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In re: Your letter dated November 17, 1977 and final revised draft document entitled "Air Quality Criteria for Lead"

Dear Dr. Hueter:

This is in reply to your letter of November 17 requesting my individual endorsement of the final draft document entitled "Air Quality Criteria for Lead". As a consultant to the SAB Lead Subcommittee, I did not anticipate such a request. I tried to reach you by telephone on Tuesday, 29 November 1977, but was unsuccessful. While I find that the final revised draft provides a sound scientific basis for the standard setting process on many of the important points, I find that there are certain important aspects in which a balanced scientific evaluation is not provided. Because of these reservations, I cannot endorse it in toto. On the basis of a very brief review, I shall state what, to me, are the strengths and weaknesses of the document.

The literary style of this revised draft represents a great improvement over earlier drafts. The material is now well organized and generally presented in a lucid manner. In this regard, I find it quite satisfactory.

The log normal distribution of blood lead concentrations is well documented. The use of the geometric mean and geometric standard deviations to predict distributions in Pb-B and the percentage of persons in a given population with Pb-B greater than certain specified levels is sound. This I consider one of the major strengths of the document. The treatment of "dust" is good, given the present "state-of-the-art" in this area.

Scattered throughout this lengthy document there are a number of recommendations for research on various points where needed information is lacking. Before the document goes to the printers for final printing, its value might be improved greatly if these scattered recommendations for research

were brought together in a single chapter entitled "Recommendations for Research".

There are certain points concerning dose-response, dose-effect relationships and metabolic interactions involving lead, as summarized in Chapter 13, which I cannot accept. It is primarily for these reasons that I cannot endorse the final document without serious reservations. While considerable emphasis is placed on dose-response (% population response) data in relation to the "no detected effect Pb-B levels," the quantitative nature of the dose-effect relationship for some effects has not received sufficient display in either Chapters11, 13 or 1. The absence of such material leaves the standard setter without adequate information on the magnitude of changes in particular effects that occur as Pb-B increases. For example, Figure 13-6 (page 13-34) is misleading and totally unacceptable. I have reviewed the Azar data, as well as many other reports on the Pb-B-ALAU relationship on which this presumed ALAU threshold is based. A number of papers, some of which are not cited on this particular point, could provide excellent graphic representation of this relationship. Azar and most other workers have used the two column ion exchange chromatographic method for the determination of ALAU in urine. As noted by Mauzerall and Granick in their original publication of this method in 1956, the technique measures other substances besides ALA in human urine and so is not specific for ALA at very low concentrations. Other studies employing more specific chromatographic methodology have shown that about one third of the material measured as "ALA" in the method used by Azar is, in fact, amino acetone, a substance related to variations in dietary composition, but not to lead. While it is true that statistically significant differences in the urinary excretion of "ALA-like material" are reported in the various groups studied by Azar, all of whose subjects apparently had Pb-B $\lesssim$ 40, the degree of increase in "ALA" is biologically negligible and insignificant. There are a number of reports which show quite clearly that there is no real increase of biologic significance in ALAU until Pb-B exceeds approximately 40 μg Pb/dl whole blood. A properly balanced scientific document would have included graphic representation of such data. The reports of Schlenker, et al, Druyan and Haeger-Aronsen and Chisolm, et al, who have measured ALA and amino acetone separately in human urine show clearly that about one-third of the output, which less specific methods measure, is amino acetone and furthermore that there is no change in the excretion of amino acetone, even in acute clinical lead intoxication. The writers of this document have received and rejected two of the three available reports that I am aware of in which ALA has been measured by methods more specific for ALA. In his letter to Mr. Linde dated 9/23/77, Paul B. Hammond provided data on the dose-effect relationship between Pb-B and both plasma and urine ALA in which ALA was

measured by a highly specific published gas chromatographic method. The data provided by Dr. Hammond clearly show that there is no increase in ALA in either plasma or urine which is of any biological magnitude until Pb-B exceeds 40 to 50 μg in adults. Other unpublished data were accepted at the October 7 meeting and incorporated in the final draft, but Hammond's relevant and accurate data have been ignored. Similar data by Chisolm, et al (Interrelationships among blood lead concentration, quantitative daily ALA-U and urinary lead output following calcium EDTA, in "Effects and Dose-Response Relationships of Toxic Metals," G. F. Nordberg, editor, Elsevier, New York, 1976) which show the same relationship in children between Pb-B and ALAU were also reviewed and rejected, despite the fact that a three-column ion exchange resin chromatographic technique specific for ALA was used, as well as the necessary correction for body surface area. I find no valid data which support any Pb-B threshold for the ALAU effect less than approximately 40 μg Pb/dl whole blood.

The use of the term "anemia" in Table 13-2 (page 13-25) in relation to the "lowest-observed-effect-level" at Pb-B = 40(in children) and Pb-B = 50 (in adults) is misleading and unacceptable. What has actually been reported is that the earliest detectable statistically significant decrease in hemoglobin has been observed at or above these Pb-B levels. In the case of the adult data cited in the document, the mean value was still well within the broad range of normal variation for hemoglobin concentration. There is a vast difference, biologically, between anemia and the earliest detectable decrease in hemoglobin. In Table 13-2, "earliest detectable decrease in hemoglobin" is a more appropriate term scientifically than the term "anemia".

The presentation of data on the Pb-B-FEP relationship in Figure 13-5 (page 13-32) is not entirely clear and is not adequately explained in the text. Presumably, "FEP > mean $\pm$ 2 S. D." signifies the upper limit of the normal distribution in healthy children (95% confidence limit) who are not iron deficient. This line rises above the "natural frequency" (presumably non-specific background effects unrelated to lead) when Pb-B is approximately 25 μg Pb/dl whole blood. If this is the case, then the Pb-B threshold shown in Table 13-2 (page 13-25) should be about 25 and not 15 to 20. A Pb-B "threshold" of approximately 25 μg Pb/dl whole blood would be much more consistent with a balanced scientific evaluation of the available published data on this particular point. The data of Stockman, et al (J. Lab. Clin. Med. 85:113-119, 1975), especially Figures 2 and 3, show clearly in children with Pb-B <30 that elevation in FEP is clearly related to accepted evidence of iron deficiency; namely, microcytosis and percent saturation of <15%. These figures from Stockman's work should have been reproduced in either

Chapter 11 or 13, together with some dose-effect curves showing the degree of increase in FEP in relation to rising Pb-B.

While Chapter 9 generally provides a very good summary of laboratory methods for the determination of lead and various pertinent biochemical assays, the reader unfamiliar with analytical problems in the determination of lead would not glean the precarious nature of the present state-of-the-art, particularly in regard to the measurement of Pb-B. This chapter is focused more on ways in which laboratory methodology can be improved than on the current state-of-the-art on which other data in the document are, of necessity, based. This is one of the main reasons that I feel that the use of geometric mean Pb-B values is sound. It is also a sound reason for basing interpretation of particular issues on confirmed studies which are substantially in agreement. It is likewise a strong reason for attaching only limited value to an unconfirmed, but provocative study such as that of Fahim, et al on preterm delivery and premature rupture of the membranes. Parenthetically, I might add that there are many other inadequacies in the presentation of data in this particular report which make it difficult to evaluate.

In summary, my substantive reservations are concerned with the failure to present the quantitative aspects of the dose-effect relationship between lead and metabolic indices of disturbance in heme synthesis in particular. The basic problem is to differentiate between statistically significant differences and biologically significant changes. The document would give one the impression that changes in ALAD, ALAU and FEP are specific for lead. This is not the case. There is considerable evidence that interactions between lead, iron, zinc and possibly other factors are involved; so that tiny, but statistically significant differences at low Pb-B must be viewed with great caution, particularly when it comes to the question of setting standards.

In the brief time available to me for review of this enormous document, I have found several errors in fact, as well as some apparently typographical errors. These are listed on the attached sheets. I enjoyed participating in this endeavor and hope that the information which I have been able to provide has been helpful to the group in preparing the document. I regret that I cannot endorse it in toto.

Yours sincerely,

J. Julian Chisolm, Jr., M. D.

JJC:ov
Enc.
cc: Dr. R. McClellan, Chmn.,
SAB Comm. on Lead, EPA
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bcc: Paul B. Hammond, M. D.