Bioavailability of Soilborne Lead in Adults, by Stable Isotope Dilution

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Using stable isotope dilution, we determined the bioavailability of soilborne lead (Pb) in human adult volunteers. Soil from a residential yard at a mining-impacted federal Superfund site that had negligible amounts of other priority pollutants was dried and screened through a 25- μm mesh sieve. The < 250-μm fraction, which likely represents that ingested via hand-to-mouth activity, was then sterilized by exposure to radiation. Ten replicate samples yielded a mean (SD) soil Pb concentration of 2924 ± 36 ppm, and a mean $^{206}Pb/^{207}Pb$ ratio of 1.1083 ± 0.0002, indicating remarkable soil homogeneity. Six adults with $^{206}Pb/^{207}Pb$ ratios of > 1.190 were admitted to the clinical research center and fasted overnight prior to dosing with 250 μg Pb/70 kg bw (i.e., 85.5 mg soil/70 kg) in a gelatin capsule. Blood for Pb and $^{206}Pb/^{207}Pb$ ratios was obtained at 14 time points through 30 hr. Results of the isotopic analyses from these subjects indicate that on average 26.2% ± 8.1 of the administered dose was absorbed. Six additional subjects were subsequently studied but ingested soil immediately after a standardized breakfast. Bioavailability in this group was only 2.52% ± 1.7. Collectively, this study provides the first experimental estimates of soil Pb absorption in humans, and should allow for more precise estimates of health risks due to Pb-contaminated soil. — *Environ Health Perspect* 106(Suppl 6):1589–1594 (1998). *http://ehpnet1.niehs.nih.gov/docs/1998/Suppl-6/1589-1594maddaloni/abstract.html*

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The regulation of environmental contaminants such as lead (Pb) should reflect the potential impact on human health and the environment. With respect to soilborne Pb contamination, the bioavailability of Pb in that medium will to a great extent determine its capacity to adversely affect human health. The U.S. Environmental Protection Agency (U.S. EPA) employs the integrated exposure uptake biokinetic (IEUBK) model for lead to assess environmental Pb hazards in children (*1*) and has developed an interim simplified biokinetic model for use in adults (*2*) while the U.S. EPA explores expansion of the IEUBK model to accommodate all age groups. In addition, there are a number of biokinetic models available (*3–5*) that are intended for use in adults. The output of these models is affected by a host of exposure and kinetic factors, with the bioavailability of Pb in soil among the more prominent (*6*). Unfortunately, this parameter is among the most poorly understood and likely contains a high degree of uncertainty.

In the past, investigators have employed animal models to study the bioavailability of Pb in soil (*7,8*). These studies, however, have primarily focused on predicting bioavailability in children rather than in adults. For example, using immature swine as a surrogate for young children, Casteel et al. (*7*) conducted a bioavailability study of soils from the Smuggler Mountain Superfund site in Aspen, Colorado. Two soils were tested at three different doses and were administered in daily feed material for 15 days. The average absolute bioavailability in all six test groups was 28%. Employing a rat model, Freeman et al. (*8*) studied the bioavailability of Pb-contaminated mining waste from the Butte, Montana, Superfund site. Soils with high (3908 ppm) and low (810 ppm) Pb concentrations were mixed with varying amounts of feed material to mimic the soil ingestion pattern of children with pica. Relative bioavailability was measured against a Pb acetate standard that was added as a solution to the feed material. The dietary feeding study was conducted over 39 days. Analysis of blood Pb (PbB) data yielded a relative bioavailability of 20%.

Until now, however, there have been no controlled studies assessing the bioavailability of soilborne Pb in humans. Past human dietary studies employing solubilized Pb in an aqueous vehicle (*9–11*) may provide some insight regarding the extent of Pb absorption from soil. However, the Pb/soil matrix is believed to influence absorption through factors such as Pb speciation, particle size distribution, and organic/mineral content of the soil (*12*). Steele et al. (*12*) and Mushak (*13*) have reviewed the influence of soil characteristics on Pb absorption using epidemiologic studies, *in vitro* tests, and animal bioassays. For example, particle size affects both the dissolution of Pb in *in vitro* systems (*14*) and the bioavailability of Pb in animal models (*15*). The dissolution rate of Pb is proportional to the Pb-bearing surface area. As particle size decreases, there is a corresponding increase in surface area per unit weight of material.

Medlin (*14*) developed a method for estimating the bioavailability of soilborne Pb through use of an *in vitro* test for measuring the dissolution of Pb from various Pb-bearing minerals. Among six minerals studied (galena [PbS], slag, cerussite, pyromorphite, Pb oxide, and anglesite [$PbSO_4$]), an average 5-fold increase in solubility occurred when the < 38-μ particle size was compared to the 150- to

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Abbreviations used: CPMC, Columbia Presbyterian Medical Center; ICCR, (Columbia Presbyterian) Irving Center for Clinical Research; IEUBK, integrated exposure uptake biokinetic model for lead in children; PbB, blood lead; U.S. EPA, U.S. Environmental Protection Agency.

250-μ size range. Barltrop and Meek (*15*) observed a nonlinear inverse relationship between particle size and PbB when rats were administered metallic Pb particles ranging in size from 5 to 200 μ in their diet over a 48-hr period.

The chemical species of Pb influences its solubility. Ruby et al. (*16*) have demonstrated a direct relationship between Pb solubility, as measured by a physiologically based extraction test and bioavailability in animal models. Additional evidence of the impact of speciation on bioavailability can be illustrated by the relationship between soil Pb concentration and PbB in communities impacted by either smelting or mining waste. Pb associated with mining waste consists primarily of PbS altered to $PbSO_4$ in the surficial waste piles, whereas the prevalent forms of Pb at smelter sites are the more soluble oxides (lead monoxide [PbO] and lead dioxide [PbO_2]) (*17*). Steele et al. (*12*) reviewed epidemiologic studies that related PbB to soil Pb concentration (i.e., slope studies) and derived an average slope of 1.7 μg/dl PbB per 1000 ppm Pb in soil from mining-impacted soilborne Pb, as opposed to 4.6 μg/dl PbB per 1000 ppm Pb in soil from smelting-impacted waste.

In addition, Pb uptake in the gastrointestinal tract is affected by the presence of such nutrients as calcium, iron, phosphate, vitamin D, fats, and fiber, as they occur with meals or snacks. In adults, it is well known that Pb uptake is markedly lower when ingested with meals than under fasting conditions (*9–11*). Human data, in the aggregate, indicate that calcium, iron, and other cations interact strongly as competitors of Pb uptake so that Pb absorption generally increases as dietary levels of these nutrients decrease (*13,18*).

This study is the first of its kind to directly measure the absorption of soilborne Pb in humans. It included extensive characterization of soil matrix factors that impact bioavailability. The results of this study are intended to improve biokinetic modeling of soilborne Pb hazards at sites (i.e., industrial) in which adults rather than children are the primary targets of exposure.

Stable Isotope Dilution: Principles and Applications

Lead has four stable isotopes, ^{204}Pb, ^{206}Pb, ^{207}Pb, and ^{208}Pb, of which the last three are continually being produced by radioactive decay. Thus, Pb in industrial use can vary greatly in its stable isotope ratios according to the geologic age of the Pb deposit. For example, the ratio of $^{206}Pb/^{207}Pb$ in the Broken Hill, Australia, Pb deposit is 1.03; in the younger U.S. deposits of the Mississippi Valley it is as high as 1.42 (*19*).

An individual's body burden of Pb possesses an isotopic fingerprint reflecting the sources of Pb exposure in that person's environment. We previously reported frequency distributions of blood $^{206}Pb/^{207}Pb$ ratios for human populations in three different geographic locations; American subjects had higher $^{206}Pb/^{207}Pb$ ratios than subjects from Australia or Scotland (*20*). The sensitivity of the stable isotope dilution technique as an analytical tool to study bioavailability is driven by the difference between the blood $^{206}Pb/^{207}Pb$ isotopic ratio and that of the exogenous Pb source (i.e., in this case, soil) (Figure 1).

Soil samples from U.S. EPA Superfund sites around the United States were obtained to find a soil that contained a $^{206}Pb/^{207}Pb$ isotopic ratio strikingly different from the blood $^{206}Pb/^{207}Pb$ isotopic ratios previously established for American subjects in New York. Soil $^{206}Pb/^{207}Pb$ ratios ranged from a low of 1.057 at Bunker Hill, Idaho, to a high of 1.253 at Triumph, Idaho (Table 1). Sample calculations were performed to test analytical sensitivity by matching soils with low $^{206}Pb/^{207}Pb$ ratios to American subjects, and soils with high $^{206}Pb/^{207}Pb$ ratios to Scottish and Australian subjects. Thus, we estimated that if American subjects with blood $^{206}Pb/^{207}Pb$ ratios > 1.190 were to ingest soil (250 μg Pb/70 kg bw) from Bunker Hill, we would be able to precisely estimate bioavailability even if it were extraordinarily low.

Preparation and Characterization of the Bunker Hill Soil Sample

A 2.5-kg surface soil sample was obtained from a residential yard at the Bunker Hill Superfund site. Historical information indicated that mine tailings had been utilized extensively as fill material in this area (*21*). After mixing, a subsample was screened for priority pollutants by the U.S. EPA Region II's Edison, New Jersey, laboratory (*22*). Lead and arsenic were the only contaminants found above trace or nondetectable levels. At 34 ppm, the calculated dose of arsenic to be administered in this study (approximately 3 μg) would be well below the 340 μg typically found in 8 oz of lobster meat (*23*). In contrast, the concentration of Pb in the gross soil sample was 2240 ppm.

Soil drying was accomplished by air drying in a filtered incubator at room temperature for 8 days. The soil contained

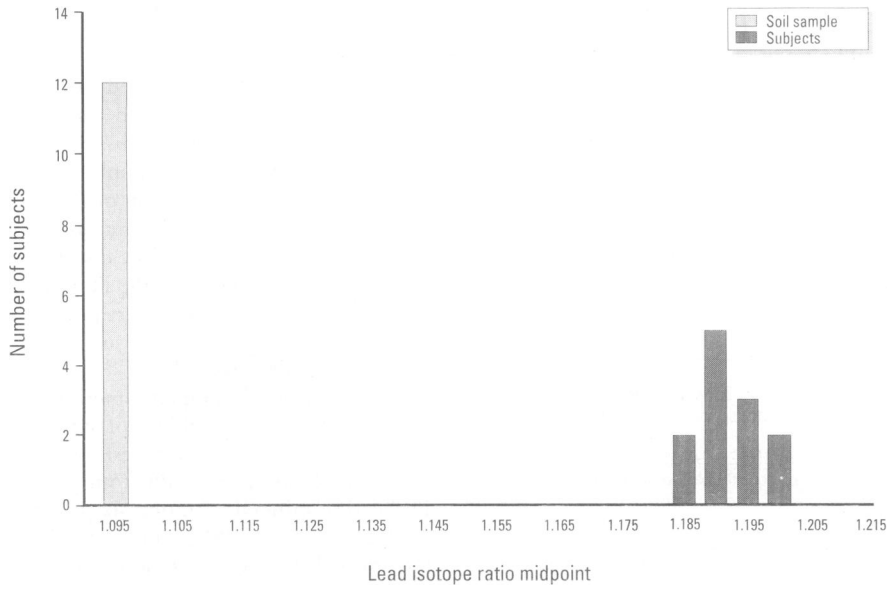

Figure 1. Frequency distribution of $^{206}Pb/^{207}Pb$ isotope ratios in normal volunteers recruited for this study compared to the $^{206}Pb/^{207}Pb$ isotope ratio of the Bunker Hill soil sample.

Table 1. Lead isotope ratios from various sites.

Location	Superfund site	$^{206}Pb/^{207}Pb$
Bunker Hill, Idaho	Bunker Hill	1.057
Butte, Montana	Silver Bow Creek	1.148
Leadville, Colorado	California Gulch	1.170
Buffalo, New York	Bern Metal	1.205
Triumph, Idaho	Triumph Mine	1.253

2.4% residual moisture. The soil was then manually sieved through a 250-µm mesh; the yield was 24% by weight. Relative to the bulk soil sample, the concentration of Pb in the sieved fraction increased from 2240 to 2924 ppm. The resultant sieved soil fraction was then sterilized by γ irradiation (Medical Sterilization Inc., Syosset, NY).

Ten replicate soil samples were analyzed for Pb concentration and $^{206}Pb/^{207}Pb$ ratio. Soil Pb was extracted by leaching in hot concentrated nitric acid for 8 hr. The mean ± SD Pb concentration was 2924 ± 36 ppm and the mean ± SD $^{206}Pb/^{207}Pb$ ratio was 1.1083 ± 0.0002, indicating remarkable soil homogeneity (Table 2).

Duplicate samples of the sterilized material were characterized for Pb speciation and particle size distribution. A 10-g aliquot of the soil was divided in two and particle mineralogy was identified using an electron microprobe, according to the method of Davis et al. (*24*).

Particle size distribution was determined using an electrozone sensor in an Elzone 280 PC System (Particle Data Laboratories, Elmhurst, IL). The particle size distribution indicated that 79.5% of the particles were < 20 µm (Figure 2). The Pb speciation profile was dissimilar between the split samples. Because the variability in the speciation profile was inconsistent with the homogeneity demonstrated via Pb concentration, isotopic ratio, and particle size distribution, a repeat Pb speciation profile was performed. The repeat analysis resulted in a more homogenous profile, suggesting a possible "nugget effect" in one of the original duplicate samples. A nugget effect occurs when a particle with a heavily concentrated predominant Pb form skews the species profile. In any case, mean values from the four speciation profiles are presented in Figure 3.

Clinical and Laboratory Methods

The soil ingestion study was approved by the Columbia Presbyterian Medical Center (CPMC) Institutional Review Board and written informed consent was obtained from all subjects. The subjects, healthy adults between 21 to 40 years of age, were screened prior to study to assure that they had normal urinalyses, blood chemistries, blood counts, and physical exams, and that their PbB was < 5 µg/dl and blood $^{206}Pb/^{207}Pb$ ratio was > 1.190. All were within 10% of their ideal weight for height based on the Metropolitan Life tables. Subjects were admitted to the Columbia Presbyterian Irving Center for Clinical

Table 2. Soil homogeneity.

Sample no.	Weight, g	Lead, ppm	$^{206}Pb/^{207}Pb$
1	0.1091	2858	1.1084
2	0.0968	2952	1.1082
3	0.0944	2928	1.1083
4	0.1037	2965	1.1083
5	0.0963	2931	1.1080
6	0.1003	2914	1.1084
7	0.0919	2912	1.1087
8	0.0988	2942	1.1081
9	0.0921	2967	1.1083
10	0.0988	2876	1.1084
Mean ± SD	0.0982 ± 0.0053	2924 ± 36	1.1083 ± 0.0002

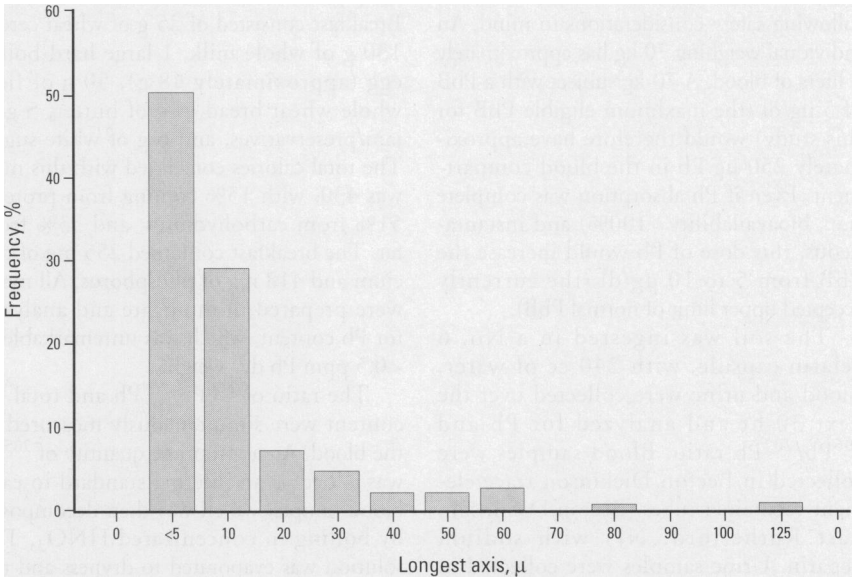

Figure 2. Frequency distribution of the soil grain size in the Bunker Hill residential soil sample.

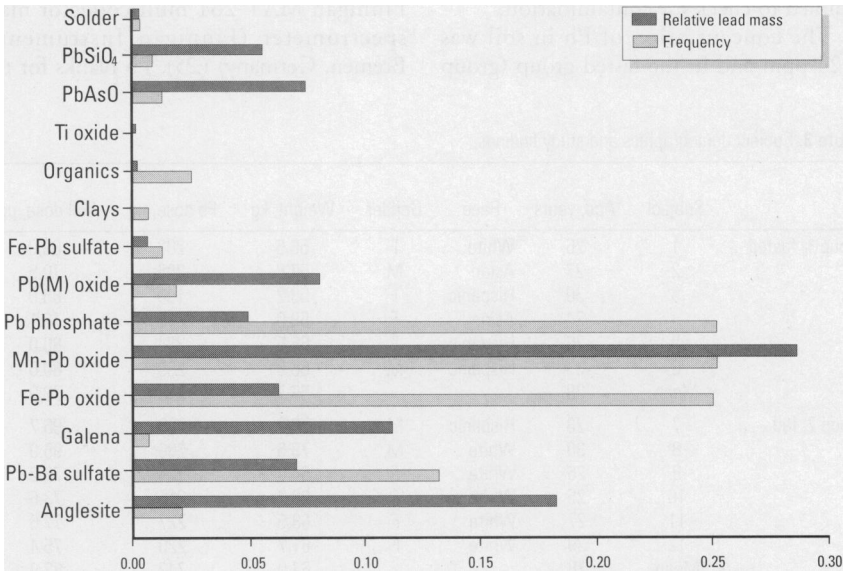

Figure 3. Distribution of the lead speciation profile of the Bunker Hill soil sample. Values are the mean results of four separate analyses.

Research (ICCR) on day 1 at 5:00 P.M. and remained in the ICCR for the duration of the study (until 1:00 P.M. on day 3). Following admission, they received a regular hospital dinner and then fasted overnight except for water. At 6:00, 6:30, and 7:00 A.M. on day 2, baseline PbB and $^{206}Pb/^{207}Pb$ samples were taken. A baseline urine sample was also collected from admission until 7:00 A.M. on day 2.

Immediately following the 7:00 A.M. blood drawing on day 2, subjects ingested soil that contained 250 µg Pb/70 kg bw. This dose was chosen as the maximum dose that could be safely administered with the following safety considerations in mind. An individual weighing 70 kg has approximately 5 liters of blood. A 70-kg subject with a PbB of 5 µg/dl (the maximum eligible PbB for this study) would therefore have approximately 250 µg Pb in the blood compartment. Even if Pb absorption was complete (i.e., bioavailability = 100%) and instantaneous, this dose of Pb would increase the PbB from 5 to 10 µg/dl (the currently accepted upper limit of normal PbB).

The soil was ingested in a No. 6 gelatin capsule, with 240 cc of water. Blood and urine were collected over the next 30 hr and analyzed for Pb and $^{206}Pb/^{207}Pb$ ratio. Blood samples were collected in Becton Dickinson trace element vacutainer tubes (Becton Dickinson, East Rutherford, NJ) with sodium heparin. Urine samples were collected in acid-washed plastic bottles. All tubes and bottles were purchased in one lot prior to the start of the study and were randomly sampled to check for contamination.

The concentration of Pb in soil was 2924 ppm and in the fasted group (group 1) the mean subject weight was 59.7 kg, resulting in an average administered soil dose of 72.9 mg (Table 3). In the nonfasted group (group 2), the mean subject weight was 67.9 kg, resulting in an average soil dose of 82.9 mg.

On day 2, the subjects in group 1 received no breakfast, a standardized liquid lunch at noon, and a standardized dinner at 5:00 P.M. They received a standardized breakfast and lunch on day 3. The protocol was identical for group 2, except that this group received a standardized high-fat breakfast at 6:45 A.M. on day 2 immediately prior to the soil Pb administration. Breakfast consisted of 25 g of wheat cereal, 130 g of whole milk, 1 large hard-boiled egg (approximately 48 g), 50 g of firm whole wheat bread, 6 g of butter, 5 g of jam/preservatives, and 6 g of white sugar. The total calories consumed with this meal was 430, with 15% coming from protein, 51% from carbohydrates, and 33% from fat. The breakfast contained 255 mg of calcium and 418 mg of phosphorus. All meals were prepared in duplicate and analyzed for Pb content, which was unremarkable at < 0.5 ppm Pb dry weight.

The ratio of $^{206}Pb/^{207}Pb$ and total Pb content were simultaneously measured in the blood. An appropriate quantity of ^{205}Pb was added as an internal standard to each blood sample, which was then decomposed by boiling in concentrated HNO_3. The solution was evaporated to dryness and the residue charred at 250°C. Pb was then extracted by anion exchange chromatography and isotopically analyzed on a Finnigan MAT 261 multicollector mass spectrometer (Finnigan Instruments, Bremen, Germany) (*25*). Pb blanks for the method were consistently < 25 pg Pb. The accuracy of the spike calibration was verified by analysis of standard SRM 955a, Lead in Blood (National Institute of Standards and Technology). Accuracy of the isotopic analyses was monitored by analyzing SRM 981, Common Pb. All other blood and urine analyses were performed by the CPMC clinical laboratories.

Results

The demographic characteristics of the study subjects are presented in Table 3. Prior to ingestion of the soil, the mean PbB in the fasted group was 1.59 µg/dl and the mean $^{206}Pb/^{207}Pb$ ratio was 1.195. Thirty hours after soil administration, the PbB rose to a mean value of 2.6 µg/dl ($p = 0.02$) and the $^{206}Pb/^{207}Pb$ ratio fell to a mean value of 1.166 ($p = 0.0001$). In contrast, the PbB in the fed group rose by only 0.3 µg/dl, whereas the $^{206}Pb/^{207}Pb$ ratio fell by only 0.004 These changes were essentially complete by 24 hr. Typical absorption profiles from subjects in the fed and fasted groups are presented in Figure 4A and B, respectively. The absorption profile presented in Figure 4, for example, demonstrates the remarkable sensitivity of the stable isotope dilution technique. This subject had both the lowest baseline PbB (0.7 µg/dl) and the smallest increase in PbB among fasted subjects (0.5 µg/dl) following ingestion of the soil, yet soil and nonsoil Pb sources could readily be distinguished.

On average, at 24 hr, we could account for 14.4% ± 4.5 of the administered Pb dose in the blood compartment of the fasted subjects. Bioavailability is traditionally estimated by comparing the kinetics of an oral dose to those of an intravenous

Table 3. Subject demographics and study findings.

	Subject	Age, years	Race	Gender	Weight, kg	Pb dose, µg	Soil dose, µg	PbB, µg/dl		$^{206}Pb/^{207}Pb$		Bioavailability, %
								Start	24 hr	Start	24 hr	
Group 1, fasted	1	26	White	F	56.5	202	69.0	1.94	3.34	1.193	1.165	35.6
	2	27	Asian	M	57.8	206	70.5	1.52	2.16	1.193	1.169	22.6
	3	30	Hispanic	F	53.2	190	65.0	2.04	2.81	1.191	1.173	19.0
	4	24	Asian	F	59.0	211	72.1	0.71	1.28	1.199	1.160	18.0
	5	26	Hispanic	F	65.5	234	80.0	1.57	2.82	1.194	1.158	36.6
	6	33	Hispanic	M	66.0	236	80.6	1.77	2.75	1.200	1.175	25.4
	Mean	28			59.7	213	72.9	1.59*	2.53*	1.195**	1.167**	26.2
Group 2, fed	7	28	Hispanic	M	79.2	283	96.7	4.60	5.10	1.196	1.195	1.8
	8	30	White	M	78.5	280	95.9	2.12	2.37	1.201	1.195	5.2
	9	26	White	F	64.0	229	78.2	1.02	1.06	1.201	1.194	2.3
	10	25	White	F	60.2	215	73.6	2.55	2.59	1.186[a]	1.186	0.2[a]
	11	27	White	F	63.5	227	77.6	1.22	1.31	1.190	1.185	2.3
	12	29	White	F	61.7	220	75.4	1.92	2.12	1.195	1.191	3.3
	Mean	28			67.9	242	82.9	2.24	2.42	1.195	1.191	2.52

Abbreviations: F, female; M, male. [a]This subject's $^{206}Pb/^{207}Pb$ ratio dropped from 1.194 at the initial screening to 1.186 just prior to administration of the soil capsule. The cause of this change is unknown but likely had an effect on this value. When this value is deleted, the mean bioavailability in group 2 is 2.98%. *$p = 0.0268$; **$p = 0.0001$.

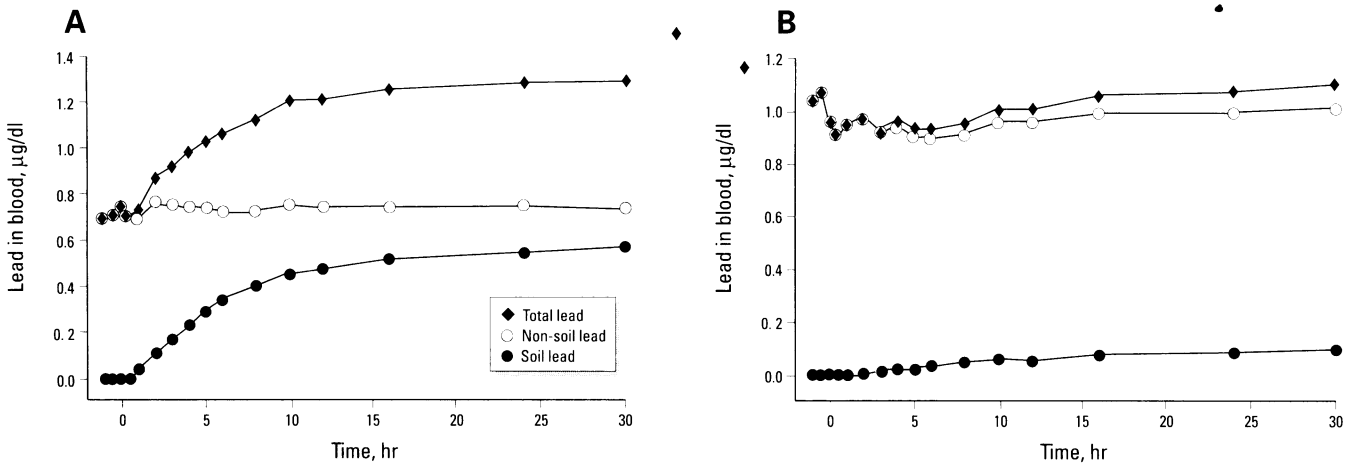

Figure 4. Change in blood lead concentration after ingestion of a soil containing 250 µg Pb/70 kg bw in a fasted (*A*) and a nonfasted (*B*) subject. ◆, total blood lead concentration. By the technique of stable isotope dilution, we were able to differentiate the relative contribution of soil lead (●) and endogenous lead (○) to total lead.

dose. Previous studies of intravenous ^{203}Pb (*26–28*) indicate that at 24 hr, 55% of an administered dose is still in the blood compartment. In this manner, we estimated the mean fraction of Pb absorbed from the soil sample to be 26.2% ± 8.1, with a range of 18.0 to 36.6%. In the six fed subjects, 1.4% ± 0.9 of the administered Pb dose was present in the blood compartment at 24 hr. Consequently, the estimated mean fraction of Pb absorbed in this group is 2.52% ± 1.7 (range 0.2–5.2%).

Discussion

The hazard posed by Pb-contaminated soils has and continues to be of great interest to organizations, such as the U.S. EPA, with public health and regulatory mandates. The intent of this research project is to provide experimental data that will better enable the U.S. EPA and similar agencies to assess and regulate the widespread soilborne Pb contamination in nonresidential areas throughout the United States.

Biokinetic models that assess the impact of Pb-contaminated soil have had to estimate the bioavailability of soilborne Pb by extrapolating from dietary exposure studies in humans and/or soil-feeding studies in animals. The strength of the current study is that it directly examines human Pb bioavailability in a contaminated soil sample obtained from a hazardous waste site. In addition, the soil sample contains a Pb concentration (2924 ppm) that is commonly encountered at sites undergoing remedial investigation, and the amount of soil administered (72.9 and 82.9 mg) approximates the range estimated [20–80 mg (*29*)] for normal daily soil ingestion by adults.

Although the study design strived to mimic an actual exposure scenario, it is unlikely that the daily soil ingested by an adult occurs as a bolus. Estimates of incidental daily soil ingestion in adults, though poorly defined, are associated with mouthing activities. The repetitive nature of these activities (e.g., smoking, eating, etc.) leads to soil ingestion throughout the day. Ideally, experimental soil administration should occur in a pattern that simulates real-life exposure; however, practical considerations make this an extraordinarily difficult task. Therefore, as a concession to practicality, we administered the soil as a bolus and recognized the possible limitations of this dosing regimen. However, the comparatively small tracer dose of Pb administered, even as a bolus, seems unlikely to result in saturable kinetics (*8,30*).

The lack of speciation homogeneity between duplicate soil samples raised a concern regarding the results of the soil bioavailability study. Possible differences in the Pb speciation profile across the administered soil samples introduces the possibility that the variance in absorption fraction within each of the test groups could have included variance due to Pb speciation rather than simply variance due to interindividual variability. Also, a lack of homogeneity in soil Pb speciation reduces the confidence in projecting the results of the soil bioavailability study as being representative of a particular profile of physicochemical soil/Pb characteristics. Nevertheless, this type of microheterogeneity in speciation likely occurs at many sites around the world.

Various investigators (*9–11*) have demonstrated absorption in the range of 30 to 70% when solubilized Pb was administered to fasted subjects. These same investigators (*9–11*) demonstrated significantly reduced absorption (range 3.5–9%) when solubilized Pb was administered with a meal. The results of our soil bioavailability study are consistent with that trend, in that absorption was approximately an order of magnitude different (2.5% vs 26.1%) between the fasted and fed states, respectively.

In conclusion, we believe that this experimental model provides important new information that supplements that obtained from observational epidemiologic studies of soil Pb/PbB relationships. The generalizability of these findings to other soils or to remediated sites is not known but can be determined experimentally using this *in vivo* model.

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