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THE IMPACT OF AIR-LEAD ON BLOOD-LEAD IN MAN—A CRITIQUE OF THE RECENT LITERATURE*

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Summary—The nature of the relationship between air-lead and blood-lead in man was evaluated using all the available information from published studies in which subjects were in an approximately steady state with regard to lead exposure, and blood-lead could be related to air-lead measurements made in the individual's breathing zone. The observed blood-lead–air-lead relationship was compared with the relationships predicted by applying the two kinetic models which have been proposed to describe lead disposition in man. The models were found to be inconsistent with observed lead disposition kinetics. Each model generates a linear blood-lead–air-lead relationship with predicted blood-lead levels well above the actual levels except within the very lowest blood-lead range ($< 5\ \mu g/m^3$). The observed blood-lead–air-lead relationship is curvilinear with slope decreasing as blood- and air-lead increase. The implications of this curvilinearity with regard to the dependence of x, the increment in blood-lead associated with a given increment in air-lead, both on the magnitude of the air-lead increment and on the baseline blood-lead value are illustrated and discussed.

Introduction

A document published in 1972 (NAS-NRC, 1972) was intended to review and evaluate all the literature bearing on the question of the significance of airborne lead for human health and welfare. The committee that prepared this document was unable to arrive at a firm conclusion concerning the contribution of lead in air to the total body burden. It identified two general exposure routes, the inhalation of lead aerosols and the hand-to-mouth transfer of lead-bearing street dust, a potential problem among young children.

More recently, a World Health Organization task group (WHO, 1977) and the US Environmental Protection Agency (EPA, 1977) have been confronted with the same issues. All three of these study groups considered the possibility of estimating the importance of air-lead by calculating directly transfer from air (or street dust) into the body. This approach was found by the NAS-NRC study group to be impractical because of the uncertainties surrounding airway deposition and clearance rates for the lead aerosols of interest. The importance of hand-to-mouth transfer of fallout lead in street dust was even more difficult to assess because, in addition to uncertainties regarding the gastro-intestinal absorption of lead in children, there was absolutely no information concerning how much street dust a child might swallow. This particular problem, therefore, was simply cited as being one which required attention.

With regard to the impact of the inhalation of lead aerosols, the NAS-NRC committee concluded from the sparse epidemiological data available at the time that there was no perceptible impact of the concentration of lead in air (PbA) on the concentration of lead in blood (PbB) below a PbA level of 2–3 $\mu g/m^3$. The committee recommended that more precise studies be conducted concerning the relationship between ambient-air-lead concentration and blood-lead concentration, perhaps by use of personal monitors. This specific recommendation was implemented in one study (Azar, Snee & Habibi, 1973a).

Between the time of publication of the NAS-NRC document and the preparation of the WHO document, which actually took place in 1975, some new information became available concerning the disposition of lead, both inhaled and swallowed. Still more information was available to the US EPA in the preparation of its 1977 document. Yet, in both documents summary judgement as to the impact of inhaled lead on the body burden relied mainly on epidemiologic information concerning the relationship between PbB and PbA. The impact of lead in street dust on the body burden of lead in children was judged in both documents still to be surrounded by great uncertainty.

The present critique will take a fresh look at the impact of air-lead on blood-lead in man, considering all the useful information currently available. The problem still is basically divisible into two, the inhalation of lead aerosols and the hand-to-mouth transfer of fallout lead in the environment. Consideration will be given only to the first problem.

There are two approaches to estimating the impact of inhaled lead aerosols on the body burden of lead. The first is to use measured rates of uptake (or loss) of lead from an experimental study together with a disposition model to project either total body burden or the amount of lead in any of the presumed kinetic compartments at any time. This approach must take

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into consideration uptake from all sources by all absorption routes since the concern is with the relative importance of inhaled lead to the total body burden.

Two different disposition models have been used to describe lead kinetics. Rabinowitz, Wetherill & Kopple (1976) applied a three-compartment model to human exposure data from their studies of the kinetics of stable labelled lead. Bernard (1977) proposed a five-compartment model to describe human lead kinetics. Both models are shown schematically in Fig. 1.

The second approach to estimating the impact of inhaled lead aerosols on the body burden of lead is purely empirical: the observed relationship between PbA and PbB is evaluated mathematically. For this approach to be valid certain criteria must be satisfied. First, steady-state or near steady state conditions must prevail, wherein the amount of lead inhaled per unit time must have been reasonably constant over a period of time long enough for virtual equilibration to occur between PbA and PbB. The input of lead from other sources must also be approximately constant, since it is not negligible relative to the input of lead from air.

In this paper we will evaluate the nature of the PbB–PbA relationship within the range of normal ambient-air lead concentrations as observed by Azar *et al.* (1973a). PbB values predicted by this relationship both within and beyond the range of PbA levels on which it is based will be compared with individual data points from experimental studies and with those predicted by application of the Rabinowitz and Bernard models. All the data used apply only to adults.

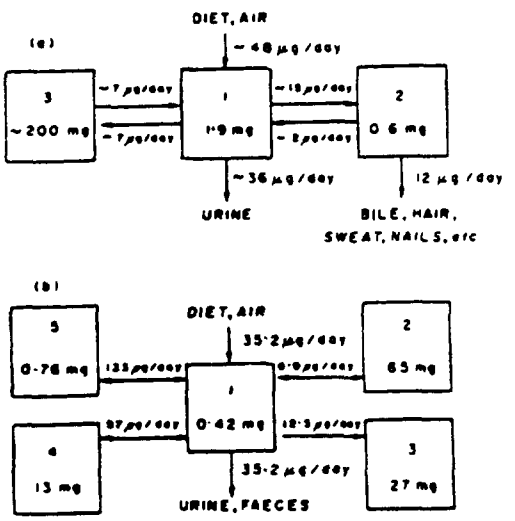

Fig. 1. Models proposed to describe lead disposition kinetics by (a) Rabinowitz *et al.* (1976) and (b) Bernard (1977). The amounts of lead in each compartment, exchanging daily between compartments, and excreted daily are shown for steady state conditions of continuous exposure to food, water, and air lead. The amounts of lead shown entering the central compartment in each case are the amounts that are assumed to be absorbed daily into the systemic circulation from all sources.

Observations: graded exposure levels

Azar *et al.* (1973a) monitored the PbA exposure of 150 adults from five locations in the United States, continuously and individually for 2–4 wk. The subjects were in a steady state condition with regard to exposure; the average number of years spent on the current job varied from 16–19·1 at the five different locations. Air-lead exposure, calculated as a time-weighted average, was monitored using personal air samplers and ranged up to about 4 μg total PbA/m^3 in the group with the lowest exposures and up to about 9 μg total PbA/m^3 in the group with the highest exposures. The concentration of respirable lead was somewhat less.

Statistical analysis of these data could be performed using regression models of varying degrees of complexity. For this calculation it was decided to use the simplest model available: that is, a straight-line fit with PbB depending upon PbA, and also to include a component representing differences among the five geographic locations. Further, the values of PbA and PbB could first be transformed, e.g. by taking their logarithms, or they could remain untransformed. However, any particular choices in this respect might well be criticized as being somewhat arbitrary. In this analysis, therefore, it was decided to use an empirical approach to the problem of transforming PbA and PbB (Box & Cox, 1964) to obtain the optimal transformations. This requires that a variable of interest, Y, be transformed by the expression $(Y^{\lambda} - 1)/\lambda$ where λ is chosen so that the assumptions of normality and homogeneity of variance in regression analysis are best satisfied.

In order to avoid unrealistic predicted values for PbB when PbA = 0, the component C_i, where $i = 1, \ldots, 5$, representing each of the five geographic locations, was incorporated into the model as follows:

$$PbB = A + B(PbA + C_i).$$

C_i represents the non-air lead contribution to PbB, expressed in terms of equivalent PbA.

The Azar *et al.* data were analysed by applying the above transformation both to PbB and PbA, and the optimal parameters in the model were found to be

$$(PbB)^{-1\cdot019} = -0\cdot09786 + 0\cdot17904(PbA + C_i)^{-0\cdot104}$$

where $C_1 = 6\cdot55627$, $C_2 = 1\cdot61865$, $C_3 = 0\cdot38578$, $C_4 = 5\cdot98683$, and $C_5 = 2\cdot76079$ for the five locations, with $R^2 = 0\cdot49$, the proportion of variation explained by the model. The average relationship between PbB and PbA was found by substituting the average C_i value, 3·46186, and solving for PbB:

$$PbB = [-0\cdot09786 + 0\cdot17904(PbA + 3\cdot46186)^{-0\cdot104}]^{-1/1\cdot019} \quad (1)$$

This result can be interpreted as the reciprocal transform for PbB and almost the logarithmic transform for PbA. The PbB–PbA relationship, shown in Fig. 2, is curvilinear with slope decreasing as PbA and PbB increase.

Observations: discrete exposure levels

The criteria for including data points in this analysis were: first, that the individuals studied were in an

approximately steady state of lead exposure; and second, that PbB could be related to PbA measurements made in the individual's breathing zone. Two studies were considered to meet these criteria adequately. Both involved the exposure of human volunteers to known concentrations of artificially generated lead sesquioxide.

Kehoe (summarized by Gross, 1979) exposed individuals singly, and often the same individuals sequentially, at many different air-lead concentrations for periods of time ranging from 98 to 772 days. Griffin, Coulston, Wills, Russell & Knelson (1975) exposed groups of volunteers for 14–19 wk at only two air-lead concentrations. Hence, standard deviations were calculated for the Griffin *et al.* data. It is assumed that in both of the above studies the PbAs monitored by the investigators were the concentrations actually in the breathing zone of the subjects. Hand to mouth transfer of settled lead-bearing dust probably was minimal. Kehoe subjects dusted the chambers frequently (Kehoe subject JOS, personal communication 1980). A similar housekeeping program prevailed in the Griffin study (T. B. Griffin, personal communication, 1980).

In order to minimize the effect on these data of non-air sources of lead, all the experimental data points were normalized to the same control value. For this purpose, the control period PbA range of 0·1–0·2 $\mu g/m^3$ measured in the Griffin *et al.* study was used. No control period PbA measurements had been reported for the Kehoe study. From the line of best fit to the Azar *et al.* data, the PbB values corresponding to PbA values of 0·1–0·2 $\mu g/m^3$ were found to be 16·1–16·2 $\mu g/dl$. Since the Kehoe PbB data were given only to two significant figures, these values were rounded off and a control period PbB of 16 $\mu g/dl$ was used to normalize experimental data. The adjustment was made by subtracting from individual or mean PbB values, as appropriate, the difference between measured control period PbB and 16 $\mu g/dl$.

These data are summarized in Table 1 and shown in Fig. 2.

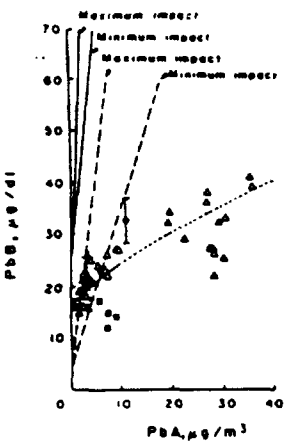

Fig. 2. Predicted and observed PbB level as a function of PbA. Data are taken from Table 1. The Kehoe data points (△▲■) represent 12 individuals, some studied more than once; data points from individuals exposed to large particle aerosols (▲); data points from one individual, DH, whose measured PbB from non-air lead sources was exceptionally high (■). All data points are adjusted to a PbB from non-air lead sources of 16 $\mu g/dl$. Standard deviations are shown for Griffin *et al.* points (●). The line of best fit to the Azar *et al.* data is shown dashed beyond the range of actual measurement. The Rabinowitz (——) and Bernard (– – –) predicted lines (after 5 yr) are taken from Table 2; maximum and minimum impact conditions are discussed in the text.

Prediction: linear kinetic models

The differential form of the Rabinowitz model (Fig. 1)* is

$$dM_1/dt = (0{\cdot}002/0{\cdot}6)M_2 + (0{\cdot}007/200)M_3 - (0{\cdot}015 + 0{\cdot}007 + 0{\cdot}036/1{\cdot}9)M_1$$
$$dM_2/dt = (0{\cdot}015/1{\cdot}9)M_1 - (0{\cdot}002 + 0{\cdot}012/0{\cdot}6)M_2$$
$$dM_3/dt = (0{\cdot}007/1{\cdot}9)M_1 - (0{\cdot}007/200)M_3$$

where dM_1/dt, dM_2/dt and dM_3/dt represent the rates of change in the mass M of lead in compartments 1, 2 and 3 respectively as determined by rates of transfer into and out of the three compartments. In these equations time t is in days and the coefficients of the various Ms have the dimension [day^{-1}].

The differential form of the Bernard model* is

$$dM_1/dt = (0{\cdot}133/0{\cdot}76)M_5 + (0{\cdot}057/13)M_4 + (0{\cdot}0125/27)M_3 + (0{\cdot}00686/65)M_2 + (0{\cdot}2442/0{\cdot}419)M_1$$
$$dM_2/dt = (0{\cdot}00686/0{\cdot}419)M_1 - (0{\cdot}00686/65)M_2$$
$$dM_3/dt = (0{\cdot}0125/0{\cdot}419)M_1 - (0{\cdot}0125/27)M_3$$
$$dM_4/dt = (0{\cdot}057/0{\cdot}419)M_1 - (0{\cdot}057/13)M_4$$
$$dM_5/dt = (0{\cdot}133/0{\cdot}419)M_1 - (0{\cdot}133/0{\cdot}76)M_5$$

where time t is in days and five equations are necessary to describe the net rates of change in the five model compartments.

The compartments depicted do not have discrete anatomical dimensions. Thus, compartment 1 in both models includes but is not necessarily limited to blood. Therefore, it is not surprising that the amounts of lead associated with specific compartments are different in the two models.

The PbB levels predicted by the Rabinowitz and the Bernard models after exposure for 5 yr (260 wk) and 19 yr (1000 wk) were computer simulated in the following way. The amount of lead absorbed each day into the systemic circulation was entered into the computer program as a single unit. This daily increment was allowed to be distributed and excreted in accordance with the magnitudes of the model rate constants (that is, in accordance with the equations given). The initial condition was the complete absence of lead from all body compartments. Table 2 gives the predicted PbB levels at the end of the stated exposure periods as functions of the total amount of lead absorbed each day from all sources.

*Both models are given here for disposition only; that is, it is assumed that intake has ceased. If exposure continues throughout the disposition phase, functions describing the rates of input must be incorporated into the equations for dM_1/dt.

Table 1. *Individual and mean steady state PbB levels in persons exposed to lead sesquioxide aerosols and values derived from the line of best fit to the data of Azar* et al. *together with the associated values of* z

Subject or no. of subjects	Control period* PbB (μg/dl)	Experimental period PbA† (μg/m³)	PbB (μg/dl)	PbB (μg/dl) adjusted to baseline of 16 μg/dl	z‡	References
MB	24	29·4§	40	32	0·55	Kehoe (Gross, 1979)
MOB	26	22·4	39	29	0·58	
	26	28·4§	32	22	0·21	
PB	23	28·4	33	26	0·35	
SB	21	27·4	32	27	0·40	
FC	22	30·6	39	33	0·56	
	22	30·1§	31	25	0·30	
LD	18	9·3	29	27	1·21	
	18	19·7	36	34	0·92	
	18	27·1	40	38	0·82	
	18	35·9	41	39	0·64	
DH	30	5·6	31	17	0·18	
	30	7·3	26	12	−0·56	
	30	7·6	29	15	−0·14	
	30	8·8	28	14	−0·23	
NK	20	0·6	20	16	0	
	20	1·2	21	17	1·00	
	20	1·9	23	19	1·76	
	20	2·4	26	22	2·73	
	20	3·3	26	22	1·94	
	20	3·6	30	26	2·94	
	20	4·0	29	25	2·37	
HR	21	2·4	25	20	1·82	
	21	3·7	21	16	0	
	21	7·5	27	22	0·82	
JOS	21	9·4	32	27	1·20	
	21	19·3	37	32	0·84	
	21	27·1	41	36	0·74	
	21	35·7	46	41	0·70	
JUS	21	28·1§	32	27	0·39	
SS	19	0·6	20	17	2·5	
	19	1·3	20	17	0·91	
	19	1·8	18	15	−0·62	
	19	2·4	19	16	0	
	19	2·7	23	20	1·60	
	19	3·4	24	21	1·56	
	19	4·3	24	21	1·22	
	19	2·4	24	21	2·27	
	19	3·2	21	18	0·67	
	19	5·4	27	24	1·54	
	19	6·2	26	23	1·17	
	19	7·0	26	23	1·03	
	19	7·2	29	26	1·43	
8	20·3 ± 3·2	10·9	36·8 ± 4·3	32·5 ± 4·3	1·54	Griffin *et al.* (1975)
12	20·3 ± 4·2	3·2	26·0 ± 3·8	21·7 ± 3·8	1·90	
		1·0		17·108	1·135	Line of best fit to data of Azar *et al.* (1973a)
		2·0		18·133	1·074	
		5·0		20·741	0·946	
		10·0		24·285	0·825	
		20·0		30·151	0·704	
		30·0		35·378	0·644	
		40·0		40·386	0·608	

* The PbA during control periods is not known for the Kehoe studies but was 0·1–0·2 for the Griffin *et al.* (1975) studies. For calculation of z (see footnote ‡), baseline PbA was assigned the value 0·2 μg/m³ for the Kehoe studies.

†All PbA levels are expressed as if exposure had been continuous. For example, if a subject were exposed for 8 hr/day, 5 days/week, to a chamber air-lead concentration of 150 μg/m³, the value in the table would be [(8 hr/day)(5 day/wk)/(168 hr/wk)] 150 μg/m³ = 35·7 μg/m³.

‡z is the ratio ΔPbB:ΔPbA, where ΔPbB is the magnitude of the increment in PbB resulting from an increment in PbA of ΔPbA. The values of ΔPbB are calculated as the PbB values in column 5 minus 16 μg/dl, the baseline value. The values of ΔPbA are calculated as the PbA values in column 3 minus 0·2 μg/m³. Calculation of z from the line of best fit to the Azar *et al.* data starts from the baseline assumptions that PbA = 0·2 μg/m³ and PbB = 16·2 μg/dl. The value of z depends on the choice of baseline; see text for a discussion of this point.

§Large-particle aerosols.

These values are means ± 1SD.

Table 2. *The impact of PbA on PbB as predicted by the Bernard and the Rabinowitz models under different conditions*

Total Pb absorbed daily from all sources (μg)	PbB level predicted by Bernard model (μg/dl)		PbB level predicted by Rabinowitz model (μg/dl)		PbA corresponding to daily retention; 'minimum impact' conditions* (μg/m³)	PbA corresponding to daily retention; 'maximum impact' conditions† (μg/m³)
	After 5 yr (260 wk)	After 19 yr (1000 wk)	After 5 yr (260 wk)	After 19 yr (1000 wk)		
35·2	13·5	16·5	54·3	55·4	3·05	1·28
70·4	30·5	34·2	110·0	111·9	6·63	3·64
105·6	48·4	52·4	166·8	169·4	14·22	5·99
140·8	66·7	70·9	224·5	227·7	19·81	8·35
176·0	85·2	89·6	283·0	286·7	25·40	10·70
211·2	103·9	108·3	342·1	346·1	30·98	13·06

*'Minimum impact' conditions are chosen to minimize the predicted impact of PbA on PbB. They are: total volume of air breathed daily, 18 m³; 35% of inhaled Pb deposited in lung and absorbed. Lead absorbed from diet (food plus water) is assumed to be constant at 16 μg (0·08 × 200 mg)/day.

†'Maximum impact' conditions are chosen to maximize the predicted impact of PbA on PbB. They are: total volume of air breathed daily, 23 m³; 65% of inhaled Pb deposited in lung and absorbed. Lead absorbed from diet is assumed to be 16 μg/day.

The total lead absorbed daily was considered to be the sum of the amounts absorbed from the diet and from the air. It was assumed that total dietary (food plus water) lead was constant at 200 μg/day (Rabinowitz *et al.* 1976) and that 8% of this dietary lead, or 16 μg, was absorbed. The remainder of the amount absorbed was attributed to air-lead.

To convert the amount of lead absorbed from air to a concentration of lead in air, certain assumptions must be made about the volume of air breathed daily and about the fraction of inhaled lead absorbed from the lung. Chamberlain, Heard, Little, Newton, Wells & Wiffen (1978) have shown that the fraction absorbed is dependent on particle size. At the same time they investigated the particle size distribution of lead in ambient air. They found that in general the diffusional mean equivalent diameter (DMED) of mature aerosols such as those typical of rural areas and of urban areas away from the influence of major traffic arteries was about 0·06 μm while the mass median equivalent diameter (MMED) was larger, about 0·2–0·3 μm. The DMED of freshly generated lead aerosols measured near major highways was smaller, 0·03 μm, and the MMED was much smaller, 0·04 μm.

In our simulations two sets of assumptions were evaluated separately: one consistent with maximum impact of PbA on PbB, and one consistent with minimum impact of PbA on PbB. For maximum impact it was assumed that the individual is "reference man" and breathes 23 m³ air/day (ICRP, 1975) and that 65% of the lead inhaled is deposited in the lung and absorbed into the systemic circulation. This absorption level approximates the midpoint of the range reported by Chamberlain *et al.* (1978) for lead aerosols with very small DMED, 0·02–0·94 μm, at breathing cycles of 4–8 sec. For minimum impact it was assumed that reference man breathes 18 m³ air/day and that 35% of the lead inhaled is absorbed. This absorption magnitude approximates the midpoint of the range reported by Chamberlain *et al.* for lead aerosols having a larger DMED, about 0·09 μm at breathing cycles of 4–8 sec. The PbB levels predicted by the Rabinowitz and Bernard models after exposure for 5 yr are shown in Fig. 2.

Results and discussion

Figure 2 allows direct comparison of the PbB–PbA relationships predicted by the Rabinowitz and the Bernard models, calculated from the data of Azar *et al.* and those observed in experimental studies.

It should be noted that at steady state the Bernard model will generate a PbB level of 19·0 μg/dl for a total daily absorption of lead from all sources of 35·2 μg, corresponding for the conditions of this simulation to a PbA of between 1 and 3 μg/m³ depending on whether maximum impact or minimum impact conditions are considered. However, because of the very slow return of lead from two of its peripheral compartments (compartments 2 and 3, Fig. 1) the Bernard model has not yet achieved a steady state even after a 19-yr simulated exposure (Table 2).

Figure 2 shows that the line of best fit to the Azar *et al.* data provides a good fit to the data points from experimental studies while simulation based on the kinetic models of either Rabinowitz or Bernard predicts entirely inappropriate PbB values. One of the reasons for the poor quality of fit is that both kinetic models are linear while the observed relationship between PbB and PbA is curvilinear.

Both the Rabinowitz and the Bernard models are linear mammillary models consisting of a central compartment into which the foreign compound enters and from which it is eliminated by excretion or metabolism. Exchange takes place continuously between this central compartment and one or more peripheral compartments into which the compound is distributed. These exchanges as well as the elimination processes are first order (kinetically linear); that is, the unidirectional transfer rate is directly proportional to the amount available for transfer. Compartments as defined kinetically are not necessarily congruent with specific tissues or organ systems; however, the blood is usually considered to be part of the central compartment. In general, linear mammillary

models differ from one another only in the number of peripheral compartments assigned to each and in the values of the transfer rate constants.

The utility of linear kinetic models in describing the behaviour of foreign compounds, particularly of drugs, is firmly established. Linear models are founded on reasonable assumptions about the kinetic nature of transfer across biological membranes, assumptions which have been verified experimentally in many instances. Furthermore, they are the simplest biologically reasonable models. Thus a linear mammillary model is generally the first choice in modelling the kinetics of a foreign compound unless specific information about observed kinetic behaviour dictates otherwise.

The mathematical expression for the time-dependence of the amount in the central compartment of a linear mammillary model after acute administration (the integrated form of the differential equations given) leads directly to the identification of certain attributes shared by all linear mammillary models. One of these is a direct proportionality between the amount of material in each compartment and dose or dose rate at steady state. The theoretical proportionality constant is a function of the excretion rate constant as well as of the dose or dose rate. One implication of representing the kinetic behaviour of a foreign compound by a linear mammillary model is that tissue concentration should be proportional to exposure at steady state. However, it is clear from Fig. 2 that the PbB–PbA relationship is not linear at steady state. The linear models are not accurate representations of lead disposition kinetics.

A measure in common use to describe the PbB–PbA relationship is α or ΔPbB–ΔPbA, the increment in PbB associated with a given increment in PbA. As a result of the curvilinearity of the PbB–PbA relationship, α is not a constant. To begin with, α is dependent on the magnitude of the PbA increment used in its calculation. This dependence is illustrated in Fig. 3, in which α values for individual or mean data points from the Kehoe and Griffin *et al.* studies can be compared with α calculated from the line of best fit to the Azar *et al.* data. For the Azar *et al.* line baseline PbB was taken to be 16·2 μg/dl, the PbB value associated with a PbA of 0·2 μg/m^3. For the calculation of α from Kehoe data, for which PbA is not known for the control periods, control PbA was arbitrarily assigned the value 0·2 μg/m^3. The calculated α values are presented in Table 1.

It is apparent from Fig. 3 that within the range 0–20 μg Pb/m^3 of air, α is a decreasing function of PbA rather than the constant value which would be expected on the basis of a linear model; that is, as ΔPbA increases, α decreases. Values of α calculated from the Griffin *et al.* and Kehoe data points parallel the behaviour of the Azar *et al.* line.

The wide scatter of α values among the Kehoe subjects exposed to <10 μg Pb/m^3 is due to variation *within individuals* as well as *between individuals*. Thus, for example, subject NK (Table 1) had α ranging from 1·00 to 2·94 over the narrow ΔPbA range of 1–3·8 μg/m^3 (adjusted). Nevertheless, when individual subjects were exposed to a wide range of PbAs, e.g. subjects LD and JOS, there was a clear decrease in α with increasing PbA.

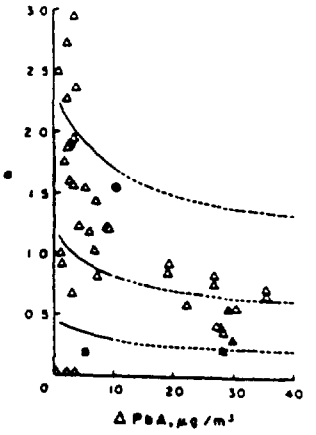

Fig. 3. α as a function of ΔPbA. Data are taken from Table 3. The line of best fit to the Azar *et al.* data and the 95% confidence limits to the line (above and below) are shown dashed beyond the range of actual measurement. Griffin *et al.* mean values (●); Kehoe data points (△). Kehoe data points from individuals exposed to large-particle aerosols (▲); the only positive value of α from subject DH (Kehoe), whose measured PbB from non-air lead sources was exceptionally high (■). The four negative values for Kehoe subjects (see Table 1) have not been plotted.

α is dependent not only on ΔPbA but also on the baseline PbB value; that is on the amount of lead already in the systemic circulation, PbB_0. This dual dependency is illustrated by the simulation in Fig. 4, based on the Azar *et al.* line. Figure 4 shows that the largest calculated values of α should be obtained for groups of subjects with low baseline PbB levels (PbB_0) exposed to small increments in PbA (ΔPbA). In practical terms this behaviour is most marked in the PbB range below about 25 μg/dl, the range associated with ambient air lead levels. When baseline PbB equals or exceeds about 30 μg/dl, α is small, about 0·5 μg/dl for ΔPbA = 1·0 μg/m^3, and is affected only slightly if at all by the magnitude of the experimental increment in PbA.

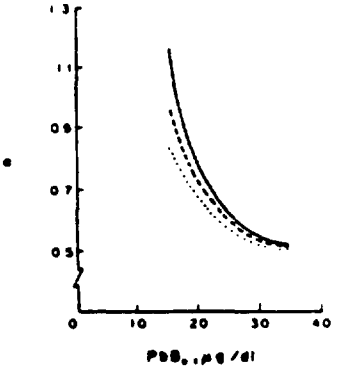

Fig. 4. The relationship of α, simulated using the line of best fit to the Azar *et al.* data, with baseline PbB for three different arbitrary ΔPbAs: ΔPbA = 1·0 μg/m^3 (——); ΔPbA = 5·0 μg/m^3 (– – –); ΔPbA = 10·0 μg/m^3 (· · ·).

The curvilinearity of the PbB–PbA relationship in human subjects is supported by reports of a curvilinear relationship between PbB and drinking-water lead (Moore, Meredith, Campbell, Goldberg & Pocock, 1977), and further evidence comes from related observations in experimental animals. Studies by Azar, Trochimowicz & Maxfield (1973b) and Prpić-Majić, Mueller, Beritic, Stanley & Twiss (1973) suggest that in rats, dogs and rabbits as well as in man, PbB is not directly proportional to lead dose. In the dog and rat studies, the lead salts were added to the diet. In the rabbit study lead acetate was given iv daily for 6 days.

It might be expected that the chemical form and particle size characteristics of lead aerosols would influence absorption rate and efficiency and thereby affect the shape of the observed PbB–PbA curve, made-up as it is of data points taken from studies of exposure to air lead having different particle size ranges and chemical makeup. It is unlikely that the chemical form of the lead aerosol is an important factor in determining airway deposition and clearance characteristics, however. Studies by Chamberlain *et al.* (1978) indicate that the chemical form of the lead aerosol generally has little influence on the fractional deposition and clearance of inhaled lead.

On the other hand these studies (Chamberlain *et al.* 1978) have established that the particle size of lead aerosols within the submicron particle size range does influence substantially the degree of deposition in the lungs. This point is illustrated in Fig. 2. Many of the subjects in the Azar *et al.* study were cab drivers exposed while on duty to ambient urban air lead. Chamberlain *et al.* (1978) found the MMED of airborne lead measured either over London streets or in an enclosed London car park to be 0·3 μm. In general the MMED of the lead sesquioxide particles introduced into the Kehoe exposure chambers was 0·26 μm with 90% of the particles having equivalent diameters less than 0·68 μm, but in a few instances large particle aerosols (MMED of up to 3·98 μm) were prepared. [The geometric diameters reported by Kehoe (Gross, 1979) were converted to equivalent diameters for this comparison by using the Stokes-Cunningham equation (NAS-NRC, 1972, Appendix A).] Data points from these experiments are identified as solid triangles in Fig. 2. As would be predicted for exposure to these larger diameter particles, these data points tend to give relatively low α values.

Another identifiable group of four data points, shown as solid squares in Figs 2 and 3 also deviates from the behaviour shown by the others. These are the data from Kehoe subject DH, who had an unusually higher baseline PbB, 30 $\mu g/dl$. Their positioning in Fig. 2 as a group below the other Kehoe data points is probably an artefact of the procedure used for baseline adjustment with these data, and is a reflection of the curvilinearity of the PbB–PbA relationship. The ΔPbB associated with a specified ΔPbA is dependent on PbB_0, as discussed above. When PbB_0 is low, ΔPbB for a specified ΔPbA is larger than when PbB_0 is high. Therefore the additive baseline adjustment, while it is the only practical adjustment to use, is not entirely appropriate. It results in a bias in the adjusted PbB data points toward low values. This bias is probably not serious when PbB_0 does not differ greatly from the baseline value of 16 $\mu g/dl$, but becomes more serious as PbB_0 increases, so that its effect is clearly apparent in the group of data points from subject DH. Analogous reasoning suggests that the α values calculated for subject DH should be disproportionately low, and indeed three of the four negative calculated α values (Table 1) are associated with subject DH.

It would be of great interest to know how PbB–PbA relationships in children compare with those described here in adults. Unfortunately, there are no data available that would meet or approximate the criteria set forth in the present analysis of the PbB–PbA relationship. In no case has continuous sampling of air lead been done in the breathing zone of children. Only outdoor stationary monitors have been used. Moreover, data in which baseline PbBs were as high as 16 $\mu g/dl$ are scarce. In one study, however, a comparison was made of the impact of PbA on PbB in adults and children (Johnson, Tillery & Prevost, 1975). Two populations of females and males were compared in which faecal lead excretions were roughly comparable but PbA was 6·3 $\mu g/m^3$ in one case and 0·64 $\mu g/m^3$ in the other. Using the low PbA group as a baseline, α for the high PbA adult males was approximately 1·1 as compared to 1·9 for the male children. In females, α for adults was approximately 0·8 as compared to 0·9 for the children (Johnson *et al.* 1975). Thus, α may be higher for children than for adults, but probably by a factor of less than 2.

It is also interesting to consider the junction of the line of best fit to the Azar *et al.* data with measured PbB–PbA relationships in populations industrially exposed to lead. For many studies of workers no measures of PbB levels in comparable control populations are available, as a result of which the contribution of non-air lead sources is not known. Furthermore, in industrial studies PbA has not always been sampled in the workers' breathing zone. One study in which workers did wear personal air monitors and in which a control population PbB was reported is that of Williams, King & Walford (1969), who studied subjects working in various different departments of a lead-acid battery factory. When the PbB means for the three worker groups are normalized to a control value of 16 $\mu g/dl$, as described above for Griffin *et al.* and Kehoe data points, and plotted against the time-weighted average PbA (WHO, 1977), they lie well above the extrapolated line of best fit to the Azar *et al.* data in the PbA range 33–53 $\mu g/m^3$. This discrepancy is unlikely to be attributable to an effect of particle size, since the particular jobs on which the men worked are associated with lead dusts of larger particle size than the lead sesquioxide generated in the Griffin *et al.* and Kehoe studies. It may be at least partly attributable to hand to mouth lead transfer in the worker groups. Williams *et al.* found a significant correlation between personal working habits and total lead exposure within one of their three study groups.

In any case, it should be emphasized that the line of best fit to the Azar *et al.* data presented here represents an empirical fit. As such it cannot be extrapolated beyond the limited concentration range within which it has been shown to be in agreement with

experimentally measured data points; that is, beyond PbA values of about 40 $\mu g/m^3$. It cannot be applied to industrial data, with PbAs as high as 300 $\mu g/m^3$.

In general, significant deviation from linearity of the PbB–PbA relationship as evaluated for industrial populations has not been shown (OSHA, 1978). This observation, which applies to the occupational PbA range 50–300 $\mu g/m^3$, is not inconsistent with the relationship reported here. Figures 2 and 3 show that the curvilinearity of the PbB–PbA relationship diminishes as PbA increases. This behaviour is also reported by Moore *et al.* (1977) in their studies of drinking-water lead.

It is interesting to speculate about the basis for the form of the PbB–PbA relationship. By analogy with observations in animals it seems unlikely that nonlinearities in either absorption or elimination are the primary determinants of the shape of the PbB curve, since if this were the case the effect should be seen in other tissues at about the same exposure level at which it is seen in the blood. In animals, at least, most tissues tend to accumulate lead to a degree much more directly proportional to dose than does the blood. When curvilinearity of the tissue-Pb–PbA relationship is observed, it tends to appear only at exposure levels higher than those associated with the curvature of the PbB–PbA relationship. That the curvilinearity is not a result of nonlinearities in absorption is further supported by its appearance in rabbits administered a lead salt iv (Prpić-Majić *et al.* 1973). It therefore appears most likely that distributional nonlinearities are primarily responsible for the form of the PbB–PbA relationship. It is possible that these nonlinearities are related to the number, kind, and location of lead binding sites in different tissues.

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