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June 15, 1981

TO: All Members of the ILZRO Environmental Health Committee

FROM: Jerome F. Cole

SUBJECT: Attached Paper: "The Impact of Air Lead on Blood Lead in Man - A Critique of the Recent Literature"

For your information, I am pleased to enclose a copy of the above paper. This paper will be published in a special issue of Food and Cosmetics Toxicology. The authors, Hammond, O'Flaherty and Gartside prepared this paper at the request of ILZRO and presented it in part at the International Conference on Management and Control of Heavy Metals in the Environment in London in 1979.

The paper points out that the relationship between air lead and blood lead is curvilinear with the alpha value (blood lead to air lead ratio) being greater at lower air lead levels.

Sincerely,

Jerome F. Cole
Vice President

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Att.

To be published
Food & Cosmetics Toxicology - Special Issue

The Impact of Air Lead on Blood Lead in Man - A Critique of the Recent Literature*

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Running Title:

Ambient Air Lead and Blood Lead in Man

* Presented in part at the International Conference on Management and Control of Heavy Metals in the Environment, London, September 18-21, 1979.

Summary

The nature of the relationship between air lead (PbA) and blood lead (PbB) in humans was evaluated by using all information available from published studies in which (1) subjects were in an approximate steady state with regard to lead exposure, and (2) PbB could be related to PbA measurements made in the individual's breathing zone. The observed PbB/PbA relationship was compared with the relationships predicted by applying the two kinetic models which have been proposed to describe lead disposition in humans. The models were found to be inconsistent with observed lead disposition kinetics. Each model generates a linear PbB/PbA relationship with predicted PbB's well above actual PbB's except within the very lowest PbB range (< 5 $\mu g/m^3$). The observed PbB/PbA relationship is curvilinear with slope decreasing as PbA and PbB increase. The implications of this curvilinearity with regard to the dependence of α, the increment in PbB associated with a given increment in PbA, both on the magnitude of the PbA increment and on the baseline PbB value are illustrated and discussed.

The Impact of Air Lead on Blood Lead in Man - A Critique of the Recent Literature*

P. B. Hammond, E. J. O'Flaherty, P. S. Gartside

In 1972 a now widely circulated document was published by the National Academy of Sciences, U.S.A. entitled "Airborne Lead in Perspective" (NAS-NRC, 1972). Its purpose was to review and evaluate all literature bearing on the question of the significance of airborne lead for human health and welfare. The committee which prepared this document was unable to arrive at any firm conclusion concerning the contribution of lead in air to the total body burden. It identified two general pathways of transfer. The first and more obvious of the two was inhalation of lead aerosols. The second was 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 U.S. Environmental Protection Agency (U.S. 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 directly calculating transfer from air (or street dust) into the body. This approach was not found by the NAS-NRC study group to be practical because of 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 gastrointestinal 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.

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* Presented in part at the International Conference on Management and Control of Heavy Metals in the Environment, London, September 18-21, 1979.

In regard to the impact of the inhalation of lead aerosols, the NAS-NRC committee concluded from the sparse epidemiologic data available at the time that there was no perceptible impact of air lead (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 et al., 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 U.S. EPA in the preparation of its 197[illegible] document, "Air Quality Criteria for Lead." Yet, in both documents summary judgment 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 issue of the impact of air lead on blood lead in man, giving consideration to all useful information currently available. The problem still is basically divisible into two general subproblems - transfer to the body by 1) inhalation of lead aerosols and 2) 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 into consideration uptake from all sources by all absorption routes since the concern is with the relative importance of inhaled lead to total body burden.

Two different disposition models have been used to describe lead kinetics. Rabinowitz, Wetherill and Kopple (1973,1976) 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 Figure 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 the concentration of lead in air (PbA) and the concentration of lead in blood (PbB) is evaluated mathematically. In order 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 ambient air lead concentrations as observed by Azar et al. (1973a). Blood lead 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.

Methods

Observation: graded exposure levels

Azar et al. (1973a) monitored the air lead exposure of 150 individuals from five locations in the United States, continuously and individually for 2-4

weeks. The subjects were in a steady state condition with regard to exposure; the average number of years spent on the current job varied from 16.0-19.1 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 and Cox, 1964) in order to obtain the optimal transformations. This requires that a variable of interest, Y, be transformed by the expression

$$\frac{Y^{\lambda} - 1}{\lambda}$$

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 in the following manner:

$$PbB = A + B(PbA + C_i) \ ,$$

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

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

$$(PbB)^{-1.019} = -0.09786 + 0.17904\ (PbA + C_i)^{-.104}$$

where $C_1 = 6.55627$, $C_2 = 1.61865$, $C_3 = 0.38578$, $C_4 = 5.98683$, and $C_5 = 2.76079$ for the five locations, with $R^2 = 0.49$. The average relationship between PbB and PbA was found by substituting the average C_i value, 3.46186, and solving for PbB:

Equation (1)

$$PbB = \left[-0.09786 + 0.17904(PbA + 3.46186)^{-.104}\right]^{-\frac{1}{1.019}}.$$

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

Observation: discrete exposure levels

The criteria for including data points in this analysis were: first, that the individuals studied were in an approximate steady state with regard to 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 98-772 days. Griffin et al. (1975) exposed groups of volunteers for 14-19 weeks 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 PbA's monitored by the investigators were the concentrations actually in the breathing zone of the subjects.[1]

In order to minimize the effect on these data of non-air sources of lead, all 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 µg/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 µg/dl was used to normalize experimental data. The adjustment was made by substracting from individual or mean PbB values, as appropriate, the difference between measured control period PbB and 16 µg/dl.

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

Prediction: linear kinetic models

The differential form of the Rabinowitz model (Figure 1)[2] is

$$\frac{dM_1}{dt} = \frac{.002}{0.6} M_2 + \frac{.007}{200} M_3 - \left(\frac{.015 + .007 + .036}{1.9}\right) M_1$$

$$\frac{dM_2}{dt} = \frac{.015}{1.9} M_1 - \left(\frac{.002 + .012}{0.6}\right) M_2$$

$$\frac{dM_3}{dt} = \frac{.007}{1.9} M_1 - \frac{.007}{200} M_3$$

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[1] Hand to mouth transfer of settled lead-bearing dust probably was minimal. Kehoe subjects dusted the chambers frequently (personal communication with Kehoe subject JOS). A similar housekeeping program prevailed in the Griffin study (personal communication with T. B. Griffin).

[2] 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 $\frac{dM_1}{dt}$.

where $\frac{dM_1}{dt}$, $\frac{dM_2}{dt}$ and $\frac{dM_3}{dt}$ represents 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 M's have the dimension $[da^{-1}]$. The differential form of the Bernard model[1] is

$$\frac{dM_1}{dt} = \frac{.133}{.76} M_5 + \frac{.057}{13} M_4 + \frac{.0125}{27} M_3 + \frac{.00686}{65} M_2 - \frac{.2442}{.419} M_1$$

$$\frac{dM_2}{dt} = \frac{.00686}{.419} M_1 - \frac{.00686}{65} M_2$$

$$\frac{dM_3}{dt} = \frac{.0125}{.419} M_1 - \frac{.0125}{27} M_3$$

$$\frac{dM_4}{dt} = \frac{.057}{.419} M_1 - \frac{.057}{13} M_4$$

$$\frac{dM_5}{dt} = \frac{.133}{.419} M_1 - \frac{.133}{.7} M_5$$

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 five years' (260 weeks') exposure and after 1,000 weeks' exposure 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.

Total lead absorbed daily was considered to be the sum of the amounts absorbed from diet and from air. The assumption was made 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 et al. (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 µ while the mass median equivalent diameter (MMED) was larger, about 0.2-0.3 µ. The DMED of freshly generated lead aerosols measured near major highways was smaller, 0.03 µ, and the MMED was much smaller, 0.04 µ.

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 m^3 of air per day (ICRP, 1975) and that 65% of the lead inhaled is deposited in the lung and absorbed into the systemic circulation. This absorption magnitude approximates the midpoint of the range reported by Chamberlain et al. (1978) for lead aerosols with very small DMED, 0.02-0.04 µ,

at breathing cycles of 4-8 seconds. For minimum impact it was assumed that reference man breathes 18 m^3 of air per 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 .09 μ, at breathing cycles of 4-8 seconds. The PbB levels predicted by the Rabinowitz and Bernard models after five years' exposure are shown in Figure 2.

Results and Discussion

Figure 2 allows direct comparison among the PbB/PbA relationships predicted by the Rabinowitz and the Bernard models, calculated from the data of Azar et al. and 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 (Table 2), corresponding for the conditions of this simulation to a pBA of between 1 and 3 $\mu g/m^3$ depending on whether maximum impact or minimum impact conditions are considered. However, consequent to the very slow return of lead from two of its peripheral compartments (compartments 2 and 3, Figure 1) the Bernard model has not yet achieved steady state even after a 19 year simulated exposure.

It is apparent from Figure 2 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. Linear mammillary models consist 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 behavior 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. For these reasons a linear mammillary model is generally the first choice in modelling the kinetics of a foreign compound unless specific information about observed kinetic behavior 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 of the implications of representation of the kinetic behavior 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 Figure 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 an 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 Figure 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 $\mu g/m^3$. 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 $\mu g/m^3$. The calculated α values are presented in Table 3.

It is apparent from Figure 3 that within the range 0-20 $\mu gPb/m^3$ 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 Griffin et al. and Kehoe data points parallel the behavior of the Azar et al. line.

The wide scatter of α values among the Kehoe subjects exposed to <10 $\mu gPb/m^3$ is due to variation within individuals as well as between individuals. Thus, for example, subject NK (Table 3) had α's ranging grom 1.00 to 2.94 over the narrow ΔPbA range of 1-3.8. Nevertheless, when individual subjects were exposed to a wide range of PbA's, e.g. subjects LD and JOS, the downward drift of α becomes clearly apparent.

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_o. This dual dependency is illustrated by the simulation in Figure 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_o) exposed to small increments

in PbA (ΔPbA). In practical terms this behavior 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 per 1.0 $\mu g/m^3$, and is affected only slightly if at all by the magnitude of the experimental increment in PbA.

The curvilinearity of the PbB/PbA relationship in human subjects is paralleled by reports of a curvilinear relationship between PbB drinking water lead (Moore et al., 1977), and further supported by related observations in experimental animals. Studies of Azar et al. (1973b) and of Prpić-Majić et al. (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 lead salts were added to the diet. In the rabbit study lead acetate was given intravenously, daily for six 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 not likely that the chemical form of the lead aerosol is an important factor in determining airway deposition and clearance characteristics, however. Recently reported 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, the Chamberlain studies 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 Figure 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.[2] Data points from these experiments are identified as solid triangles in Figure 2. As would be predicted for exposure to these larger diameter particles, these data points tend to lie below the others on the same graph.

Another identifiable group of four data points, shown as half-solid triangles in Figure 2 and Figure 3, also deviates from the behavior shown by the others. These are the data from Kehoe subject DH, who had an unusually high baseline PbE, 30 μg/dl. Their positioning in Figure 2 as a group below the other Kehoe data points is probably an artifact of the procedure used for baseline adjustment with these data, and is a reflection of the curvilinearity of the PbB/PbA relationship. The increment in PbB associated with a specified increment in PbA is dependent on PbB_o, as discussed above. When PbB_o is low, ΔPbB for a specified ΔPbA is larger than when PbB_o 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_o is not greatly different from the baseline value of 16 μg/dl, but becomes more serious as PbB_o 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 3) are associated with subject DH.

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[2] 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).

It would be of great interest to know how PbB-PbA relationships in children compare to those described here in adults. Unfortunately, there are no data available meeting or even approximating the criteria set forth in the present analysis of PbB/PbA. In no case has continuous sampling of air lead been made in the breathing zone of children. Outdoor stationary monitors only have been used. Moreover, data in which baseline PbB's were as high as 16 µg/dl are scarce. In one study, however, a comparison was made of the impact of PbA on PbB in adults and children (Johnson et al., 1975). Two populations of females and males were compared in which fecal lead excretions were roughly comparable but in which 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 childrn (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. In 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, PbA in industrial studies has not always been samples 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 et al. (1969), of groups of subjects employed in different departments of a lead-acid battery factory. When PbB means for the three worker groups are normalized to a control value of 16 µg/dl, as described above for Griffin et al. and Kehoe data points, and plotted against the time weighted average PbA calculated as if exposure had been continuous (Environmental Health Criteria: Lead, 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 here presented 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, for which workplace PbA may be 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 (U.S. 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. Figure 2 shows, and Figure 3 emphasizes, that the curvilinearity of the PbB/PbA relationship diminishes as PbA increases. This behavior 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 determinant 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 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 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 (Prpic-Majic et al., 1973) administered a lead salt by intravenous injection. Therefore it 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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Legends to Figures

Figure 1. Models proposed to describe lead disposition kinetics by (a) Rabinowitz et al. (1973, 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 those amounts which are assumed to be absorbed daily into the systemic circulation from all sources.

Figure 2. Predicted and observed PbB level as a function of PbA. Data points are taken from Table 1. The Kehoe data points represent 12 individuals, some studied more than once. All data points are adjusted to a PbB from non-air lead sources of 16 μg/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 are taken from Table 2; maximum and minimum impact conditions are discussed in the text. Solid triangles represent data points from individuals exposed to large particle aerosols. Half-solid triangles represent data points from one individual, MB, whose measured PbB from non-air lead sources was exceptionally high.

Figure 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 are shown dashed beyond the range of actual measurement. Solid triangles represent data points from individuals exposed to large-particle aerosols. The half-solid triangle represents the only positive value of α from subject MB, whose measured PbB from non-air lead sources was exceptionally high. The four negative α values for Kehoe subjects (see Table 3) have not been plotted. Mean values were used in the calculation of α from Griffin et al. data.

Figure 4. The dependence of α, simulated using the line of best fit to the Azar data, on baseline PbB for three different arbitrary ΔPbA.

Table 1. Individual and Mean Steady State PbB Levels in Persons Exposed to Lead Sesquioxide Aerosols

		Control Period		Experimental Period			
Subject	n[a]	PbB[b], µg/m^3	PbB, µg/dl	PbA[c], µg/m^3	PbB, µg/dl	PbB, µg/dl, adjusted to baseline of 16 µg/dl	Reference
MB	--	--	24	29.4[d]	40	32	Kehoe (Gross, 1979)
MOB	--	--	26	22.4	39	29	
	--	--	26	28.4[d]	32	22	
PB	--	--	23	28.4	33	26	
SB	--	--	21	27.4	32	27	
FC	--	--	22	30.6	39	33	
	--	--	22	30.1[d]	31	25	
LD	--	--	18	9.3	29	27	
	--	--	18	19.7	36	34	
	--	--	18	27.1	40	38	
	--	--	18	35.9	41	39	
DH	--	--	30	5.6	31	17	
	--	--	30	7.3	26	12	
	--	--	30	7.6	29	15	
	--	--	30	8.8	28	14	
NK	--	--	20	0.6	20	16	
	--	--	20	1.2	21	17	
	--	--	20	1.9	23	19	
	--	--	20	2.4	26	22	
	--	--	20	3.3	26	22	
	--	--	20	3.6	30	26	
	--	--	20	4.0	29	25	
HR	--	--	21	2.4	25	20	
	--	--	21	3.7	21	16	
	--	--	21	7.5	27	22	

Table 1 (Continued)

Subject	n[a]	Control Period PbB[b], µg/m³	Control Period PbB, µg/dl	Experimental Period PbA[c], µg/m³	Experimental Period PbB, µg/dl	PbB, µg/dl, adjusted to baseline of 16 µg/dl	Reference
JOS	--	--	21	9.4	32	27	Kehoe (Gross, 1979) cont'd
	--	--	21	19.3	37	32	
	--	--	21	27.1	41	36	
	--	--	21	35.7	46	41	
JUS	--	--	21	28.1[d]	32	27	
SS	--	--	19	0.6	20	17	
	--	--	19	1.3	20	17	
	--	--	19	1.8	18	15	
	--	--	19	2.4	19	16	
	--	--	19	2.7	23	20	
	--	--	19	3.4	24	21	
	--	--	19	4.3	24	21	
	--	--	19	2.4	24	21	
	--	--	19	3.2	21	18	
	--	--	19	5.4	27	24	
	--	--	19	6.2	26	23	
	--	--	19	7.0	26	23	
	--	--	19	7.2	29	26	
--	8	0.1 - 0.2	20.3 ± 3.2[e]	10.9	36.8 ± 4.3	32.5 ± 4.3	Griffin et al. (1975)
--	12	0.1 - 0.2	20.3 ± 4.2	3.2	26.0 ± 3.8	21.7 ± 3.8	

[a] Number of subjects.

[b] PbA during control periods is not known for the Kehoe studies.

[c] All PbA levels are expressed as if exposure had been continuous. For example, if a subject were exposed for 8 hours a day, 5 days a week, to a chamber air lead concentration of 150 µg/m³, the value given in the table would be

$$\left(\frac{8 \text{ hr/da})(5 \text{ da/wk})}{168 \text{ total hr/wk}}\right) 150 \text{ µg/m}^3 = 35.7 \text{ µg/m}^3.$$

[d] Large particle aerosol.

[e] Standard deviation.

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[a]: µg/m^3	PbA corresponding to daily retention; "maximum impact" conditions[b]: µg/m^3
	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	8.63	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

[a] "Minimum impact" conditions are chosen so as to minimize the predicted impact of PbA on PbB. They are: total volume of air breathed daily, 18 m^3; 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 x 200 mg)/day.

[b] "Maximum impact" conditions are chosen so as to maximize the predicted impact of PbA on PbB. They are: total volume of air breathed daily, 23 m^3; 65% of inhaled Pb deposited in lung and absorbed. Lead absorbed from diet is assumed to be 16 µg/day.

Table 3. The Magnitude of the Increment in PbB Resulting from a Measured Increment in PbA: $\Delta PbB/\Delta PbA = \alpha$. Based on Data from Table 1.

Subject	n	ΔPbB: µg/dl	ΔPbA[a]: µg/m^3	α	Reference
MB	--	16	29.2	.55[b]	Kehoe (Gross, 1979)
MOB	--	13	22.2	.58	
	--	6	28.2	.21[b]	
PB	--	10	28.2	.35	
SB	--	11	27.2	.40	
FC	--	17	30.4	.56	
	--	9	29.9	.30[b]	
LD	--	11	9.1	1.21	
	--	18	19.5	.92	
	--	22	26.9	.82	
	--	23	35.7	.64	
DH	--	1	5.4	.18	
	--	-4	7.1	-.56	
	--	-1	7.4	-.14	
	--	-2	8.6	-.23	
NK	--	0	0.4	0	
	--	1	1.0	1.00	
	--	3	1.7	1.76	
	--	6	2.2	2.73	
	--	6	3.1	1.94	
	--	10	3.4	2.94	
	--	9	3.8	2.37	
HR	--	4	2.2	1.82	
	--	0	3.5	0	
	--	6	7.3	.82	
JOS	--	11	9.2	1.20	
	--	16	19.1	.84	
	--	20	26.9	.74	
	--	25	35.5	.70	
JUS	--	11	27.9	.39[b]	
SS	--	1	0.4	2.5	
	--	1	1.1	.91	
	--	-1	1.6	-.62	
	--	0	2.2	0	
	--	4	2.5	1.60	
	--	5	3.2	1.56	
	--	5	4.1	1.22	
	--	5	2.2	2.27	

Table 3 (Continued)

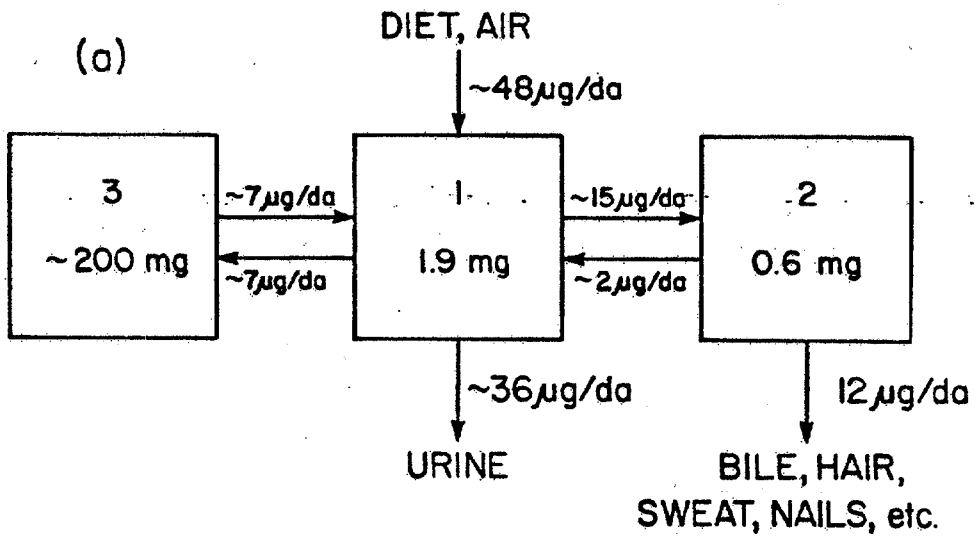
Subject	n	ΔPbB: μg/dl	ΔPbA[a]: μg/m^3	α	Reference
SS (cont'd)	--	2	3.0	.67	Kehoe (Gross, 1979) cont'd
	--	8	5.2	1.54	
	--	7	6.0	1.17	
	--	7	6.8	1.03	
	--	10	7.0	1.43	
--	8	16.5	10.7	1.54	Griffin et al. (1975)
--	12	5.7	3.0	1.90	
--	--	.908	0.8	1.135	Line of best fit to data of Azar et al. (1973a)[c]
--	--	1.933	1.8	1.074	
--	--	4.541	4.8	.946	
--	--	8.085	9.8	.825	
--	--	13.951	19.8	.704	
--	--	19.178	29.8	.644	
--	--	24.186	39.8	.608	

[a] Baseline PbA was assigned the value 0.2 μg/m^3 for the Kehoe study.

[b] Large particle aerosol.

[c] Calculation of α from the line of best fit to the Azar et al. data starts from the baseline assumptions that PbA = 0.2 μg/m^3 and PbA = 16.2 μg/dl. The value of α depends on the choice of baseline; see text for a discussion of this point.

(a)



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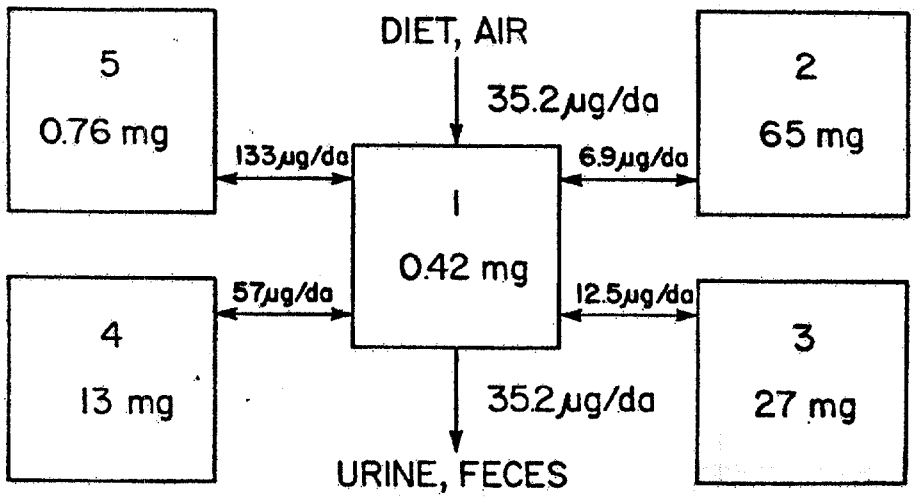

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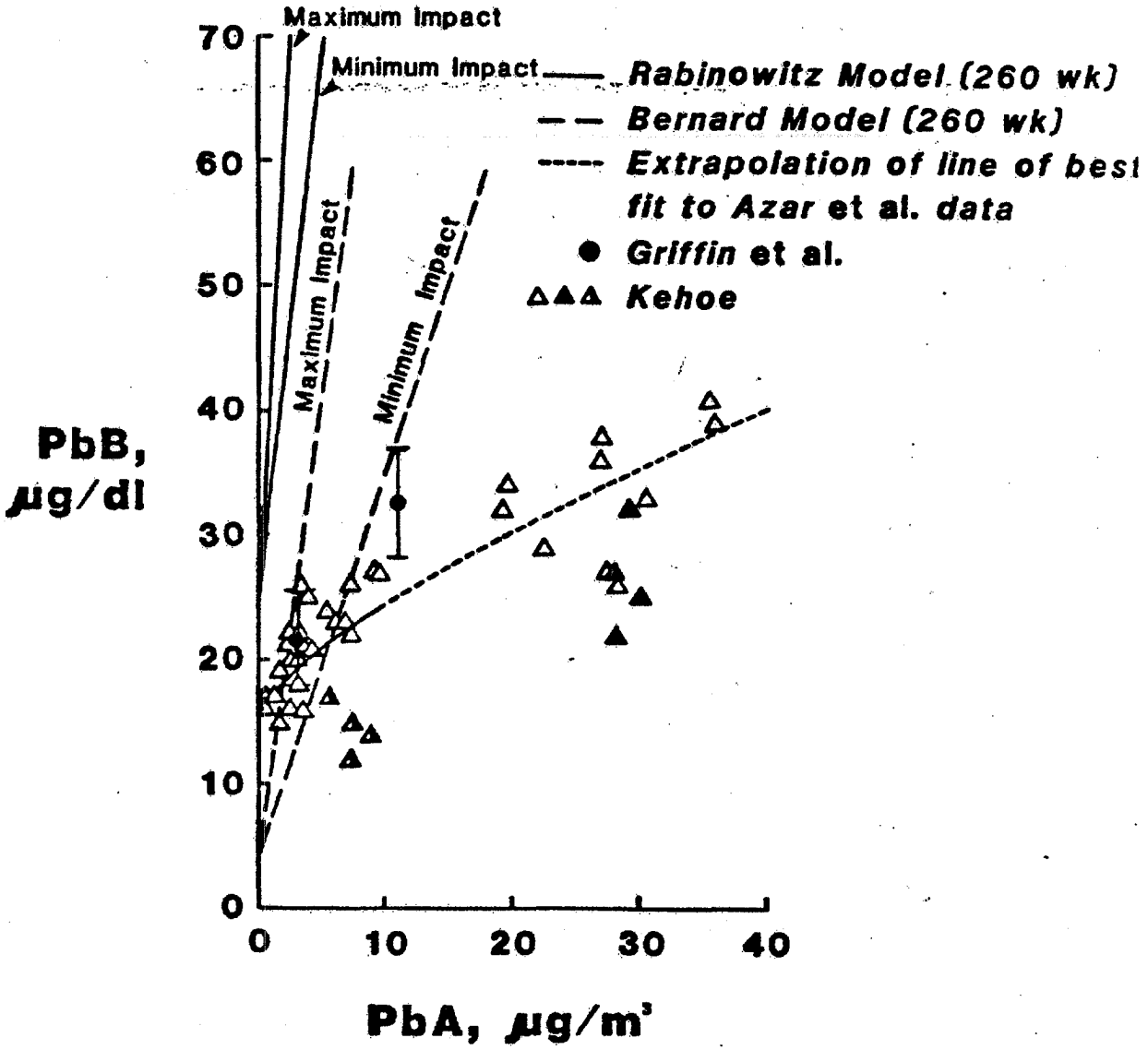
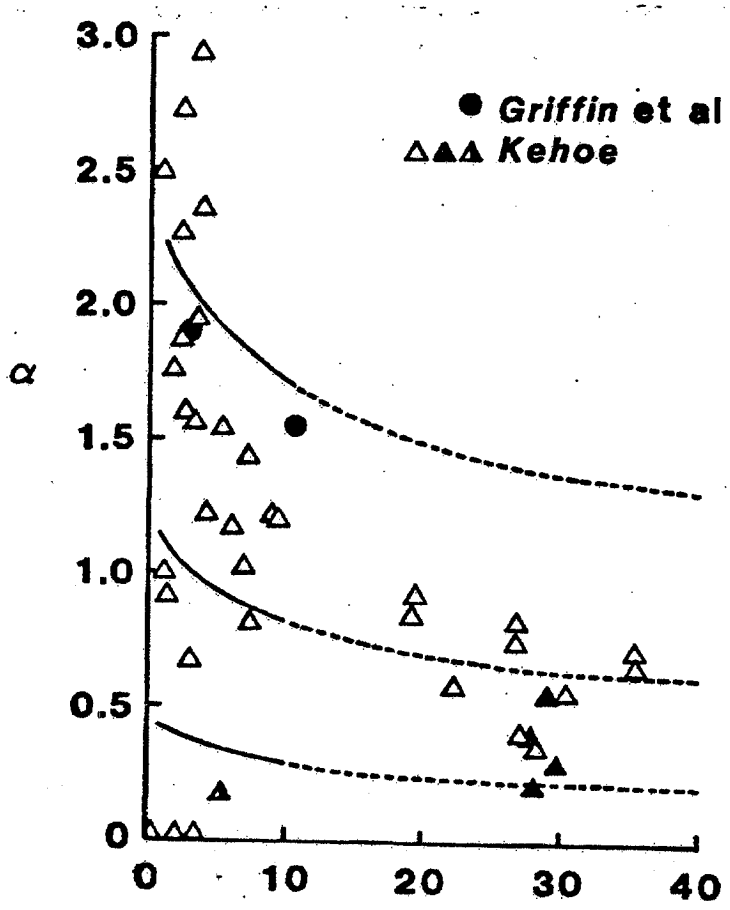

Maximum Impact
Minimum Impact
Rabinowitz Model (260 wk)
Bernard Model (260 wk)
Extrapolation of line of best fit to Azar et al. data
Griffin et al.
Kehoe
Maximum Impact
Minimum Impact
PbB, µg/dl
PbA, µg/m³
0
10
20
30
40
50
60
70
0
10
20
30
40

TEH 0470147



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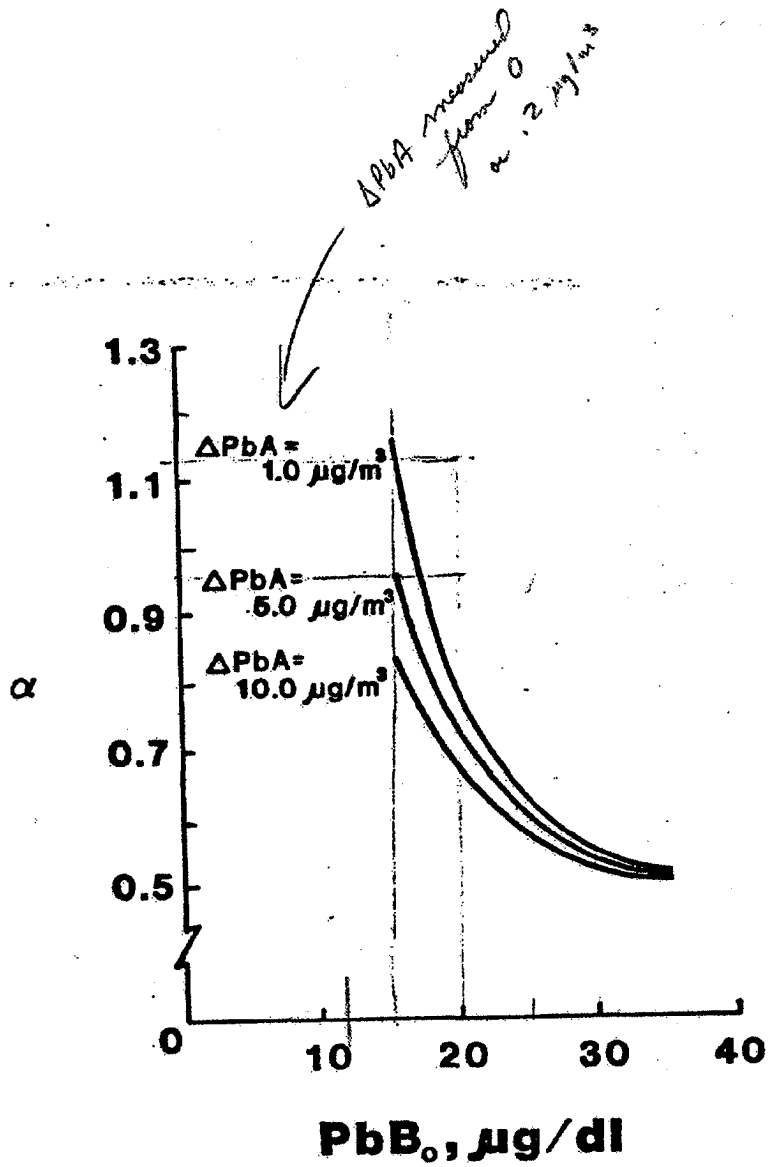

ΔPbA increased from 0 to .2 μg/m³
1.3
1.1
0.9
0.7
0.5
0
α
ΔPbA = 1.0 μg/m³
ΔPbA = 5.0 μg/m³
ΔPbA = 10.0 μg/m³
10
20
30
40
PbB₀, μg/dl

Two Methods of Computing an AQS Fth Year

DuPont

Calculate 99.5 percentile at Air Pb = 0 and assume percentile will increase according to a model

medair = 12 99.5% = 23.6

30 = Desired Percentile

(30 − 23.6)/Slope = 2 = 3.2

(30 − 23.6)/Slope = 1.2 = 5.3

(30 − 23.6)/Slope = 1.5 = 4.3

EPA

Fit 99.5 percentile

Composite median

apply model to median

99.5 Percentile = 30 => median = 15

Desired median = 12

(15-12)/(Slope = 2) = 1.5

(15-12)/(Slope = 1.5) = 2.0

(15-12)/(Slope = 1.2) = 2.5

Key Assumption

Different percentiles are different functions of air Pb as per C.B. Pfeifer memo

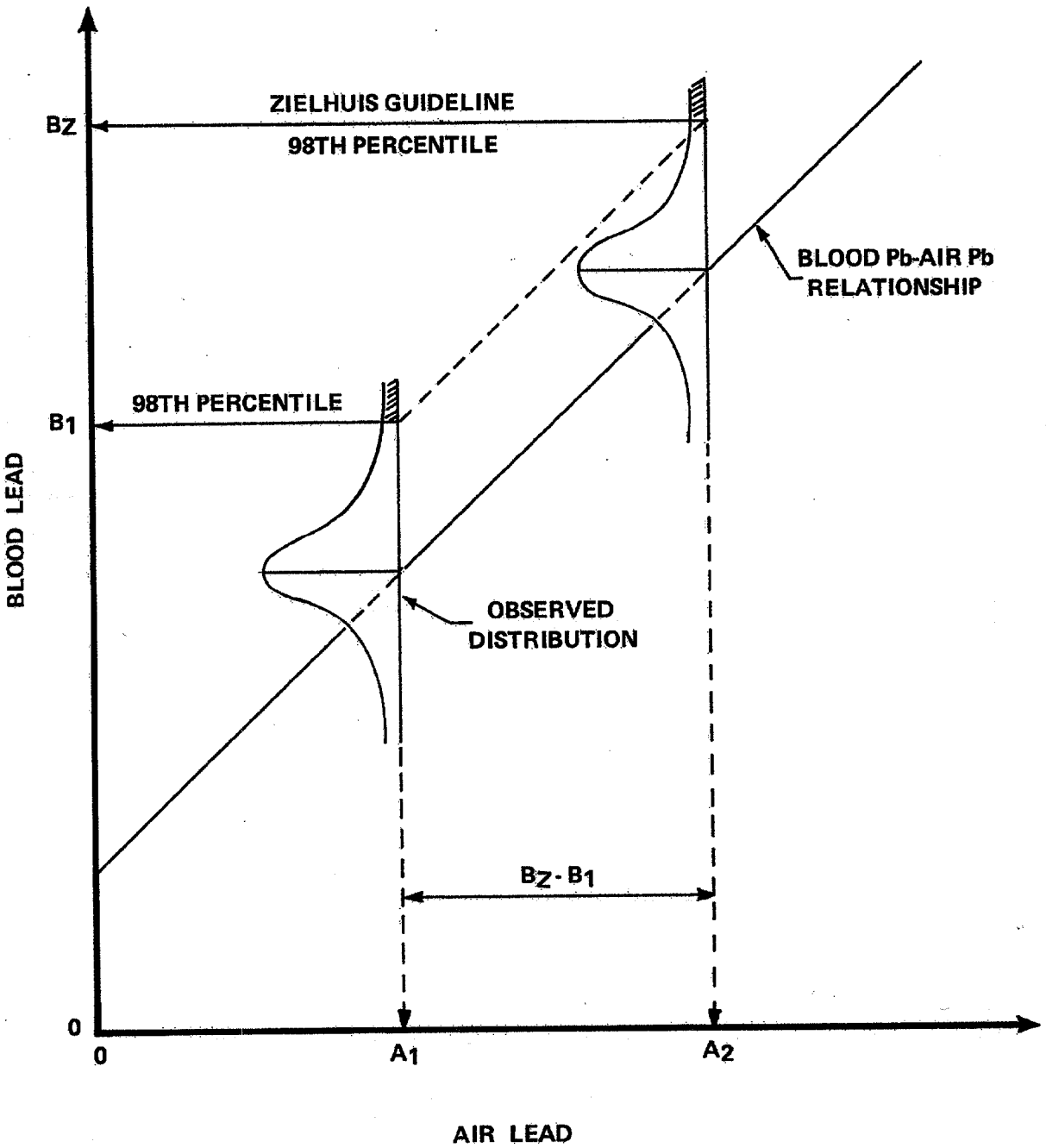
Doesn't make sense because air Pb should have smaller effects at high blood lead not higher

Ref: Snee - Pb Exposure model

Hammond et al Paper

TEH 0470151

DUP050082970



TEH 0470152

DUP050082971

TABLE 5
SEVEN CITIES SURVEY
ESTIMATION OF AN AIR QUALITY STANDARD FOR LEAD ASSUMING BLOOD LEAD VALUES ARE LOG NORMALLY DISTRIBUTED

Site	Air Pb	Percentile	Blood Pb[1] (mcg/100 ml)	AQS (mcg/m^3)[2] Log Model	AQS (mcg/m^3)[2] Linear Model
Okeana	0.32	50	15.6	5.9	4.7
		90	23.6	5.6	6.7
		97.5	29.3	3.7	6.0
		98	30.2	3.0	5.1
Ardmore	1.15	50	18.0	3.3	3.2
		90	27.1	3.2	4.1
		97.5	33.6	1.9	2.6
		98	34.6	1.3	1.6
Rittenhouse	1.67	50	20.5	1.2	1.2
		90	29.3	2.1	2.4
		97.5	35.4	1.5	1.3
		98	36.4	1.0	0.3
Pasadena	3.39	50	17.5	7.7	5.9
		90	24.9	10.1	8.5
		97.5	30.0	8.6	8.4
		98	30.8	7.5	7.6
Los Alamos Male	0.17	50	17.2	2.8	3.0
		90	23.2	5.8	7.0
		97.5	27.2	5.6	8.0
		98	27.8	4.9	7.4
Los Alamos Female	0.17	50	15.0	6.9	5.2
		90	20.6	10.8	9.6
		97.5	24.3	10.3	10.9
		98	24.9	9.1	10.3
Washington, DC	1.19	50	19.1	2.0	2.1
		90	25.7	4.7	5.5
		97.5	30.1	4.6	6.1
		98	30.7	4.0	5.5
Port Washington	1.13	50	15.4	8.5	4.6
		90	21.1	13.2	10.0
		97.5	25.5	12.5	11.2
		98	25.5	11.2	10.6
Greenwich Village	2.08	50	16.6	7.5	5.5
		90	22.7	12.0	9.4
		97.5	26.8	11.3	10.3
		98	27.5	10.0	9.6
Lombard	1.18	50	14.0	13.7	7.2
		90	19.1	20.9	12.1
		97.5	22.5	20.1	13.7
		98	23.0	18.2	13.2
Bridgeport	1.76	50	17.6	4.9	4.2
		90	23.9	11.8	7.9
		97.5	28.0	8.3	8.8
		98	28.7	7.3	8.1
Houston	.85	50	12.6	20.0	8.2
		90	17.8	25.9	13.0
		97.5	21.5	22.4	14.3
		98	22.1	19.8	13.7

(1) Blood Pb value estimated from a log normal distribution.
(2) Air Quality Standard - Air Pb levels (mcg/m^3) at which the upper portion of the observed blood Pb distribution would be equal to the Zielhuis biological guideline for Pb.

TEH 0470157

TABLE 5
SEVEN CITIES SURVEY
ESTIMATION OF AN AIR QUALITY STANDARD FOR LEAD ASSUMING
BLOOD LEAD VALUES ARE LOG NORMALLY DISTRIBUTED

Site	Air Pb	Percentile	Blood Pb(1)	AQS(2) Lead Exposure Model	AQS(2) Linear Model
Okeana	0.32	50	15.6	5.9	4.7
		90	23.6	5.6	6.7
		97.5	29.3	3.7	6.0
		98	30.2	3.0	5.1
Ardmore	1.15	50	18.0	3.3	3.2
		90	27.1	3.2	4.1
		97.5	33.6	1.9	2.6
		98	34.6	1.3	1.6
Rittenhouse	1.67	50	20.5	1.2	1.2
		90	29.3	2.1	2.4
		97.5	35.4	1.5	1.3
		98	36.4	1.0	0.3
Pasadena	3.39	50	17.5	7.7	5.9
		90	24.9	10.1	8.5
		97.5	30.0	8.6	8.4
		98	30.8	7.5	7.6
Los Alamos Male	0.17	50	17.2	2.8	3.0
		90	23.2	5.8	7.0
		97.5	27.2	5.6	8.0
		98	27.8	4.9	7.4
Los Alamos Female	0.17	50	15.0	6.9	5.2
		90	20.6	10.8	9.6
		97.5	24.3	10.3	10.9
		98	24.9	9.1	10.3
Washington, DC	1.19	50	19.1	2.0	2.1
		90	25.7	4.7	5.5
		97.5	30.1	4.6	6.1
		98	30.7	4.0	5.5
Port Washington	1.13	50	15.4	8.5	4.6
		90	21.1	13.2	10.0
		97.5	25.5	12.5	11.2
		98	25.5	11.2	10.6
Greenwich Village	2.08	50	16.6	7.5	5.5
		90	22.7	12.0	9.4
		97.5	26.8	11.3	10.3
		98	27.5	10.0	9.6
Lombard	1.18	50	14.0	13.7	7.2
		90	19.1	20.9	12.1
		97.5	22.5	20.1	13.7
		98	23.0	18.2	13.2
Bridgeport	1.76	50	17.6	4.9	4.2
		90	23.9	11.8	7.9
		97.5	28.0	8.3	8.8
		98	28.7	7.3	8.1
Houston	.85	50	12.6	20.0	8.2
		90	17.8	25.9	13.0
		97.5	21.5	22.4	14.3
		98	22.1	19.8	13.7

(1) Blood Pb value (μg/dl) estimated from a lognormal distribution.
(2) Air Quality Standard - Air Pb levels (μg/m^3) at which the upper portion of the observed blood Pb distribution would be equal to the Zielhuis biological guideline for Pb.

TEH 0470158

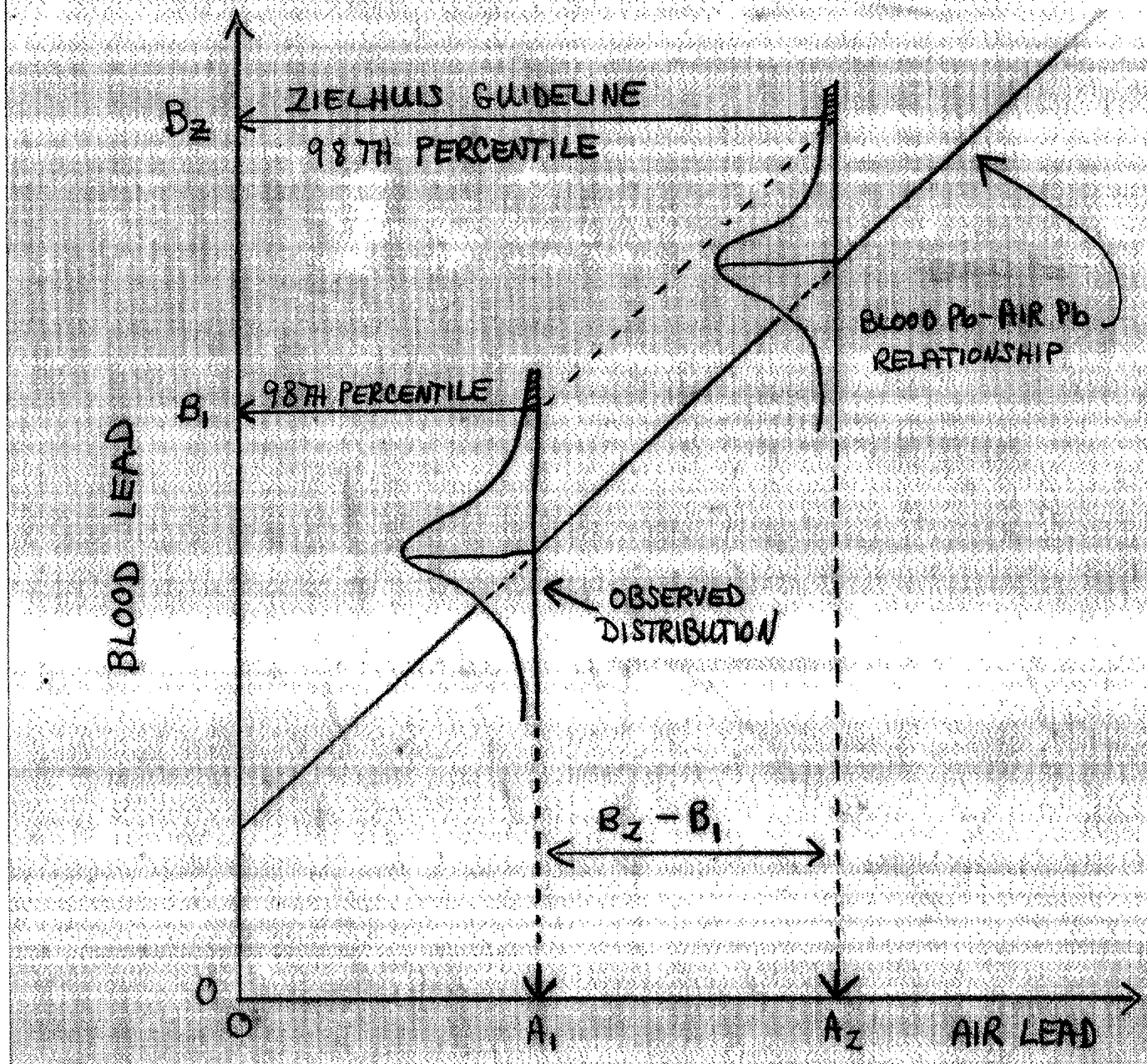


FIGURE 1 - SCHEMATIC OF CALCULATION PROCEDURE FOR DETERMINING THE AIR LEAD LEVEL AT WHICH A PERCENTILE OF AN OBSERVED DISTRIBUTION WILL BE CONSISTENT WITH THE ZIELHUIS GUIDELINE. LINEAR BLOOD Pb-AIR Pb MODEL AND 98TH PERCENTILE SHOWN IN FIGURE

TEH 0470159