INTESTINAL ABSORPTION OF LEAD

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Our lot is cast in a perilous age ...
But where shall we fly to escape from
east winds and dogdays, from pesti-
lences that come and pestilences that
do not come, from ships that bring us
yellow fever and quarantines that
nourish and cultivate it, from cattle
diseases that can only be exterminated
by exterminating the cattle, from lead
pipes for water contrived to kill every-
body except the animalcules, from
fraudulent food and deleterious physic,
from drugs that are poisonous and poisons
that are adulterated, from infectious
patients whose pulses must be felt
with a pair of tongs and their chest
explored with a tarred stethoscope ?

Jacob Bigelow
Address at the Fourth National
Quarantine and Sanitary Convention
1860

INTESTINAL LEAD ABSORPTION

Lead has been known to be toxic for more than two thousand years and it continues to be the cause of numerous episodes of chemical intoxication of industrial and accidental origin as well as it remains a main problem of public health.

Lead ingestion

Lead ingestion results from the contamination of food during its production, its prepration and during the storage of food ; air contamination from motor exhaust gases may deposit dry particles of lead on foods, or on other objects wich may be brought to the mouth especially in children. Drinking water may be rich in lead from the use of lead piping, particularly when combined with the use of a water-softener wich usually decrease the pH of water.

Finally there are multiple circumstances which may increase the amount of ingested lead : glazed ceramic often release much lead when used for keeping acid beverages like fruit juices or cola-drinks. The paint covering of most pencils is a healthhazard for pencil chewers (40). Some popular brands of toothpaste are potentially hazardous as a result of the lead content in the tube, the tube coating and in the toothpaste itself (22bis).

Lead intake : some values	Mean (mg/d)
Kehoe, 1961 (26) (27)	0.30
Imamura, 1957 (22)	0.15 (0.09-0.18)
Jaworowski, 1967 (23)	
Kehoe, 1962 (30)	0.30 (0.05-2.00)
Patterson, 1965 (39)	0.33 (0.23-30)
Schroeder, 1961 (43)	0.33
Schroeder, 1968 (42)	0.1-0.54
Parry Howells, 1971 (37)	0.44
Thompson, 1971 (47)	0.27
Bogen, 1968 (3)	0.27

The values for lead intake are obtained by different methods, measurement of the actual content of foods, measurement of the lead content of feces with appropriate corrections to get back to intake.

The amount ingested in fodd and in water has been studied by some authors :

Lead content (mg/d)	Food (mg/d)	Water (mg/d)	
0.280	0.260	0.020	Schroeder, 1968 (42)
0.410	0.400	0.010	Patterson, 1965 (39)

Total

Lead content (mg/d)	Food	Water		
0.093-0.187	0.089-0.127	0.004-0.033	(water)	Imamura, 1957
		0.027	(tea)	(22)

Lead intake : infants

Lead intake in infants without evidence of pica, have been estimated by measuring fecal output of lead. If one uses an absorption coefficient of 25 % instead of 8 % as for adults, one gets approximately the following values :

References	Fecal output	Estimated intake
Kehoe, 1933 (24)	0.080 mg/d	0.100 mg/d
Barltrop, 1967 ()	0.123	0.150
Chisholm, 1956 ()	0.132	0.165

GASTROINTESTINAL ABSORPTION OF LEAD

Methods of study

Different methods have been used to estimate the fraction of absorbed lead wich would correspond to the f_1 factor of ICRP.

1. Intake and output studies (16)

   One measures the amount of lead in urine and in stools and one calculates the ratio $\frac{\text{urinary lead}}{\text{fecal + urinary lead}}$

   This method supposes that the equilibrium is reached i.e. that
   intake = output
   that no lead is accumulated in the body
   that the amount of lead lost through sweat & hair is negligible

   Measurement of oral intake (food & water) as well as fecal output permits to calculate the ratio $\frac{\text{fecal output}}{\text{oral intake}}$

   Finally, the urinary excretion of lead is a rough estimate of the amount absorbed. These differents methods do not allow to estimate how much lead is actually absorbed, how much is actually secreted by the liver & how much is secreted by the intestinal wall. It permits only to konw the net result of absorption and secretion.

2. Measurement of f_1 with Pb212 (20)

   An oral dose of Pb212 is administered and fecal and urinary excretion are measured.

3. Measurement of the amount excreted via the bile (4)

   Measurement of the elimination of Pb210 in the bile after IV injection of 100 µg of lead

4. Measurement of intestinal wall excretion of lead

Measurement of fecal elimination of RaD after IV administration of a carrier-free tracer dose, taking account if necessary of bile excretion

Urinary lead as an estimate of absorbed lead

Usually 5-10 % of dietary lead is absorbed and the following values have been reported for lead in 24h urine output :

Lead in 24h urine collection	Authors
0.030 mg (0.010-0.080)	Parry Howells (37)
(0.00 -0.290)	Horiuchi (17)
0.030 (0.010-0.080)	Kehoe (30)
0.044 (activation analysis)	Kopito (35)

In children the 24h urinary excretion in subjects presumably free from pica was

0.026 mg	Webster (49)

Incidentally it may be mentioned that an international atudy of urinary lead concentration was published by Kehoe et al, 1940 (25) wich showed the following values : (see also (12))

Country	Lead concentration (ug/liter)
France	0.020
Mexico	0.022
USA	0.029
Germany	0.027

In UK, we find a value of 0.050 (42), but the methods, the authors & the time being different it is difficult to draw firm conclusions.

Anyway, lead concentration in urine in the absence of values for urinary volumes should be interpreted with caution.

Urine and fecal lead as an estimate of absorbed lead

Holtzman (16) calculates the ratio of the daily urinary output (which he gives as 0.037 mg), to the fecal output ; $f_1 = 0.037/0.33 = 0.11$.

However, by accouting for the atmospheric lead contribution of 0.009 mg/d, we obtain, says Holtzman, $f_1 = 0.08$. The intake proposed by the author is 0.46 mg/d. The value calculated corresponds to the 8 % of ICPR (21).

It seems preferable to me to use the ration U/U + F.

This methodcan be criticized since it does not take account of sweat and hair loss which in basal conditions amount to about 0.1 mg/day.

Absorbed fraction in adults

Authors	f_1	Method
Kehoe (29)	0.10	Intake output
Kehoe (30)	0.08-0.10	Same
Patterson (39)	soluble (in water) : 0.10	
	insoluble (food) : 0.05	
Schroeder (42)	0.10	
Imamura (22)	0.20 to 0.40	Intake output
Hursh (20)	0.01, 0.08 & 0.16	Absorption of Pb212
Harrison (15)	0.06, 0.16 & 0.18	Absorption of Pb203
Horiuchi (17) (18)	0.06, 0.16 & 0.18	Intake output
Thompson(47)	0.06	Intake output
	0.08	Intake output : Food-feces/ food
	0.13	Intake-output : U/U + F
Fairhall (11)	0.01 to 0.03	Intake-output

Absorbed fraction in infants and children

The date are very scarce. It is generally know that the absorbed fraction is higher in infants, for heavy metals like Sr or Ca. Moreover it has been shown that the absorbed fraction in the intestine is increased in the early stages of life (36).

Applying the Intake-output method to Kehoe's data (24), yields a ratio of 0.25. If calculated by age there are some variations but it does not seem there is an age trend.

Variability of the absorption fraction

There are many factors of variation of the absorption fraction. Some are known, others are suspected or may reasonably be supposed to modify the intestinal absorption.

Such studies must take account of the magnitude of salivary excretion of lead which adds up to the oral intake (41).

There are good reasons to believe that some of the factors which regulate Ca (& Sr) absorption may play a role. It is not unlikely that the amount of vitamin D, of phosphate & of some complexant agents like inositohexaphosphate in food are relevant. It has been shown that rats and men on a low Calcium diet absorb more lead, since their fecal output of lead was higher and the urinary output was lower than the controls. It is likely that pregnant women, growing children particularly in populations showing dietary deficiencies, are critical groups with a higher risk of increased absorption (45) (11).

TABLE 1

Relevant Physical Properties of Metallic Lead and Certain of Its Alloys and Compounds

Material	Melting point, °C	Pouring temperature, °C	Boiling point, °C	Solubility, in 100 ml			
				cold water	hot water	Acid	Alkali
Metallic lead (common)	327.4	382	1525	Insol.	Insol.	HNO_3 Acetic	
Lead acetate (anhydrous)	280			44.3	221.20		
Lead arserate (insecticide) mono, di, meta and ortho	Decomp.			Insol.	Sl.sol.	Sol.	Sol.
Lead bromide	373		916	0.455	4.71	Sol.	Sol.
Lead carbonate (white lead)	Decomp.			Insol.	Insol.	Sol.	Sol.
Lead chloride	501		954	0.673	3.34	Sol.	Sol.
Lead chromate (chrome yellow)	844		Decomp.	0.00005		Sol. (Insol. acetic)	Sol.
Lead fluoride	855		1290	0.064		Sol. HNO_3-H_2SO_4	Insol.
Lead nitrate	Decomp. at 470		Decomp.	38.8	138.8	Sol.	Sol.
Lead sesquioxide	Decomp. at 360		Decomp.	Insol.	Decomp.	Sol.	Sol.
Lead oxide (red lead)	Decomp. at 500		Decomp.	Insol.	Insol.	Sol.	Insol.
Lead monoxide	888			0.0017			Sol.
Lead suboxide	Decomp.			Insol.		Sol.	Sol.
Lead dioxide (peroxide)	Decomp. at 290			Insol.	Insol.	Sol.	Sol.
Lead silicate (glazes)	766			Insol.		Decomp.	Sol.
Lead sulfate	1170			0.0028	0.0056	Sol.conc., insol. acetic	
Lead sulfide	1114			Essentially insol.		Sol.	Insol.
Lead tetraethyl	- 130		* 200	Insol.	Insol.	Insol.	Insol.
Lead tetramethyl	- 27.5		* 110	Insol.	Insol.	Insol.	Insol.

Lead seems to be more readily absorbed from water than from food and Patterson (39) suggests the following factos :

Absorbed fraction	%
Food	5
Water	10

Some physiological factors are probably relevant, like the fraction secreted by the liver and the fraction secreted by the intestinal wall (19).

There have been some contradicting reports in the literature as whether bile or intestinal wall are a more significant pathway of lead excretion. In sheep and in rats, about 8 % of the IV dose of lead acetate was excreted throug the biliary tract which was about hundred times more than through the walls of the intestines (4).

Two human subjects who received an IV injection of Pb212 excreted 0.29 & 0.25 per cent dose in the 0 to 48 h fecal collection (20).

Inhalation of particulate lead-212 was followed by a fecal excretion of 2-3 % in the 0 to 72 hours collection, while inhalation of lead-212 as a vapour showed an excretion of 37 % during the same period. It is not known whether the swallowed fraction differed in the two situations (41).

Constipation increases the absorbed fraction (24).

The chemical form of the ingested lead is probably very important.

Table 1, taken in part from Kehoe (30) shows the some of the chemical and physical chemincal characters of the main compounds of lead.

However, solubility is not the whole story. For instance, lead sulfide is not absorbed in the lungs but is readily absorbed in the gastro-intestinal tract if gastric acidity is present. Lead sulfide is converted to lead chloride which is readily abosrbed before it reaches the colon, where it reverses back to sulfide. The lead compounds which are absorbed are those which are soluble or which are converted to absorbable compounds.

Experimental ingestion of lead arsenate showed that the arsenate was completely broken down in the body and the lead was poorly absorbed : 1.3 % to 3.2 % of the ingested lead appeared in the urine (11).

The following compounds are readily abosrbed through the gastrointestinal tract : Lead acetate, Lead chloride, Lead oxide & Lead tetraethyl ; less soluble but still absorbed are othe compounds like Chromate, Sulfide, Sulfate and Carbonate.

Nothing is known regarding the mechanism of absorption trough the intestinal wall. Is there a protein which limits the amount absorbed (like irone) ? What is the role of complexants and ligands ?

All the konwn biological ligands contain dissociable protons which may be replaced by heavy metals in complex formation.

Metal binding by biological ligands is not specific ; the order of affinities and the relative concentrations of the different ligands only count.

On the other hand, chelation may be highly specific and introduces exceptions to the rule of relative affinities (38).

The effect of lead on epithelial membranes is restricted, as fas as we know, to the affect on the cells of the renal tubule, where it produces a pattern of aminoaciduria which is rather specific (aluninuria) (38).

The load of lead may probably raise the value of the absorbed fraction (50) (26) (27) (28) (29).

The size of the lead particles which is very important in inhalation is probably irrelevant in the case of oral intake.

Are lead blood levels a good index of absorbed lead ? (6) (13) (48)

Blood levels of methylmercury are a reasonable good estimate of chronic exposure but the same is not true for lead.

Ninety per cent of blood lead is fixed on the red cells (bound by the ligands of the cell membrane or rattached on the surface as a phosphate colloid).

A small amount of lead is within the red blood cells themselves.

Anyway, the lead which is fixed on the erythrocytes is not in equilibrium with the plasma.

Plasma lead is probably of two types, like calcium, a diffusible and a non-diffusible form. The diffusible fraction is very small, contrary to calcium. It probably accounts for the lead excreted : through the kidneys.

Blood levels show some correlation with absorbed lead in the case of exposure to inorganic lead. No such relation has been shown in the case of organic lead exposure.

It must be kept in mind that blood level is not the most sensitive index of the total body burden of lead.

Are there other qualitative indices of lead absorption ?

It is not the purpose of this discussion to develop the systemic effects of lead absorption. Still one should mention that lead once abosrbed into the body, interferes with some blood enzymes and with the sinthesis of hemoglobin.

There is a correlation between blood lead levels and the blodd activity of ∂-aminolevulinic acid dehydrase while the enzyme substrate ∂-aminolevulinic acid accumulates in the urine. There is a close relationship between the latter's amount in the urine and the blood levels. Urinary excretion of coproporphyrin may also be used as an estimate of absorbed lead.

ORAL VERSUS RESPIRATORY INTAKE OF LEAD

Today in the USA, high levels of blood lead indicating high intake of lead are most frequently found in ghetto children.

However more recently, high blood levels or slightly increased levels have been described in middle-class children.

Geochemical evidence suggests that human lead levels may well have been a factor of 100 below current levels (39) and that almost half of the increase occurred within the last 50 years, i.e. since the introduction of tetraethyl lead into gasoline in 1923.

In the USA, 25 % of the total lead used consisted in gasoline additives in 1968.

The average content of the earth's crust is about 10 to 15 ppm, but the dust which deposits in cities contains about 1 %, which is near the concentration in lead ores.

Lead in urban air ranges between 1 to 10 µg per m3, but near highways it reaches 40 µg per m3.

In Los Angeles at peak traffic hours it reaches 71.3 µg per m3.

Moreover urban air lead & lead in rainfall correlates with local gasoline sales.

Goldsmith & Hexter have estimated that about 30 to 60 % of the body burden of lead comes from the atmosphere.

Lead inhaled

Inhaled lead depends mostly on atmospheric lead.

Lead intake is distributed as follows :

		Amount inhaled	Reference
Oral intake	food :	0.40 mg	(23)
	fluids :	0.01-0.09 mg	(23) (20)
Respiratory		0.01-0.04 mg	(23) (20)
urban (20 m3/d, 1.3γ/m3)		0.026 mg	(34)
rural (20 m /d, 0.05γ/m3)		0.001 mg	(34)

Absorption of inhaled lead

Respiratory absorption of lead is sure to be a significant factor, as shown by recent studies suggesting that blood lead levels parallel the atmospheric concentrations of lead in the area where the exposed population lives (10).

Inhaled lead in industrial surroundings is more readily absorbed than ingested lead. The absorption coefficient is about 25 to 60 %. (10) (23) (26) (30) (39) (42) (14).

The following table is obtained from Patterson (39)

Substance	Intake/d	Pb concentration	Pb ingested γ Pb/d	Fraction absorbed	Pb absorbed γ Pb/d
Food	2 kg	0.2 ppm	400	0.05	20
Water	1 kg	0.01 ppm	10	0.1	1
Urban air	20 m3	1.3γ/m3	26	0.4	10
Rural air	20 m3	0.05γ/m3	1	0.4	0.4
Tobacco smoke 30 cigarettes		0.8γ/1cig.	24	0.4	10

Pb ingested means lead getting entrance into the gastrointestinal or the respiratory tract.

If we accept 0.030 to 0.040 mg of lead as the amount absorbed through the intestine, it appears that if the air in urban communities contains 1.5 to 2.0 µg per m3, an adult would retain and absorb 0.015 to 0.020 mg of lead, assuming 50 % absorbed and respiring 20 m3.

These values may show some variation : absorbed fraction may be low, but air concentration may be higher (9.8 µg/m3) in Paris in 1966.

It should be remarked that blood lead shows a definite correlation with lead in the air (and presumably with lead intake through the respiratory tract) ; however if lead in the air increases by hundred times, blood lead only doubles.

What does all this mean for children ?

It seems there is some suggestive epidemiological evidence that inhaled lead is an important path of intake. Exposure to 6 µg/m3 results in increased coproporphyrin excretion. In Sofia, it has been shown that a group of 48 children aged 5 to 7 years excreted more coproporphyrin than a control group in the suburbs.

It seems that the amount of inhaled lead is lower than the amount absorbed from oral intake. However the above values are only representative and it is clear that in many situations absorbed lead from the atmosphere may equal that absorbed from the gastrointestinal tract.

One may of course object that the above values for absorbed fraction was obtained with the traditional methods of toxicological investigations, i.e. by means of balance studies or of epidemiological studies relating blood levels to atmospheric lead concentration.

Horiuchi (19) administered RaD acetate intratracheally intoguinea-pigs and observed that 11 % was eliminated through the kidney, 34,8 % through the stools and 31 % remained in the body. It means that about 77 % was absorbed through the respiratory tract.

Size of the particles and respiratory absorption

Particles of less than 1µ diameter are better retained and 50 % of the lead is absorbed. Particles which have more than 2 µ diameter are deposited on the mucous lining and are transported through the mucociliary flows to the esophagus and swallowed.

Seventy five per cent of exhaust gases particles carrying lead are less than 0.9 μ diameter, which suggests that most of the atmospheric lead from automobile exhausts is deposited in the respiratory tract which is a system with a high absorption coefficient.

Is research needed and what research ?

The first question is : is further research necessary ? Do we know enough on the problem of intestinal absorption of lead for the purposes of public health and preventive medicine ?

Any new research should use radionuclides and apply a metabolic model fitted to the data.

If such is the case, one should thereafter study the effects of different factors on the different parameters : growth, gastric acidity, dietary composition and phytine content, intake of phosphate and calcium, chemical form of the ingested lead compound, dietary deficiencies.

A second aspect which needs to be clarified is to know what happens to the lead compounds once ingested ? What are the effects of the different biological ligands and complexants present in the lumen of the GI tract ?

Finally, the mechanism of lead transfer through the intestinal wall is unknown. Extrapolation of data from rodents, or dogs is questionable in view of the known species differences of the metabolism of bone-seeking radioisotopes.

Summary

1. Oral intake of lead amounts to about 0.44 mg in adults and 0.15 mg in children.

2. The coefficient of intestinal absorption is around 0.08 in adults and 0.25 in children. However the value for children is questionable and needs confirmation.

3. Absorption in the intestine depends on known factors (chemical form, dietary Ca) and presumably significant factors (vitamin D intake, diet composition, load of lead, gastric acidity ...).

4. Inhaled lead contributes a significant part to lead intake. It varies mainly with the atmospheric concentration of lead, the size of the particles and some physiological factors.

5. Further studies, if necessary, should concentrate on the fractions absorbed and secreted at the different levels of the GI tract, on the effect of biological complexants and ligands in the intestinal lumen and on the mechanism of transfer through the intestinal wall.

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