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ABSORPTION OF ^{212}Pb FROM THE GASTROINTESTINAL TRACT OF MAN

by

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For the calculation of radiation hazard from ingestion of lead isotopes it is necessary to specify the fractional amount which is absorbed from the gastrointestinal tract. The ICRP 1959 Report lists a value of 8 per cent based on experiments with stable lead. Because of the possibility that carrier-free lead of high specific radioactivity might behave differently, ^{212}Pb, the 10.6 hour half-life daughter of thoron, was administered to four volunteer subjects. Subject A received one oral and one intravenous dose, subjects B and C each received a single oral dose, and subject D received a single intravenous dose. Based on the fractional amount excreted in the urine after intravenous injection, it was estimated that absorptions of 1.3, 8.1, and 16 per cent had occurred when ^{212}Pb was taken by mouth.

Preparation of dose. The ^{212}Pb dose for oral consumption was prepared by passing a stream of 50 per cent O_2—50 % CO_2 through a 0.7 mCi, ^{228}Th

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stearate, filter cartridge source (HURSH & LOVAAS), sweeping the released thoron gas through a fritted glass bubbler stick into 250 ml of beer at a gas flow rate of 50 ml per min. The beer was contained in a 2-liter glass bottle. Recovery of ^{212}Pb using beer as the vehicle was superior to recovery using coca-cola, weak ascorbic acid solution, or physiologic saline. It was assumed that the foam generated by the bubbling process tended to hold the 55.6 s half-life thoron captive until decay occurred. Although the end product was somewhat 'flat', the subjects found it palatable. The period of thoron flow was adjusted so as to provide a ^{212}Pb activity equal to about 5μCi at the time of ingestion. A delay of $>$ 10 hours was introduced between preparation and ingestion to ensure transient equilibrium between ^{212}Pb and its 60.5 min half-life ^{212}Bi daugther.

A similar method was used to prepare the intravenous dose except that 20 ml of physiologic saline in a 1-liter plastic bottle was used as the vehicle. Subsequently the saline solution containing ^{212}Pb was transferred to a silicone-coated penicillin bottle for sterilization prior to the injection of 10 ml (about 1 μCi ^{212}Pb) into the antecubital vein.

In all cases gamma measurement of the preparation bottles, plastic syringes or drinking vessels, and transfer vessels showed that delivery of dose was better than 99 per cent complete. Aliquots of the dose were routinely set aside for later verification.

Doses were administered 1 to 2 hours after a light breakfast.

Sample collection and measurement. The subjects saved all urine and feces voided until the radioactive content decreased below the sensitivity of the counting method. Collection was made directly into 1-liter plastic cartons. The samples were measured for gamma activity by placing the collection carton on the upper surface of a 10 cm diameter, 10 cm thick NaI(Tl) crystal detector surrounded by a shielded compartment. The phototube output was fed into the first quarter of a 512-channel spectrum analyzer, calibrated to 16 keV per channel. The ^{212}Pb band was taken from 0 to 0.4 MeV and the ^{212}Bi band from 0.416 to 2.00 MeV. Calibration constants were established by measuring freshly prepared standardized ^{212}Pb solutions at intervals during the growth of ^{212}Bi and by including a solution volume range equivalent to that of the samples. These data enabled calculation of the correction factor to be applied to the counts in the ^{212}Pb band to take account of the Compton contribution from the ^{212}Bi gammas. For example, given a urine sample of 200 ml, the conversion constant for ^{212}Pb was 195 cpm per nCi and for ^{212}Bi was 130 cpm per nCi. The Compton correction was 0.87 times the cpm in the ^{212}Bi band. Backgrounds were about 350 cpm for the ^{212}Pb band and 215 cpm for the ^{212}Bi band. Counting times were 20 to 40 min per sample. Sample volumes were estimated by weighing.

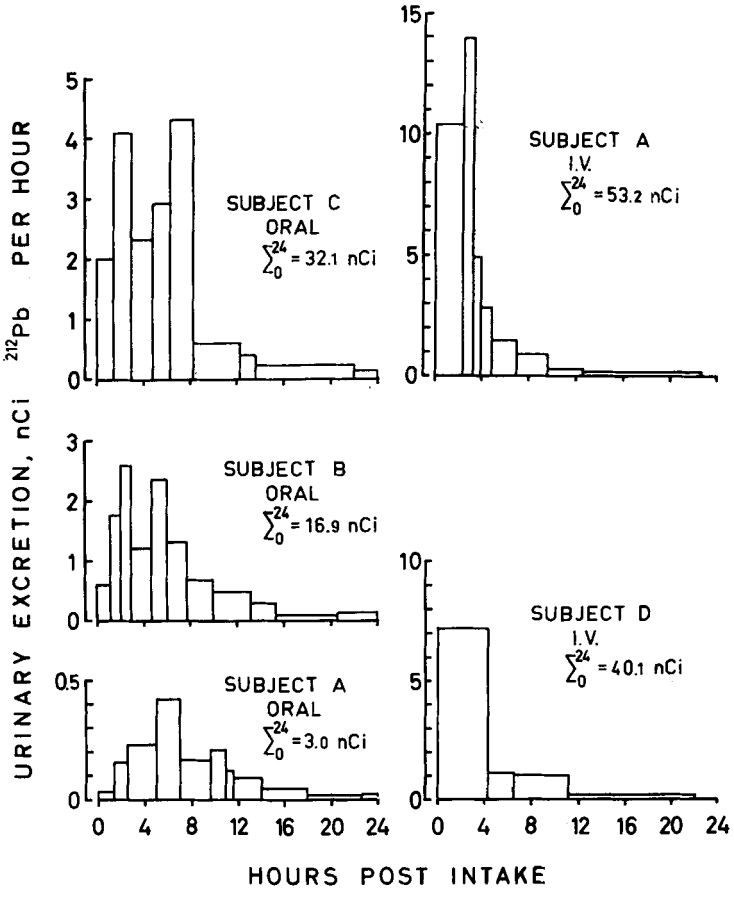

Fig. 1. ^{212}Pb urinary excretion rate as a function of time for oral and intravenous intake.

Twenty milliliters blood samples were taken from the antecubital vein, using heparin as anticoagulant, and sampling at the times noted in the report of the results. The blood was centrifuged within 3 min after collection and the plasma was separated from the cells. Each fraction was weighed and counted for gamma radioactivity. A 5 cm diameter, 5 cm thick NaI(Tl) crystal was used as detector and two measurements were taken for each sample using single channel analyzer settings such that the ^{212}Pb and ^{212}Bi activity could be estimated separately. The blood fractions were next digested with conc. HNO_3 and hydrogen peroxide. The ^{212}Pb without addition of carrier was separated by use of the dithizone method (GIBSON). The 10 ml weak nitric acid solution containing

Table 1

Absorption of orally administered ^{212}Pb calculated by comparing the urinary excretion with that after intravenous administration

Subject	Age yr.	Wgt kg	Dose μCi	Mode	Urinary loss* nCi/24 hours	Absorption	
						μCi	% dose
A	59	75	1.08	iv	53.2	—	—
D	39	76	1.17	iv	40.1	—	—
A	59	75	5.05	oral	2.98	0.067	1.3
B	40	84	5.01	oral	16.9	0.404	8.1
C	27	63	4.80	oral	32.1	0.768	16.0

* Activity decay-corrected to midpoint of collection interval.

the separated ^{212}Pb was evaporated on a 5 cm diameter stainless steel planchet yielding an essentially weight-free deposit. After a lapse of 6 hours or more to permit ^{212}Pb—^{212}Bi equilibrium to occur, the planchet was counted for alpha activity in close proximity to a zinc-sulfide layer phototube detector. The overall counting efficiency was 34 per cent as determined by comparison with a RaD + E standard. Chemical recovery was estimated by performing 10 analyses in which known amounts of ^{212}Pb were added to red cell and plasma samples from non-radioactive donors. The results indicated an average recovery of 90 per cent with a standard deviation of ± 7 per cent. This correction was applied to the experimental data.

Whole body counting. At intervals, the subjects were counted in the low background laboratory (LINDELL & MAGI) at this institute. The procedure included scanning measurements and a series of localization studies. For both purposes the subject lay in a supine position. The arrangement for scanning used three 12.7 × 10.2 cm NaI(Tl) crystals placed equidistant on a collar surrounding the subject with each crystal face 40 cm from the subject's longitudinal axis. During measurement the collar has a reciprocating motion as well as a movement parallel to the subject axis. Details are available in the 'whole Body Counter Directory' of IAEA. For localization studies, a single crystal 'looked' through a 5 cm wide aperture formed by two 1 cm thick lead plates. The counting rate of a point source (^{212}Pb) moved along the longitudinal axis of the subject position decreased by half when removed in either direction from a point directly under the crystal center to a point 10 cm distant. In the experimental procedure each position was counted from the dorsal and the ventral aspect of the subject. The

counts obtained were stored in a 400 channel spectrum analyzer, read out, and converted to activity according to techniques in general use.

Conversion to absolute activity units. The basis for estimating absolute activity depended on direct or indirect alpha counting rate comparison with a U.S. Bureau of Standards RaD + E standard. Secondary standards prepared by passing thoron through 0.5 N HNO_3 solutions were calibrated by evaporating aliquots on stainless steel planchets and by counting rate comparisons with the standard. The standardized solutions were useful for evaluating, by gamma counting rate comparison, the activity of substances such as beer and urine which leave residues when evaporated and were therefore not suitable for direct alpha counting.

Results

^{212}Pb in feces and urine. In the original planning of this research it was hoped that the personal habits of the subjects would conform to the ICRP gastrointestinal model and that the oral dose would be completely cleaned from the gut by 31 hours as specified. In sober fact, by 31 hours after intake, subjects A, B, and C had cleared 23, 0, and 17 per cent of the oral dose; by 48 hours, 82, 69, and 77 per cent; by 72 hours, 82, 69, and 77 per cent; and by 96 hours, 99, 69, and 77 per cent. The above data are based on fecal sample measurements, with the measured activity decay-adjusted to time of oral intake. The intervals without increase are periods in which no fecal samples were voided. As this pattern of excretion became apparent in the first oral experiment, it became evident that gastrointestinal absorption of ^{212}Pb could not uniformly be determined by whole body counting techniques. For example, if 10 per cent of a 5 μCi oral dose were absorbed, and if complete gut clearance required 96 hours, the absorbed ^{212}Pb would have decayed to 0.95 nCi, an activity below the threshold for measurement by this method. Accordingly, other methods were sought. The use of fecal measurements alone for a direct assessment of the unabsorbed ^{212}Pb was unsatisfactorily imprecise because of the large decay correction factor for low activity samples excreted at late times. Determination of absorption on the basis of the amount excreted in the urine in the first 24 hours was the method chosen. Accordingly, as stated above, the oral experiments were supplemented by two experiments in which ^{212}Pb was injected intravenously in order to define the per cent of the systemic burden which would appear in the urine.

The results of the measurements of urine samples from all five experiments appear in Fig. 1. Each sample was decay-adjusted from the time of measurement to the mid-point of the collection period. The cumulative excretion from

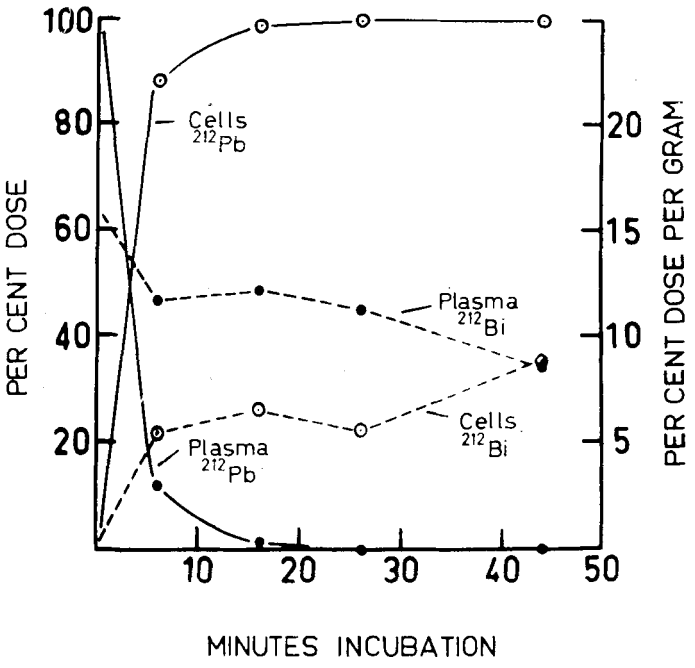

Fig. 2. In vitro uptake of ^{212}Pb and ^{212}Bi by the blood cells. The solid lines pertain to the left ordinate scale and the dotted lines to the right ordinate scale.

0 to 24 hours was noted for each experiment. By reference to the injected doses listed in Table 1, it may be calculated that, when ^{212}Pb was administered intravenously, 4.9 per cent (subject A) and 3.4 per cent (subject B) of the dose appeared in the 24-hour urine collection. The average value 4.15 per cent was used to estimate absorption in the oral experiments yielding the results entered in Table 1.

After intravenous injection, subject A excreted 0.29 per cent dose in the fecal collection period 0 to 48 hours. Subject D excreted 0.25 per cent dose for the same fecal collection period. These estimates are maximized since all sample measurements were decay-adjusted to injection time.

^{212}Pb uptake by blood cells. As an adjunct to the main experiments a preliminary in vitro experiment was performed in which 10 ml volumes of heparinized blood were incubated with added ^{212}Pb + ^{212}Bi at 37° C in a water bath. At pre-selected times the blood samples were removed and centrifuged. The plasma and cell fractions were then assayed for ^{212}Pb and ^{212}Bi activity by gamma

Table 2

^{212}Pb and ^{212}Bi content of plasma and blood cells in per cent absorbed or injected dose per gram referred to sampling time except as otherwise indicated

Subject and mode	Sample	Hours post dose	Plasma ^{212}Pb*	Cells ^{212}Pb*	Cells ^{212}Pb**	Cells ^{212}Bi**	Cells ^{212}Pb t = 0	Total cells ^{212}Pb t = 0 % dose
A	1	0.33	0.00036	0.0106	0.0104	—	0.0107	32
intravenous	2	1.67	0.00009	0.0124	0.0140	—	0.0147	44
	3	4.05	—	—	0.0150	—	0.0195	59
	4	6.75	—	0.0124	0.0113	—	0.0184	56
	5	49.75	—	0.00054	—	—	0.0139	42
B	1	2.50	0.00009	0.0073	0.0057	0.0033	0.0077	26
oral	2	6.00	0.00009	0.0130	0.0116	0.0115	0.0182	62
	3	8.00	0.00006	0.0136	0.0142	0.0111	0.0234	79
	4	24.50	0.00006	0.0058	0.0031	0.0079	0.0221	75
C	1	2.60	0.00025	0.0086	0.0076	0.0052	0.0096	24
oral	2	6.10	0.00008	0.0124	0.0123	0.0096	0.0184	47
	3	8.00	0.00011	0.0132	0.0124	0.0117	0.0216	55
	4	24.50	—	0.0048	0.0055	0.0031	0.0255	65
	5	48.50	—	0.0010	0.0010	0.0012	0.0236	60
D	1	0.35	0.00033	0.0221	—	—	0.0226	69
intravenous	2	1.58	0.00011	0.0250	0.0260	0.0210	0.0285	89
	3	7.10	0.000052	0.0190	0.0200	0.0190	0.0310	93
	4	23.63	—	0.0059	0.0061	0.0060	0.0280	86
	5	47.57	—	0.0012	0.0016	—	0.0325	100

* Measured by alpha counting

** Measured by gamma counting

measurement as described above. The results are shown in Fig. 2. It is seen that at 16 min the cells have taken up 99 per cent of the ^{212}Pb added to the whole blood. The uptake of ^{212}Bi by the cells occurred at a slower rate and gives no evidence of a tendency to concentrate with respect to the plasma.

In view of these tendencies, it is not surprising that the results after oral or intravenous administration as shown in Table 2 demonstrate only small amounts of ^{212}Pb in the plasma fraction of the drawn blood samples. The estimation of ^{212}Pb in the cells shows satisfactory agreement between the two measurement methods. The last column of the table lists results obtained by assuming that the total mass of circulating blood cells in grams is equal to 40.3 times the body-weight in kg (BEST & TAYLOR). Since the ^{212}Pb content per gram cell (as shown

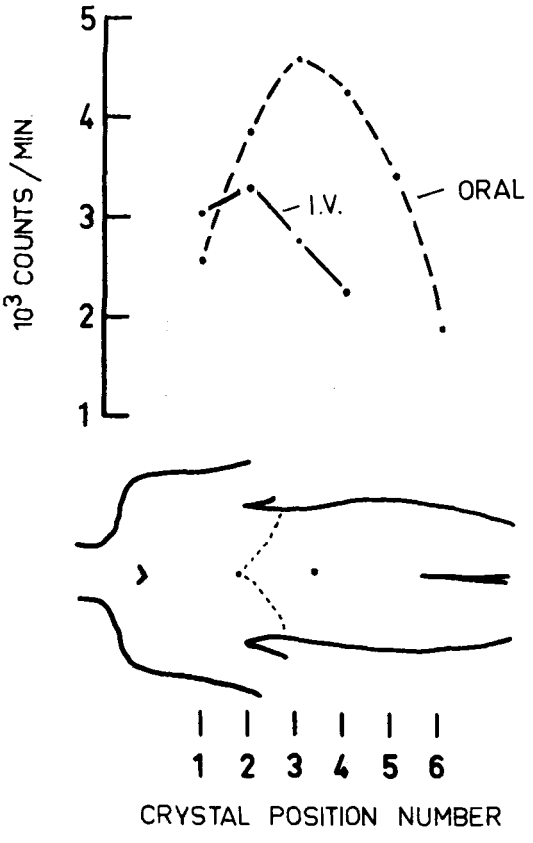

Fig. 3. Comparison of radioactivity profile after intravenous (+ 6 hours) and oral (+ 28 hours) intake for subject A. Actual counting rate was decay-adjusted to time of intake and for oral results normalized to 1 μCi intake.

in the next to last column) has been decay-corrected to time of intake, it may be seen that little, if any, ^{212}Pb is lost except by decay. The data for all subjects show an increase in cell content (last two columns) for the early sampling times believed to be due to the return of ^{212}Pb from the tissues to the blood as the plasma concentration is decreased, leading to further uptake by the cells. The generally higher estimates of ^{212}Pb uptake in the total cells for subject D are obviously in error, and it seems likely that the formula used to calculate the total cell mass resulted in an overestimate in this case. It is recognized (GLASSER) that such formulae may be in error when applied to specific normal individuals.

Comparison of ^{212}Bi and ^{212}Pb metabolism. Although the data on the fate of ^{212}Bi are less complete than are the data for ^{212}Pb, it has been found that at the time of voiding, the bismuth activity in the urine samples is about twice that of

the lead. The blood cells in general show (Table 2) slightly less ^{212}Bi than ^{212}Pb, leading to the interpretation that the rate of ^{212}Bi loss from the cells must be low in respect to its rate of formation from ^{212}Pb. HARBERS (1952) with ThX injected into rabbits, found an excess of ^{212}Bi over ^{212}Pb in the urine and the reverse to be true for the blood cells. STOVER (1959), after intravenous injection of ^{212}Pb into dogs, found an excess of ^{212}Bi over ^{212}Pb in the urine, and no disequilibrium for blood cells measured 20 min after sampling. Finally, the whole body counter localization studies in the present experiments showed no marked differences in the overall body distribution of ^{212}Pb and ^{212}Bi.

Whole body counter findings. Scanning measurements made with the whole body counter facility in the two intravenous experiments showed the expected 10.6-hour half-life decrease when small corrections were made for urinary loss. For the three oral experiments the activity found at the latest scan (about 48 hours), decay corrected to $t = 0$, yielded values of 18, 39, and 23 per cent of the ingested dose for subjects A, B, and C. As explained above, these amounts include activity in the lower bowel which was voided subsequently. With the exception of subject A, who voided 17 $\pm$ 1 per cent at 73 hours, the delay in voiding resulted in activities near the threshold of detection, subject to large correction factors for decay and not of use in the estimation of the absorbed fraction.

The measurements with the lead-columnated crystal yielded results of which the data from examination of subject A presented in Fig. 3 is a typical example. The oral experiment data, measured 28 hours after intake and normalized to time of intake and to 1 μCi dose, shows an activity peak in the lower bowel region. The survey 6 hours after intravenous injection (counts corrected to injection time) shows a concentration of activity in the blood-rich areas of the heart, lungs, and liver. This result agrees well with what might be expected from the high ^{212}Pb content of the blood cells.

Discussion

Absorption of ^{212}Pb. The wide variation between the absorption of subject A and subject C (12 times) calls for comment. The validity of the indirect method used to calculate absorption depends on the assumptions: (1) that the fraction of the systemic ^{212}Pb excreted in the urine will be the same whether entry is via the gut or by intravenous injection, and (2) that this fraction does not vary greatly from one healthy individual to another. Both these assumptions are biologically plausible but proof that they apply to excretion of lead by man is lacking.

Support for the calculated absorption values comes from the blood data in

Table 2. When the absolute concentrations of ^{212}Pb in the blood of subjects B and C are converted into per cent absorbed dose, the resulting values are quite comparable to those obtained in the two intravenous experiments. This would not be expected if the calculated systemic burdens of subjects B and C were greatly in error.

Proceeding on the grounds that the wide range in fraction absorbed is real, it is pertinent to inquire as to the possible causes of variation. The three subjects in the oral experiment were healthy active individuals. Compared with the ICRP (1959) reference man, who has 2 grams potassium per kg bodyweight, subjects A, B, and C had 1.93, 1.89, and 2.63 grams per kg. These values suggest normal and above average ratios of lean body mass to total weight. The only suggestive relationship is the decrease in absorption of ^{212}Pb with increase in subject age. The present data are insufficient to prove age dependence and may represent fortuitous sampling of extremes on a curve of normal biologic variability. Either interpretation makes it likely that there is a group of individuals for which the absorption value of 8 per cent is not conservative for health protection uses. Further experiments are needed to define the size of this group.

Concentration of ^{212}Pb in the blood cells. The concentration of lead in the blood cells was observed by early workers (DAUWE 1907, BEHRENS et coll. 1927) and confirmed many times since. HEVESY & NYLIN (1953) reported that 6 hours after intravenous injection of ^{212}Pb into man, 45 per cent of the injected amount was in the blood cells. STOVER (1959) found, for dogs, that 65 per cent of an intravenous dose of ^{212}Pb was in the blood cells at 5 hours. SCHUBERT & WHITE (1952) injected carrier-free ^{210}Pb into rats and detected 17 per cent of the dose in the blood cells at 30 minutes. The rate of loss from the red cells (not including radioactive decay) was 0.0187 per hour for dogs (STOVER) and 0.0231 per hour for rats (SCHUBERT & WHITE). HEVESY & NYLIN stated that in man the loss rate is less than 0.04 per hour.

The data in Table 2 show no consistant loss rate and render unlikely a loss rate greater than 0.007 per hour. If it be assumed for man that the death of the red cell releases the fixed lead and that the lead is removed from the body for example by secretion in the bile, a minimum release rate can be calculated. Since the average life span of the human red cell is 120 days, the equivalent lead loss rate would be 0.0083 per day, or 0.00035 per hour. Neither the data of HEVESY & NYLIN, nor our findings, can be regarded as excluding this interpretation. On the positive side a test of its feasibility can be applied by using data from the classical lead studies of KEHOE (1943). He found that the daily food intake of stable lead by occupationally unexposed individuals is about 0.35 mg and that the corresponding level in the blood is 0.030 mg per 100 ml. If the blood volume

of an adult is taken as 5 400 ml (ICRP), the total lead burden carried by the blood becomes 1.62 mg. Assuming an average absorption of 8 per cent from the gastrointestinal tract, and that 50 per cent of the absorbed lead is fixed by the blood cells, the daily uptake of lead becomes 0.014 mg. Since the lead concentration in the blood cells must be in a steady state the loss rate constant is 0.014 divided by 1.62 = 0.0086 per day, a value very near to the rate of 0.0083 per day based on the proposal that lead is lost only by death of the blood cell.

If this interpretation is valid it enables a circumstantial statement of the protection against lead poisoning given by the lead fixing property of the red blood cell. The maximum lead binding capacity of the cells can be estimated from the report by KEHOE et coll. (1943). They performed experiments in which two human subjects were given supplementary soluble lead by mouth at the rate of 1 and 2 mg per day over periods of years. From examination of their data it is found that the blood level rises to a mean value of about 0.06 mg lead per 100 ml and does not greatly exceed this. If this concentration represents saturation, the blood cell mechanism could turn over about 0.028 mg lead per day with only transient increases in the plasma concentration. Since by hypothesis the cells are able to pick up only half of the lead introduced from the gut, this would conform to a total systemic intake of about 0.056 mg per day. If the systemic intake exceeds this rate, the average plasma lead concentration must rise. This leads to proportionally increased skeletal deposition and urinary excretion. Toxicity symptoms might be anticipated at plasma lead concentrations up to 4 to 5 times above the unexposed mean levels, on the grounds that equivalent increases in urinary excretion rates have been observed (KEHOE) to be associated with lead intoxication.

Comparison of behavior of 'carrier-free' ^{212}Pb and stable lead. In terms of the discussion above, it is apparent that the ^{212}Pb in oral and intravenous administration was no longer 'carrier-free' after it entered the gut or the circulatory system. Accordingly, absorption from the gut should not differentiate between ^{212}Pb and stable ions as such. If ^{212}Pb is introduced with supplementary lead in amounts so large as to saturate the binding sites of the blood cells, marked differences in tissue distribution and urinary excretion might be expected.

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SUMMARY

The gastrointestinal absorption on administration of ^{212}Pb by mouth to three human subjects was found to be respectively 1.3, 8.1, and 16.0 %. The absorption was determined by a comparison of the 24-hour urinary excretion of these subjects with the average excretion in the same period by two subjects who received ^{212}Pb intravenously. The only obvious factor related to the wide range of absorption was that of age, increasing age being associated with decreasing absorption. The average value of 8 % is equal to that used by ICRP. It is pointed out that this choice may not be conservative for an appreciable fraction of the population. The ^{212}Pb concentrations in the blood cells as a function of time after oral or intravenous administration suggest that lead may be released from the binding sites only when the red cell dies. The relationship of this proposal to permissible intakes of stable lead is considered.

ZUSAMMENFASSUNG

Bei oraler Verabreichung von ^{212}Pb in drei Personen wurden gastro-intestinale Absorptionswerte von 1,3, 8,1 und 16 Prozent erhalten. Zur Bestimmung der Absorption wurde die 24-Stunden Urinausscheidung dieser Personen mit der durchschnittlichen Ausscheidung während derselben Periode in zwei Personen verglichen, bei denen ^{212}Pb intravenös verabreicht wurde. Der einzige Faktor der in positiver Korrelation zu dem weiten Absorptionsbereich stand, war das Alter; mit zunehmenden Lebensalter nimmt die Ausscheidung ab. Der Durchschnittswert von 8 Prozent ist derselbe wie der von ICRP angegebene; dieser sollte aber nicht als ausschlaggebend für einen beträchtlichen Anteil der Bevölkerung betrachtet werden. Die Konzentrationen von ^{212}Pb in den Blutzellen im Verhältnis zur Zeit nach der oralen oder intravenösen Verabreichung deutet darauf hin, dass stabiles Blei von den Retensionsstellen nur dann freigesetzt wird, wenn die rote Blutzelle stirbt. Diese Frage wird hinsichtlich der zulässigen Aufnahme von stabilen Blei im Organismus diskutiert.

RÉSUMÉ

Après administration de ^{212}Pb par voie orale à trois sujets humains, on a constaté des taux d'absorption gastro-intestinale de 1,3, 8,1 et 16 %. La méthode de détermination de l'absorption a été de comparer l'excrétion urinaire de 24 heures de ces sujets avec l'excrétion moyenne au cours de la même période de deux sujets à qui ^{212}Pb avait été administré par voie intraveineuse. Le seul facteur nettement en rapport avec ces taux d'absorption très différents est l'âge, l'absorption diminuant quand l'âge augmente. La valeur moyenne de 8 % est celle qui est donnée par l'ICRP. Les auteurs soulignent que ce choix ne peut pas convenir pour une partie appréciable de la population. L'étude des concentrations de ^{212}Pb dans les cellules sanguines en fonction du temps après administration orale ou intraveineuse fait penser que le plomb ne peut être libéré que quand le globule rouge meurt. Les auteurs examinent les conséquences de cette hypothèse sur la quantité admissible de plomb stable introduit dans le corps.

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