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ENGINEERING DEPARTMENT
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August 19, 1985

Dr. David Weil
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Dear David:

Attached is a copy of the paper, "Variation in the Relationship between Blood Lead and Air Lead," by R. D. Snee, S. P. Bailey, W. H. Fellner, and C. G. Pfeifer, published in Atmospheric Environment, Vol 19, pp 1017-20 (1985), which is herewith submitted to the Lead Criteria Document docket, ECAO-CD-81-2.

As in the past, we wish to continue to contribute to establishment of a sound technical basis for the Criteria Document. Accordingly, we wish to participate in any workshops or other meetings to resolve the issues on the blood lead-blood pressure relationship which were raised by Professor Royall and others at the May CASAC meeting.

Very truly yours,

ENGINEERING SERVICE DIVISION
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TEH 0412673

Atmospheric Environment Vol. 19, No. 6, pp. 1017–1020, 1985
Printed in Great Britain

0004-6981/85 $3.00 + 0.00
Pergamon Press Ltd

SHORT COMMUNICATION

VARIATION IN THE RELATIONSHIP BETWEEN BLOOD LEAD AND AIR LEAD

(*First received 28 November 1983 and received for publication 8 November 1984*)

Abstract—Estimates of the slope of the relationship between blood lead ($\mu g\ dl^{-1}$) and air lead ($\mu g\ m^{-3}$) obtained in ten independent studies are compared. No significant differences were detected among the estimates which ranged from 0.6 to 3.1 $\mu g\ dl^{-1}$ per $\mu g\ m^{-3}$ and represented male adult, female adult and child populations. A single best estimate of 1.2 $\mu g\ dl^{-1}$ per $\mu g\ m^{-3}$ (± 0.2, 95 per cent confidence limits) was obtained. It is concluded that, if the blood lead–air lead slope depends on various physical and biological factors, then studies providing more precise estimates are required to detect these differences.

Key word index: Air lead exposure, blood lead, uncertainty.

INTRODUCTION AND SUMMARY

Dr. Chamberlain (1983) provided a comprehensive review of studies investigating the relationship between blood lead and air lead. He concluded that estimates of the blood lead–air lead slope, denoted by α, varied from 0.5 to 3.0 $\mu g\ dl^{-1}$ per $\mu g\ m^{-3}$ depending on the study. He noted that the statistical uncertainty (95 percent confidence limits) in these estimates was rarely less than ± 0.7 and that

"Various explanations may be sought for the divergence in the values of α, which is not extreme for a parameter affected by both physical and biological factors. These include nonlinearity of dose response, effects of particle size, human variability in breathing patterns and ventilation rates, the varying extent to which the measurements of PbA correspond to the subject's real exposure, and the contribution of ancillary variables correlated with PbA."

Some of these factors contribute to the statistical uncertainty in the estimates. The question remains as to whether the study-to-study variation in the estimates of α are due to differences in other factors; i.e. variation above and beyond that contributed by the within-study uncertainty in the different estimates of α. A statistical evaluation of this issue is the subject of this article.

At least 10 studies of the relationship between blood lead and air lead have appeared in the literature (Table 1). The results of these studies are commonly reported as a slope (change in blood lead per unit change in air lead) and its associated uncertainty. These results are summarized graphically by the approximate 95 percent confidence intervals shown in Fig. 1. With one exception, a range from 1 to 2 $\mu g\ dl^{-1}$ per $\mu g\ m^{-3}$ is consistent with these studies. It is of interest to determine whether there are any statistically significant differences (i.e. variation) among (i) the estimated slopes in Table 1 and (ii) the estimated slopes within male adult, female adult and child populations.

If there is no between-study variation in the slopes, then all slopes are estimates of a common slope and it is appropriate to compute a weighted average slope to estimate the single "true" slope of the blood lead–air lead relationship.

Using the methodology described in the next section, it is concluded that we cannot reject the hypothesis of no differences among the slopes of the blood lead–air lead relationship reported in Table 1; and further, that there is no between-study variation among the slopes within male adult, female adult and child populations. In Table 2 we see that the weighted average slope varies from 0.9 ± 0.4 to 1.4 ± 0.6 depending on which slopes are included in the analysis. The estimate of the blood lead–air lead slope derived from all the data in Table 1 is 1.2 ± 0.2. This combined estimate is indicated by the horizontal dashed reference line in Fig. 1.

TESTING BETWEEN-STUDY VARIATION OF SLOPES

A critical step in the interpretation of a set of blood lead–air lead slopes from different studies is the determination of whether there are any statistically significant differences among the estimated values. One useful approach to the solution of this problem is the maximum likelihood procedure described in this section, which requires from each study only an estimated slope and its standard error (St. John *et al.*, 1981, 1982).

We assume an underlying model where the ith estimated slope is expressed as the sum of independently distributed normal variables denoting the true slope and estimation error. We let a_i be the ith estimated slope, σ_i its standard error, and σ_B^2 the between-study variance component. It follows that a, the vector of a_i's, is distributed normal with unknown mean vector $\alpha 1$ and variance–covariance matrix $V = \sigma_B^2 I + \mathrm{diag}(\sigma_i^2)$, where 1 is a vector of ones and I the identity matrix. V is a diagonal matrix whose ith diagonal element is $\sigma_B^2 + \sigma_i^2$ and the σ_i^2's are assumed known. The procedure provides estimates of σ_B^2 and the overall average true slope, α. If $\sigma_B^2 = 0$ then α is the single slope common to the population groups considered.

The likelihood, L, is proportional to

$$|V|^{-1/2} \exp[-1/2(a - \alpha 1)' V^{-1} (a - \alpha 1)].$$

The likelihood ratio under the null hypothesis, $\sigma_B^2 = 0$, is given by $\lambda = L_0/L_1$, where L_1 is the likelihood obtained using the maximum likelihood estimate for α and σ_B^2 and L_0 is the likelihood using the maximum likelihood estimate for α when $\sigma_B^2 = 0$. The test statistic, $-2 \log \lambda$, is approximately distributed as chi square with one degree of freedom under the null hypothesis. Large values of $-2 \log \lambda$ suggest that the null hypothesis, $\sigma_B^2 = 0$, is not true, indicating that the slopes are not all estimating a single "true" blood lead–air lead slope.

Table 2 provides a summary of the analyses performed. Significant between-study variation is mainly due to the Goldsmith adult male slope of -0.1, which is out of line with the other estimates (3.7 standard errors from the overall estimate) and implausible. No significant between-study variation among the slopes of male adults (analysis 1A).

Table 1. Studies of the relationship between blood lead and air lead

Population	Study	No. of subjects	Blood Pb–Air Pb slope* Estimate	Blood Pb–Air Pb slope* Std. Dev.
Male adults	Azar	149	0.9	0.25
	Johnson	65	0.8	0.35
	Nordman	536	1.2	0.50
	Tsuchiya	537	3.1	1.10
	Goldsmith	89	−0.1	0.35
	Fugas	352	2.2	0.35
Female adults	Tepper-Levin	1935	1.1	0.90
	Johnson	96	0.8	0.30
	Nordman	478	0.6	0.45
	Goldsmith	79	0.7	0.35
	Daines (Spring)	61	1.6	0.85
	Daines (fall)	88	2.4	0.60
Clinical adults	Griffin (3.2 $\mu g\,m^{-3}$)	13	1.7	1.06
	Griffin (10.9 $\mu g\,m^{-3}$)	8	1.5	0.28
Children	Johnson (Male)	37	1.4	0.30
	Johnson (Female)	43	1.1	0.30
	Yankel†	880	1.2	0.35
	Goldsmith†	486	2.0	0.65

* Estimates and standard deviations reported by Snee (1981).
† The Yankel and Goldsmith studies included both male and female children.

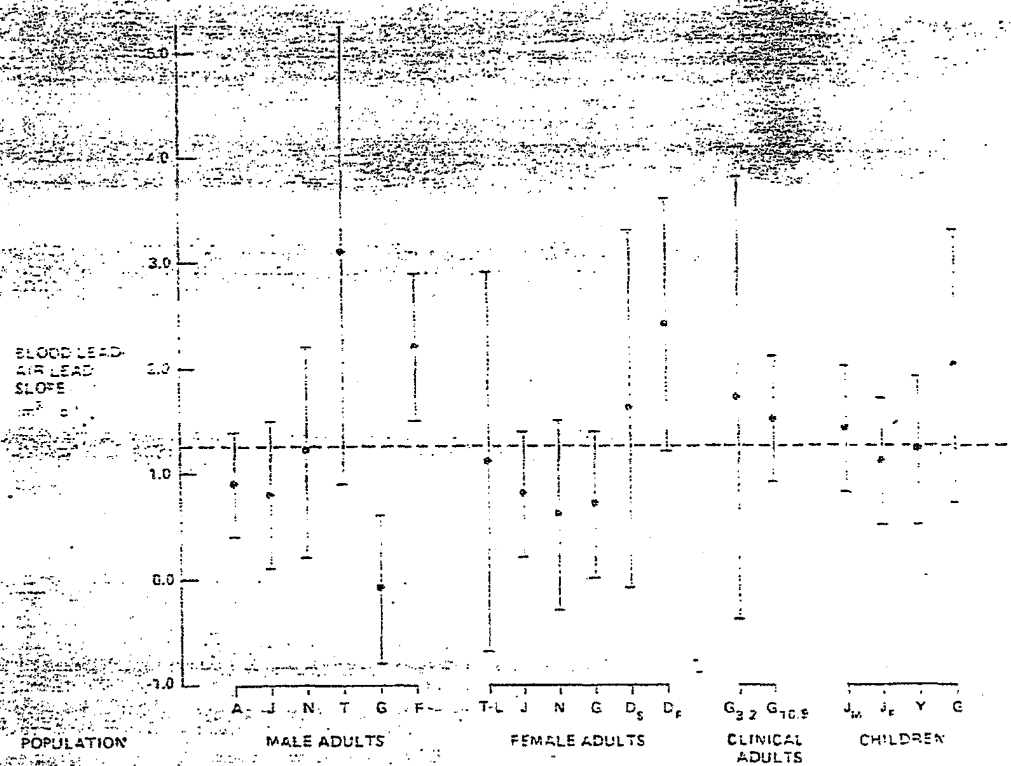

Fig. 1. Plot of blood lead–air slope estimates and associated approximate 95 per cent confidence intervals. Studies are identified by first letter of senior author's last name. The horizontal dashed reference line corresponds to the combined slope estimate from all studies.

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Table 2. Blood lead–air lead slope: combining estimates from various studies

		Populations in analysis				Average slope		Between-study
Analysis†	No. of studies	Male adults	Female adults	Clinical adults	Children	Estimate	Uncertainty‡	Chi-square§
1	6	X				1.1	±0.7	10.60*
1A	5	X				1.4	±0.6	3.57 NS
2	6		X			0.9	±0.4	0.00 NS
3	12	X	X			1.1	±0.4	9.29*
3A	11	X	X			1.2	±0.4	3.55*
4	8	X		X		1.2	±0.6	10.70*
4A	7	X		X		1.4	±0.4	2.78 NS
5	14	X	X	X		1.2	±0.4	10.20*
5A	13	X	X	X		1.2	±0.4	3.93*
6	4				X	1.3	±0.4	0.00 NS
7	16	X	X		X	1.2	±0.3	7.58*
7A	15	X	X		X	1.2	±0.3	2.31 NS
8	18	X	X	X	X	1.2	±0.3	7.88*
8A	17	X	X	X	X	1.2	±0.2	2.10 NS

* Between-study variance component significantly different from zero ($P < 0.05$).

† The Goldsmith–Adults slope of −0.1 was deleted from all analyses denoted by an A. This slope is unrealistically low and not consistent with the other estimates.

‡ Two standard deviation limits which are approximate 95 per cent confidence limits. These limits are based on estimated values of the between-study and within-study variance components.

§ Chi-square statistic ($-2 \log \lambda$) for the between-study variance in slope estimates.

NS Between-study variance component not statistically significant.

female adults (analysis 2), children (analysis 6), or all groups combined (analysis 8A) was detected. Borderline significance ($P < 0.05$) was detected in two of the other four analyses (3A and 5A) where some population groups were combined. Due to the lack of strong evidence of within or between population group variation in the slopes, it is concluded that a combined slope provides the best estimate of the relationship between blood lead and air lead.

COMPUTING THE WEIGHTED AVERAGE SLOPE

The weighted average slopes reported in Table 2 were computed by iteratively solving the following set of equations

$$\hat{\beta} = (1'V^{-1}z)/(1'V^{-1}1)$$

$$[\mathrm{Var}(\hat{\beta})]^{-1} = \mathrm{trace}(V^{-1}) = (z - \hat{\beta}1)'V^{-2}(z - \hat{\beta}1)$$

$$V = \hat{\sigma}^2_{\beta}I + \mathrm{diag}(\sigma_i^2).$$

The $\hat{\beta}$ estimates, which depend on the estimates of between-study variation, $\hat{\sigma}^2_{\beta}$, are in good agreement with those derived by Snee (1981), which were computed using only the epidemiologic studies and where it was implicitly assumed $\sigma^2_{\beta} = 0$.

Population	Blood Pb–Air Pb slope	
	Snee (1981)	This analysis
Male adults	1.0 ± 0.3	1.4 ± 0.6
Female adults	0.9 ± 0.4	0.9 ± 0.4
Children	1.3 ± 0.3	1.3 ± 0.4
All subjects	Not reported	1.2 ± 0.2

A diagnostic check on the validity of the distribution assumption underlying this analysis was made using a probability plot of the quantities $(z_i - \hat{\beta})/(\hat{\sigma}^2_{\beta} + \sigma_i^2)^{1/2}$ which showed reasonable agreement with the standard normal distribution.

CONCLUSION

This analysis has indicated that no significant differences ($P \leq 0.05$) were detected among the estimates of the slope of the blood lead–air lead relationship from the ten studies considered or from among estimates within adult male, adult female, or child population groups. It follows that at this time, the overall weighted average of 1.2 μg dl^{-1} per μg m^{-3} (±0.2, 95 per cent confidence limits) provides the best estimate of a common slope.

It is apparent that the uncertainty in many of the estimates is large with 95 per cent confidence limits of ±0.7 to ±1.0 about the estimate. It is concluded that studies which yield more precise slope estimates are needed to determine the importance of the factors noted by Chamberlain. This will necessitate the closer control of some variables and the more accurate measurement of others.

Snee (1981) recommended that studies of the relationship between blood lead and air lead should have the following key characteristics: air lead exposures be measured by personal monitors; blood samples be obtained from each subject on at least two different days; lead level in each sample be measured in duplicate; and, statistical calculations be made to ensure that sufficient subjects are included to estimate the slope with the desired precision. An uncertainty of ±0.5 or less (95 per cent confidence limits) is a reasonable goal. Persons designing such programs may wish to review the study of Azar *et al.* (1975) which had these characteristics.

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TEH 0412677

DUP050453732