoxication (Warley *et al.*, 1968; Fernando *et al.*, 1981).

Interestingly, 'surma' is Urdu for antimony and this metalloid was the element historically used in the sulfide preparation. The recent change to lead for economic reasons accounts for the rather recent history of toxicity risk associated with the use of this cosmetic preparation.

Several studies of lead isotope uptake in the human gu have been done and these indicate that the sulfide can have measurable or comparable bioavailability to that of forms considered much more soluble. Rabinowitz *et al.* (1980) found that lead as the sulfide, when ingested during meals or in fasting, was absorbed to the same amount as the lead chloride or cysteine complex. In fasting, there was 35% uptake for all three forms. Chamberlain *et al.* (1978) found that the sulfide was absorbed to the same degree as the chloride with meals, but less in fasting. The difference with fasting conditions for the sulfide in the two studies may reflect differences in particle size of the sulfide (see below).

Particle size and bioavailability of lead

Particle size of lead-bearing media is an important factor in the enteric mobilization of lead. Available experimental data indicate that the smaller the particle, the more easily it will be dissolved in the stomach or elsewhere in the GI tract.

Barltrop and Meek (1979) reported that particle size of lead in several forms was a significant determinant of blood lead in rats fed the toxicant. The smaller the particle, the higher the blood lead level. The most pronounced effect was seen with metallic lead, indicating that relative ease of both oxidation to the divalent state and dissolution were factors of importance.

Healy *et al.* (1982) found that the extent of lead sulfide solubility in gastric juice *in vitro* was inversely proportional to particle size, particles of 30-μm diameter being much more soluble than like material of 100-μm diameter. According to Healy *et al.* (1982), lead sulfide was found in cosmetic preparations (see earlier discussion) in particle sizes ranging up to 100 μm. Since the sulfide-based cosmetics, whatever the particle sizes, all appear to be associated with elevated blood lead and/or toxicity risk (see Table 5), the cosmetics with 100-μm particles of lead sulfide contain relatively bioavailable lead. A sulfide particle size of 100 μm is also within the range of concern for general bioavailability of lead encountered in lead-bearing dust and soil media. Theoretically, as particle size decreases, the Noyes-Whitney dissolution law dictates that the substances will become fully soluble at a sufficiently small mean diameter (Healy, 1984).

These laboratory data augment extensive epidemiological and environmental evidence pointing to the importance of particle size of lead-containing media. First, diverse studies document increased lead absorption in children in urban (Bornschein *et al.*, 1987; Brunekreef *et al.*, 1983; Lepow *et al.*, 1975), smelter (Roels *et al.*, 1980) and mining (Bornschein *et al.*, 1989; Gallacher *et al.*, 1984a) sites as a direct function of hand-lead concentration. Secondly, there is an inverse relationship of soil/dust particle size to the amount of material adhering to hands (Duggan *et al.*, 1985; Que Hee *et al.*, 1985). Lead-bearing particles of < 100 mesh (<150 μm) not only adhere most tightly to children's hands (Bornschein *et al.*, 1987; Duggan *et al.*, 1985; Que Hee *et al.*, 1985), but are readily mobilized in gastric or other acidic media (Healy *et al.*, 1982; Day *et al.*, 1979; Harrison, 1979). Finally, the smaller the soil/dust particle, the higher the relative concentration of lead and other elements (*e.g.* Van Borm *et al.*, 1988; Spittler and Feder, 1979).

The lead-containing matrix and lead bioavailability

Matrix effects on lead bioavailability, in the form of interactions of lead with various nutrients in the diet, have been described in an earlier section. The impact of lead-containing non-food media of a geochemical or formulary origin, *e.g.* geochemically diverse soils, gangue matrix in mill tailings or crushed ore (*e.g.* silicate, barite), polymerized oil film in leaded paint, on gastrointestinal bioavailability has not been extensively studied as a separate factor.

This is particularly the case for lead-contaminated soils, dusts and such geochemically related media as metalliferous ore particles and mill tailings. Available data make it clear that the level of physical and chemical heterogeneity within and among these media is considerable, and this factor would be reflected in lead bioavailability. Part of these differences are attributable to the already discussed parameters of chemical speciation and particle size. Matrix effects on *in vivo* lead bioavailability take on increasing importance as the toxicity threshold for risk populations continues to be revised downward. With current concerns about Pb–B levels starting at a blood level of 0.5 μmol L^{-1} (10 μg dL^{-1}) (Mushak *et al.*, 1989; US EPA, 1989, 1986), even those media from which lead is only moderately bioavailable now take on significance.

Few controlled clinical or experimental animal studies of medium matrix effects on lead bioavailability have appeared (refer, however, to several animal studies described in these Proceedings). Generally, published studies rely on environmental epidemiology, occupational exposure or field biota data to indirectly assess lead bioavailability. This is commonly done by analysing relationships of exposure or toxicity biomarkers to lead levels in various source/pathway media. Table 6 sets forth illustrative results with human subjects exposed to dust and soil lead contaminated by such sources as paint and atmospheric fallout. It must be remembered that such studies of environmental exposures as those in Table 6 provide an integrated measure in blood of bioavailability from expected dominant sources of exposure. Bioavailability assessed in this way is commonly compared to other surveys and usually cannot be fractionally apportioned to each of the specific sources present, *e.g.* leaded gasoline combustion, leaded paint weathering, point source emissions, without appropriate statistical, environmental or other analyses.

Soil and/or dust lead arising from paint weathering or chalking (Bornschein *et al.*, 1987; Clark *et al.*, 1987; Sturges and Harrison, 1985; Charney *et al.*, 1983; Stark *et al.*, 1982) and atmospheric fallout from mobile sources (leaded g (Lyngbye *et al.*, 1988; Brunekreef, 1984; Rabinowit , 1984; Brunekreef *et al.*, 1983) or point sources (smelters) (US CDC, 1986; Angle *et al.*, 1984; Yankel *et al.*, 1977) have been widely associated with significant contributions to blood (or dentine; Lyngbye *et al.*, 1988), especially when examined with regard to blood-lead elevation rates per unit increase in media lead.

Quantitative studies of lead source apportionment in household dust and child hand lead indicate that interior paint lead is a significant contributor to Pb–B in children residing in old housing of older urban areas, particularly housing in a state of deterioration (Bornschein *et al.*, 1987; Clark *et al.*, 1987; US EPA, 1986; Farfel, 1985; US CDC, 1985). The well-established bioavailability of lead from paint dust is amplified by the persistence of such dust even with leaded paint abatement. In a number of studies, failure to remove the dust associated with abatement either limits the full reduc Pb–B levels (Charney *et al.*, 1983) or may even lead to ris higher exposure (Amitai *et al.*, 1987; Rey-Alvarez *et al.*, 1987).

As can be seen in Table 6, urban and smelter sources produce a wide range of blood-lead increments per 1,000 mg PB kg^{-1} soil/dust. The US EPA (1989) has estimated an average slope for point sources, *i.e.* change in blood lead per 1,000 mg Pb kg^{-1} medium, as being somewhat above 0.1 μmol L^{-1} (2 μg dL^{-1}) per 1,000 mg kg^{-1}, but slopes for various sites cover a very broad range. The high end of the slope range can be assumed to reflect some complex mix of more bioavailable lead in media and higher host vulnerability (US EPA, 1986, 1989).

Transportable workplace lead and then contamination of these workers' homes where preschool children reside can produce both elevated body-lead burdens and toxicity (Milar and Mushak, 1982; Dolcourt *et al.*, 1978; Baker *et al.*, 1977). Milar and Mushak (1982) and Baker *et al.* (1977) noted that blood lead begins to be affected at exposure levels of 1,000 mg kg^{-1} dust using a Pb–B level of 2 μmol L^{-1} (40 μg dL^{-1}) as threshold. The present level of concern of 0.5–0.75 μmol L^{-1} (10–15 μg dL^{-1}) (Mushak *et al.*, 1989; ATSDR, 1988; US EPA, 1986) would presumably show a more robust response. The lead-bearing medium at issue is highly enriched in lead, and such lead is relatively quite bioavailable (e.g. the smelter

Table 6 *Selected epidemiological studies of dust and soil lead impact on children.*

Study group	Study design	Results*	Reference
Leaded paint contributions			
Cincinnati, Ohio inner-city children	Multi-regression analyses of Pb–B *versus* surface dust/soil scrapings with significant paint input	Effect size of 100–1,000 mg kg^{-1} surface scrapings = 0.115 μmol L^{-1} per 1,000 mg Pb kg^{-1}	Bornschein *et al.*, 1987 Clark *et al.*, 1987
New Haven, Ct inner-city children in 3 age bands: 0–1, 2–3, 4–7 years	Pb in house dust at differing levels with leaded paint as a variable	Children 0–1 years old showed a slope of 0.2 μmol L^{-1} per 1,000 mg Pb kg^{-1}	Stark *et al.*, 1982
High-risk Baltimore, MD, children 15–72 months-old w/elevated Pb (n = 14) *vs* controls (n = 35)	Dust Pb in test homes abated by cleaning team and Pb–B monitored	Pb–B of children with dust Pb removal decreased 0.35 μmol L^{-1}; dust returned to old levels quickly. No correlation Pb–B *vs* dust Pb	Charney *et al.*, 1983
British environmental sample study	Quantification of paint Pb input to street and household dusts; paints had moderate Pb	Paint Pb in street dusts up to 20%, and up to 15% in house dust; higher paint Pb would have higher % input	Sturges and Harrison, 1985
Leaded gasoline/fallout			
Nursery school children 4–6 years old (n = 195) in city and suburbs	Pb–B *vs* air Pb relationship integrating Pb fallout from mainly auto emissions in air	An adjusted slope of 0.425 μmol L^{-1} per μg Pb m^{-3}	Brunekreef *et al.*, 1983 Brunekreef, 1984
Urban Danish children (total n = 1302)	Case-referent study of Pb in shed teeth *vs* traffic density and ages *vs* traffic Pb exposure	Pb–teeth were significantly, positively correlated with traffic density at ages 0.5–2 years	Lyngbye *et al.*, 1988
Mainly middle-class Boston infants studied longitudinally (n = 249)	Environmental and Pb–B levels measured up to 24 months age Dust/soil Pb would reflect traffic density by fallout	Pb–air and Pb–B highly correlated, slope = 0.45 μmol L^{-1} per μg m^{-3}	Rabinowitz *et al.*, 1984
Smelter sites			
Children living varying distances from closed smelter in Idaho	Analysis of dust/soil Pb and Pb–B *vs* distance from smelter for relationships	Differences in Pb–B of 0.45 μmol L^{-1} for dust difference of ~2,800 mg kg^{-1} and soil ~ 3,000 mg kg^{-1}	CDC, 1986
Omaha inner-city children near primary and secondary Pb smelter	Statistical analyses for direct plus indirect (soil/dust) Pb from emissions in 1,075 samples	Slopes: Air: 0.1 μmol L^{-1} μg^{-1} m^{-3} Soil: 0.34 μmol L^{-1} per 1,000 mg kg^{-1} Dust: 0.36 μmol L^{-1} per 1,000 mg kg^{-1}	Angle *et al.*, 1984
Operating smelter community in Idaho children 1–9 years old stratified by distance (n = 919)	Multi-regression analyses of air, dust and soil Pb *vs* Pb–B	Soil: 0.055 μmol L^{-1} per 1,000 mg kg^{-1} Dust: 0.01 μmol L^{-1} per 1,000 mg kg^{-1}	Yankel *et al.*, 1977

* 1 μmol L^{-1} Pb–B = 20 μg dL^{-1}.

Table 7 *Studies of lead bioavailability in areas with mining-related wastes*

Study group	Study design	Results*	Reference
Children			
English children in mining area (Derbyshire) or control site (total n = 82)	Pb–B and Pb–soil stratified by three levels. No control for other sources, QA/QC unknown	Slope = 0.032 μmol L^{-1} per 1,000 mg kg^{-1}	Baritrop, 1975
Australian children in mining town w/ mill tailings *vs* control town (total n = 181)	Analysis of relationship of Pb–B in tailings town *vs* control site; 75% of children >7 years old; 25% 5–7 years old	Statistically significant differences in Pb–Bs in two towns	Heyworth *et al*., 1981
Children 1–3 years old (n = 61) and mothers (n = 58) in Welsh mining area *vs* control towns	Analysis of Pb–B *vs* hand Pb (pica) in children; Pb–B *vs* vegetable Pb in mothers	Children's hand Pb was important contributor to Pb–B. Mining area Pb–B > controls ($p < 0.05$). Mother's Pb–B in mining area > controls ($p < 0.0001$)	Gallacher, 1984a,b
Children <72 months in former mining town in Colorado (n = 150; 63% total)	Multi-regression of Pb–B *vs* sources, Pb–B distribution also reported	Arithmetic/geometric Pb–B mean = 0.51/0.44 μmol L^{-1} Pb–B/soil Pb slope = 0.24 μmol L^{-1} per 1,000 mg kg^{-1} Pb–B values increased at soil Pb > 500 mg kg^{-1}. Pb–B > 0.5 μmol L^{-1} = 41% Pb–B > 0.75 μmol L^{-1} = 15%	Colorado Department of Health/US ATSDR, 1[illegible]
Children ≤ 72 months in another former mining town in Colorado Colorado (n = 94) *vs* controls	Multi-regression of Pb–B *vs* environmental Pb sources. Pb–B *vs* Pb–soil in 18 month-old children	Arithmetic mean 0.3 μmol L^{-1} Effect size (for range of 100 to 1,000 mg kg^{-1} soil) 0.185 μmol L^{-1} per 1,000 mg Pb kg^{-1}; Pb–B correlated w/ hand Pb up to 24 months old	Bornschein *et al*., 1989
Children in Alaskan community with lead ore terminal	Pb–B survey of children, older residents, 1988 and 1989	1989 survey: 23% Pb–B > 0.5 μmol L^{-1} for 0–18 year-olds. No analysis of Pb–B *vs* media Pb	Maddaugh, 1989
Mill and mine workers			
Ore mill workers in Missouri lead belt (n = 15)	Pb–B and Pb–urine *vs* Pb–total air or Pb–respirable air	No significant correlation of Pb–B with respirable or total Pb–air except for non-smokers: mean respirable air *vs* Pb–B (r = 0.94, p = 0.01)	Roy *et al*., 1977
Lead miners (n = 89), flotation mill workers (n = 19), grinding/ bagging workers (n = 8)	Mean Pb–B levels for three worker categories	Mean Pb–B of miners = 1.0 μmol L^{-1}; mill workers = 2.75 μmol L^{-1}; grinders/baggers (Feb 1982 survey) = 6.1 μmol L^{-1} (May 1982 survey after clean-up) = 3.55 μmol L^{-1}	Dorman *et al*., 1986
Ecological biota			
Pet dogs (n = 129) grouped by location	Statistical comparison of mean Pb–B level for dogs in mining, smelter, urban and rural sites	Pb–Bs of mining site dogs significantly higher than those in other groups; 15% of these had Pb–B > 1.75 μmol L^{-1}	Koh and Babidge, 1986
Longear sun fish (*Lepomis megalotis*)	Pb–B and toxicity measured from tailing contaminated river vs. control site	Pb–B elevated; depressed δ–ALA–D activity; bone and collagen impairment	Dwyer *et al*., 1988
Suckers (Pisces: *Catostomidae*)	Pb–B and hematotoxic indices in tailing-impacted *vs* control rivers	Elevated Pb–B, depressed δ–ALA–D activity	Schmitt *et al*., 1984
Riparian wildlife, 5 species: bullfrogs, muskrats, green-backed herons, water snakes, swallows	Comparative tissue Pb levels, downstream *vs* upstream areas in tailing-contaminated rivers	4 of 5 species had significant elevations of Pb in tissues due to tailings impact	Niethammer *et al*., 1985

* 1 μmol L^{-1} Pb–B = 20 μg dl^{-1}

Studies of mining sites and associated wastes have been sporadic and have generally been limited in statistical design and quality assurance/quality control, but they indicate that lead in mining waste can be bioavailable, based on statistical association, with the extent of bioavailability varying with composition of these heterogeneous wastes (Table 7). The extent of such bioavailability relative to other dust and soil input sources, however, remains to be fully established in terms of specific physicochemical and geochemical forms and origins.

Such lead sources as weathered mill tailings, unprocessed ore spillage or waste rock overburden are physically and geochemically distinct media, and would be expected to be bioavailable through different mechanisms and to have different bioavailability. Given the recent emergence of these types of sources in the environmental epidemiology of lead, because of continuing downward revisions in the levels of lead exposure deemed acceptable (Mushak *et al.*, 1989; US ATSDR, 1988; US EPA, 1986, 1989), it is useful to attempt to evaluate bioavailability aspects of such lead-containing media (Table 7). Barltrop (1975) compared a lead mining community with a non-mining site in Derbyshire, UK, and reported that there was a modest blood lead rise in the mining area children *versus* controls, *i.e.* an approximate 0.3 μmol L^{-1} (6 μg dL^{-1}) rise in Pb–B when mean soil lead differed by 10,000 mg kg^{-1} (Table 7). This study provided no control for lead intakes from other media for both sites and did not utilize any apparent QA/QC protocol. Plus, the high calcium content of Derbyshire soils limits applicability of results to other site soils.

Heyworth *et al.* (1981) reported that an Australian town with widely dispersed lead-mill tailings showed statistically significant higher Pb–B levels in the town's children compared to a reference town without mill tailings. The significant difference was seen despite the fact that three-quarters of the tailing town children were over seven years of age; younger children in the 2–4 years age range who ingest larger amounts of dust and soil would be expected to show an even more robust response.

Several reports by Gallacher *et al.* (1984a, 1984b) indicated that lead exposure to mining waste in a Welsh mining area, compared with a control site, is associated with sufficient bioavailability of the toxicant to elevate blood-lead levels, either by direct contact by children from 1 to 3 years old with leaded material on their hands (Gallacher *et al.*, 1984a) or via lead transfer to garden crops and subsequent consumption by women in the mining community (Gallacher *et al.*, 1984b).

A detailed epidemiological study of a Colorado (USA) mining town heavily impacted for more than 100 years by smelter, mill and mine waste was recently reported, with data on children's blood- lead levels and their sources (Colorado Department of Health, 1990). The survey centred on young children and included measurement of blood-lead levels and inferential statistical analysis (stepwise forward regression) of blood lead–environmental media relationships. Most of the town's children <72 months old (63%) participated. The arithmetic and geometric mean Pb–B levels were 0.50 μmol L^{-1} (10.1 μg dL^{-1}) and 0.44 μmol L^{-1} (8.7 μg dL^{-1}) respectively. Children with Pb–B levels >0.50 μmol L^{-1} (10.1 μg dL^{-1}), a current level of concern, comprised 41% of the sample; levels >0.75 μmol L^{-1} (15 μg dL^{-1}) constituted 15% of these children/ Pb–B levels had a geometric standard deviation of 1.79, most likely reflecting an epicentric ('hot spot') mix of exposure sources. The strongest statistical association was found between child Pb–B and soil core samples with odds ratios showing that soil Pb >500 mg kg^{-1} produces elevated Pb–B in these children. A slope of 0.24 μmol L^{-1} (4.8 μg dL^{-1}) per 1,000 mg Pb kg^{-1} soil, over the range of 100–1,000 mg Pb kg^{-1} soil, was calculated.

Bornschein and co-workers (1989) examined the relationship of blood lead in children in another former lead mining town in Colorado, and found that young children were exposed (via the hand-lead pathway in those of 24 months old or younger) to leaded dust and soil-surface lead sufficient to elevate child Pb–B, in a relationship of 0.1–0.2 μmol L^{-1} (2–4 μg dL^{-1}) Pb–B per 1,000 mg Pb kg^{-1} in the soil/surface medium. This study does not permit precise identification of the type of mining waste at issue, *e.g.* weathered mill tailings, ore spillage or weathered waste rock, but the inverse relationship of blood lead with distance from the railroad line and the flood line of the local river, as well as no relationship to distance from the tailings site, suggests that the source of lead exposure is more apt to be cumulative loss of rail-borne ore rather than mill tailings.

Two surveys of blood lead of children and older residents in an Alaskan community with an ore-loading terminal made in 1988 and 1989 (Middaugh *et al.*, 1989) do not permit conclusions (Table 7) as to whether blood lead in very young children can be elevated by lead ore exposure. The child sample size was small and no statistical analyses of Pb–B *versus* lead in ore or other media were done. The percent of subjects 0–18 years old with Pb–B over 0.5 μmol L^{-1} (10 μg dL^{-1}), (range 0.55–0.66 μmol L^{-1}) in 1989 was found to be 23%. Freshly-mined ore with a significant number of large particles and a relatively more intact gangue matrix may not be comparable in lead bioavailability to other mining-related wastes, *e.g.*, weathered mill tailings (see below).

Steel *et al.* (1990) have attempted to help define the level of bioavailability of lead in mining-related material by including an analysis of the relationship of ore-mill lead, presumably mainly geochemical lead sulphide, to worker blood-lead levels. Such comparisons are highly limited in value for exposures of general populations to historical mine waste since: (1) the principal focus for health risk assessment in leaded mine waste exposures are very young children and pregnant women with a range of vulnerabilities and exposure rates, not adult workers who absorb much less lead compared to children, and who exhibit the well-known 'healthy worker' effect, and (2) workers are exposed to freshly-generated particles or ore and tailings rather than the weathered and more bioavailable material of, say, old tailing piles.

Nonetheless, several workplace studies have attempted to examine mill tailing and related extractive process forms in terms of worker blood-lead levels. These studies vary as to design quality and worker sample size. Roy *et al.* (1977) surveyed 15 ore mill workers for complete study for the existence of air lead–blood lead relationships and found a poor correlation of respirable or total air Pb *versus* Pb–B across the group, *i.e.* no apparent blood lead–air lead slope. The main exception to these findings was the relationship of respirable air to Pb–B of non-smokers.

This is not surprising, given the generally poor relationship for air lead *versus* Pb–B found by the large studies of many workers by Gartside *et al.* (1982) and Bishop and Hill

(1983). These surveys both showed that little of the variance in Pb–B is explained by workplace air lead. The studies of Bishop and Hill (1983) and Gartside *et al.* (1982) are supported by the epidemiological studies of Chavalitnikikul *et al.* (1984) who documented an association of workplace surface dust lead, facial lead and hand lead with Pb–B levels in battery workers. In a later study, Dorman (1986) reported group mean Pb–B results for three work categories associated with lead ore mining and processing: lead miners, mill workers using froth flotation, and grinding/bagging employees. As noted in Table 7, the miners showed hardly any elevation in Pb–B, while there were significant mean Pb–B elevations for 19 flotation workers and for 8 dry-grinding and bagging employees (Table 7).

Bioavailability of lead in mining waste sufficient to elevate blood lead has also been documented in terrestrial and aquatic biota (Table 7). Koh and Babidge (1986) reported that domesticated dogs (n = 129) in the lead mining community of Broken Hill, Australia, had significantly higher mean Pb–B levels than groups of dogs from any of three other sites, including one having a lead smelter; 15% of the dogs had a Pb–B of 1.75 μmol L^{-1} (35 μg dL^{-1}) or higher.

In the longear sunfish (*Lepomis megalotis*; Dwyer *et al.*, 1988) and species of suckers (Pisces: *Catostomidae*; Schmitt *et al.*, 1984) exposed to leaded mill tailings entering the Big River of Missouri's 'Old Lead Belt', it was found that blood lead was significantly elevated, and there was marked inhibition of δ-aminolevulinic acid dehydratase (δ-ALA-D) activity. There were also marked adverse changes in collagen and bone of fish (Dwyer *et al.*, 1988) exposed to lead and other toxic elements. Likewise, four of five species of riparian vertebrates along two rivers in the Missouri lead mining region were found to have higher Pb burdens than those biota from a reference site (Niethammer *et al.*, 1985).

Of direct relevance to the human and ecological lead bioavailability studies are several reports describing such parameters of mill-tailing lead as solubility, chemical form speciation and particle size. Mill tailing leachability data of Harwood (1984) showed that 55–69% of lead in these tailings were bound as oxide, sulphate or carbonate, depending on extraction medium. The sulphide amounted to only 7% of all chemical species present.

A detailed study of mill tailings was recently carried out at a Superfund site in Utah (Montgomery Engineering, 1989) and included particle-size distribution and toxic metal content studies. Study results, gathered under the rigorous QA/QC requirements of the US Environmental Protection Agency's Superfund site evaluation protocols, showed that about 50% of lead in lead ore mill tailings was extractable by ammonium acetate solution (*i.e.* was present in oxidised, *i.e.* non-sulphide forms). Tailing particle size distribution analysis for composite surface plus core samples showed over 60% of particles were of smaller diameter than 100-mesh and about 25% of particles were 10 μm or less in size. It was also found, consistent with the results of van Borm *et al.* (1988) and Spittler and Feder (1979), described earlier, that the majority of total mass of lead and other toxic elements were to be found on the smallest particles of tailings.

A second investigation of the Utah site is that of Drexler (1990 contract report; article in preparation) who carried out microprobe geochemical structural analysis of tailings, smelter slag and contaminated residential soils near the tailings site. Chemical speciation studies of the tailings and material in contaminated soils showed that lead was present in a considerable number of chemical forms, with lead sulphide often being the minor species. In addition, tailing particles and contaminating particles in residential soils were often seen to be less than 100–150 μm in size.

Overview of biophysico-chemical factors in GI lead-uptake

All lead that enters the human GI tract exists in some chemical/geochemical form, is often present in particulate material of highly variable size (diameter) and is enclosed in some matrix which variably interacts with the biochemical milieu of the GI tract, particularly basal and induced gastric acid.

Many forms of lead are rendered bioavailable in the human GI tract, and the behaviour of various chemical forms of lead *in vivo* is not well mimicked by such simple *in vitro* tests as solubility. For example, lead sulphide which is ingested in precise dose or inadvertently by populations using this form in cosmetics is absorbed extensively depending on particl and is also associated with documented toxicity.

Lead bioavailability in the human GI tract is also strongly affected by particle size, particularly for diameters of 100 μm or less, based on epidemiological and experimental data. Such enhanced bioavailability in smaller sizes, which becomes total at a theoretically determinable small particle size, is augmented by the known higher retention of dust lead on the hands of children for particles below 100 μm.

The chemical/geochemical matrix in which ingested lead is found can be variably transformed in the GI tract, leading to release of bioavailable lead. A major mechanism of such transformation is to be found in the stomach, via the action of both basal and induced gastric juice. The lead-encasing matrix of ingested lead is quite diverse in composition, and this determines the relative ease of lead release. While the proximate chemical form and the particle size of the lead-containing material are known determinants of reactivity, the basic i composition is also important.

The biochemical matrix of human diets has a strong influence on lead absorption, operating principally through nutrient–lead interactions discussed in this article.

Non-dietary matrices, such as leaded paint film, lead-bearing dusts and contaminated soils, are associated with a range of bioavailability. Potential or documented bioavailability of lead in dusts associated with atmospheric fallout, paint, re-entrained soil deposition and such mineral process waste as ore tailings have been documented. However, there are gradations of bioavailability within these matrix types. In mineralogical media, the available evidence collectively suggests that lead in weathered mill tailings would be more bioavailable than lead in freshly mined ore, which in turn may be more bioavailable than the element in weathering overburden mine rock.

As the tolerable levels of lead body burden in human risk populations, especially preschool children, continue to be revised downward, sources of lead which were not given much attention in the past increase in importance as inputs to exposure markers such as blood lead. This includes the potential impact of mining waste on human populations. Such wastes are quite heterogeneous in nature and this would be reflected in relative

geophysical-chemical studies document this and suggest that there is lead exposure potential in weathering tailings and perhaps other waste forms relative to a new level of concern of 0.5 μmol $^{-1}$ (10 μg dL^{-1}) for blood lead.

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