OAQPS OAQPS Docket
TTL 77-1-IV-F-2-3 Supp. Info
Hearing 2/15/78

DUPONT
REG U.S. PAT. & TM. OFF.

Petroleum Chemicals

CRITIQUE OF "AIR QUALITY CRITERIA FOR LEAD," EPA-600/8-77-017, DECEMBER, 1977

PLMR-6-78

E. S. Jacobs

January, 1978

Petroleum Laboratory
E. I. du Pont de Nemours & Co., Inc.
Wilmington, Delaware 19898

DETAILED COMMENTS ON CHAPTER 1, "SUMMARY AND CONCLUSIONS"

Page 1-3, Section 1.1.1, "Potential Exposure for Lead"

Only general information on ambient air lead levels is presented for "background," non-urban air and U.S. cities not influenced by major sources. This section fails to indicate what the air lead levels are in more urban and suburban areas. It does not define a representative 30- or 90-day ambient air lead level or the difference between these time averages and annual ambient air lead averages. Since most air lead data are in yearly quarters or annual averages, the relationship between these and shorter time averaged values is necessary in order to know anything about exposure. The Criteria Document fails to provide this information. This may be due primarily to the fact that Chapter 7, "Environmental Concentrations and Potential Exposures," also fails to contain the necessary information on this important subject. It is difficult to know how to set a time averaged air standard without such data.

Page 1-17, Lines 14-16

This is an example of a misleading statement used throughout this chapter. It states ". . . no conclusive statements can be made about the induction of chromosomal damage by lead." This implies chromosomal damage has occurred due to lead. In Chapter 11, information reported on this subject relates primarily to questioning the technique used in such studies, but the studies reported in Chapter 11, page 14, have not shown proof of chromosomal damage by lead in man.

Page 1-17, Lines 18-20

This statement implies lead is a suspected carcinogen in humans. It states ". . . some experimental animal studies relate the development of cancer to relatively high doses of lead, but as is true in the case of other suspected carcinogens, there are no data corroborating these findings in man." The additional phrase, ". . . but as is true in the case of other suspected carcinogens. . ." was added to this version only of the Criteria Document. Again the information reported in Chapter 11, page 17, does not support this implication or suspicion. It states that there is no evidence suggesting that exposure to lead salts causes cancer in humans. It further states that levels of lead exposure associated with malignant tumors in experiments on rats is considerably higher than the toxic dose in humans.

Page 1-18, Lines 10-12

This states "In children, a threshold blood lead level for production of these symptoms of anemia is approximately 40 ug/dl, while corresponding value for adults appears to be 50 ug lead/dl." Chapter 11 shows that a decrease in hemoglobin is measurable in some children with a blood lead of 40 ug lead/dl but it does not report data relating this to anemia or clinical or physical symptoms of anemia. This is an example of mis-statement and extrapolation of scientific information.

Dr. J. J. Chisolm has criticized this type of mis-statement in his December 1, 1977 letter to Dr. Gordon Hueter in which Dr. Chisolm disapproved the final draft of the Criteria Document for Lead. Dr. Chisolm stated:

> "The use of the term 'anemia' in Table 13-2 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' is a more appropriate term scientifically than the term 'anemia'."

A copy of this letter is attached as Appendix A to this Du Pont report.

Page 1-19, Lines 12-13

EPA states "An increase in free erthrocyte protoprophyrin (FEP) occurs at blood lead levels of 16 ug/dl in children." This appears to be based on data reported in studies by Piomelli and Roels as cited in Chapter 11, pages 38 to 40.

However, Du Pont analysis (Ref. 1) of these same studies show the threshold to be at least 20 ug/dl. In fact a review of the Roels' paper cited by EPA shows Roels stated the blood lead threshold for elevated FEP was 20 ug/dl. The value reported by Piomelli in only a brief abstract was developed with improper statistical model and highly selected data. Using

the proper model prescribed by EPA and all of the data, the estimated blood lead threshold for elevated FEP from the Piomelli data is 20 ug/dl, in good agreement with the correct Roels' statement.

Ref. 1 - Lucas, J. M., "Blood Lead - FEP Relationships," PLMR-8-78, E. I. du Pont de Nemours, Petroleum Laboratory, Wilmington, Delaware, February, 1978.

Page 1-19, Lines 13-15

The Criteria Document again presents incorrect data on the threshold for elevated FEP in women. As noted in Chapter 11, Roels, et al, again show unequivocally the lowest blood lead threshold for elevated FEP in women ranges from 20 to 25 ug/dl and adult males ranges from 25 to 35 ug/dl.

This is another example of extrapolation of data from the body to the summary. Dr. Chisolm also comments on this in his December 1, 1977 letter to Dr. Hueter.

Page 1-22, Lines 3-6

Again this statement represents an example of extrapolation of results, albeit only slightly, from the body of the report. Continued extrapolation and twisting of the data, however, eliminates the need for application of any additional safety margin in setting the standard.

This sentence states: "The blood lead levels at which neurobehavioral deficits occur in otherwise 'asymptomatic' children appear to start at a range of 50 to 60 ug/dl, although some evidence suggests that such effects may occur at slighly lower levels for some children."

In Chapter 11, page 83, lines 23-24 state: "The blood lead levels associated with neurobehavioral deficits in asymptomatic children appear to be in excess of 50 to 60 ug/dl." On page 84, it continues: "Great uncertainties remain, however, as to whether these blood lead levels represent the levels that were responsible for the behavioral deficits observed." No information was given to substantiate the final phrase of the Summary chapter, ". . . although some effects may occur at slightly lower levels for some children." This is speculation not supported. If anything further can be deducted from Chapter 11, it would indicate just the opposite, that the deficits observed occurred at higher blood lead levels.

Page 1-24, Lines 16-20

These statements that short-term low level air lead exposure may cause effects on human ovarian function refer to work of Panova cited in Chapter 11, page 147. This study has been severely criticized by Zielhuis and consequently should not be reported in such a positive manner.

Zielhuis concluded the study design and data were such that the author's conclusions could not be evaluated and thus needed to be further confirmed before further presentation of the study.

Page 1-24, Lines 20-24

These statements showing moderatley increased blood lead may result in testicular impairment are based on a study by Lancranjan cited in Chapter 11, page 152.

Zielhuis has very severely criticized this study as having no scientific evidence for these observations and this was noted in review of this study in Chapter 11.

This statement should not be reported in the summary.

Page 1-25

This page is out of sequence. It appears as though it should be after page 1-27.

Page 1-27, Lines 11-13

This statement is based on the study by Fahim cited in Chapter 11, page 151. This study has been repeatedly and severely criticized by Dr. J. J. Chisolm and others in written comments to the EPA Science Advisory Board Subcommittee on Lead Criteria (See record of October 7, 1977 meeting.).

The Fahim study is faulty and the results are highly questionable and this criticism has been stated when the paper was discussed in Chapter 11. On the basis of the findings reported in Chapter 11, this study should not be cited so prominently in the summary chapter.

Page 1-27, Lines 13-15

This statement is based on the discredited study by Lancranjan. Others have not been able to reproduce her findings. This study is severely criticized when reviewed in Chapter 11. This study should not be cited in the summary.

Page 1-31, Line 27

This states the relationship between blood lead and air lead ranges from 1 to 2 and children have higher values than adults.

We believe the value for children is only slightly higher than adults and should be 1.2 based on extensive analysis of the available data on children. (R. D. Snee, "Relationship Between Blood Lead and Air Lead," PLMR-10-78, E. I. du Pont de Nemours, Petroleum Laboratory, Wilmington, Delaware, February, 1978). Our analyses were based on the only three epidemiological studies on children: Johnson Southern California, Goldsmith, and Yankel and von Lindern. Because of the difference in size of the studies and uncertainty of the data, we used standard statistical weighting procedure to compute an average value of 1.2 for the relationship of blood lead to air lead for children using all three studies.

EPA chose to reject the Johnson study because of some uncertain blood lead values and concluded the blood lead to air lead relationship ranged from 1 to 2 with children at the upper end. Using the EPA criterion for unacceptability then the Goldsmith data should also have been eliminated along with the Johnson data. This leaves only one study on children -- the Yankel and von Lindern study of children in Kellogg, Idaho, which we have repeatedly stated is the best and only suitable study to determine the blood lead-air lead relationship for children. Based on this study, the blood lead contribution from a unit air lead exposure for children would be 1.2 to 1.4 over the range of ambient air lead exposure of 1 to 5 $\mu g/m^3$.

Page 1-32

Great caution should be used in extrapolating or associating any exposure relationships to the blood lead data from the New York City blood lead screening program. As stated, this was a screening program and not an epidemiological study. Thus, the information on group composition, age, sex, race, location, and number were not selected in a proper manner to evaluate any significance in trends of blood lead over the years. In addition,

there was an analytical method change midway in the program which could and possibly resulted in biasing the group included in the later years' screening. These data should be carefully examined for reasons other than exposure to cause a trend in blood lead. In addition, the effect of the lead paint poisoning program publicity on reduced exposure and awareness should be carefully considered.

Page 1-37, Lines 2-4

See comments on Page 1-31, Line 27.

Page 1-37, Lines 21-22

This states: "Lead is not conclusively known to have any biological effect in man which can be considered beneficial." This is a subjective conclusion of the Criteria Document summary, since no information on the essentiality of lead in the body was reviewed. Actually, an earlier draft cited the work of Dr. K. Schwarz showing possible essentiality of trace amounts of lead, but this was not included in the later drafts. This statement should not appear in the Criteria Document summary without some review of the work by Dr. Schwarz.

Page 1-39, Table 1-1

This table lists the lowest blood lead level for observed effects but does not agree with the World Health Organization statement. This table also has several blood lead values in error. These have been discussed earlier in reference to the threshold for elevated FEP and in relation to anemia.

The lowest blood lead value for elevated FEP in children should be 20 (See comments on Page 1-19, Line 12.), the value for women should be 20 to 25, and 25 to 35 for adult males (See comments on Page 1-19, Lines 13 to 15.).

Also, the lowest blood lead level for anemia in children and adults of 40 and 50 respectively is incorrect. The effect observed at these levels was reduced hemoglobin -- not anemia. (See comment on Page 1-18, Lines 10 to 12.)

Page 1-40, Lines 9-12

See comments on Page 1-19 regards blood lead threshold for elevated FEP.

Page 1-46

The Criteria Document for Air Lead fails to provide several pieces of needed information:

(1) It fails to show a direct link of absolute air lead to blood lead or FEP level.

(2) It fails to provide a breakdown of the percent blood lead contribution from different sources (air, food, water, dirt, paint) for different groups (rural, suburban, urban, children, adults).

(3) The Document fails to identify the adverse health effect and threshold of this effect.

(4) The EPA has chosen the elevation of FEP as adverse health effect, and set an air standard for lead based on a monthly average. However, FEP lifetime is 120 days, thus the FEP elevation measured this month may be related not to this month's air lead but to previous month's exposure. The EPA does not consider this problem in setting the standard, and failed to give data relating air lead to FEP.

DETAILED COMMENTS ON CHAPTER 6, "TRANSFORMATION AND TRANSPORT"

Page 6-14

This reports on a study by Purdue, et al of EPA showing levels of organic lead in air in six U.S. cities. This report received considerable prominence by having three tables of data presented, yet the study has been critically reviewed and criticized by Harrison as lacking accurate data. The results reported are of the same level as the accuracy and sensitivity of the author's procedure and its results should not be taken seriously. More importantly, the Criteria Document should not make such a display of this information which is inaccurate and misleading.

DETAILED COMMENTS ON CHAPTER 7,
"ENVIRONMENTAL CONCENTRATIONS AND POTENTIAL EXPOSURE"

Page 7-1, Section 7.1,
Ambient Air Exposures

This chapter fails to include useful air lead data submitted on several occasions to the EPA. These include monthly air lead values at selected sites around the U.S. which have been in continuous operation since 1970. These data were submitted by the Ethyl and Du Pont companies to the EPA in response to review of this specific chapter for earlier drafts of the Criteria Document. In view of the almost non-existent 30-day average data and any long-term trend data from ground sites, it is strange that EPA did not include the submitted air lead data.

The Du Pont data are included in a Du Pont report, "Trends in Air Lead Concentration," PLMR-3-76, and include 30-day air lead averages from 1970 on six sites in the U.S. In summary these data show:

> "Since 1970 the Du Pont Petroleum Laboratory has conducted an air monitoring program to evaluate the lead levels in the atmosphere at six locations throughout the United States. The air lead is sampled continuously, 24 hours a day, 365 days a year at Los Angeles, Houston, Tulsa, Chicago, Starke (Florida), and Du Pont (Washington).
>
> "This report summarizes the results of this air monitoring program which has been carried out to determine the trends in air lead levels. The sampling sites were selected to represent the extremes in air lead levels from high values near a heavily trafficked highway in Los Angeles to very low levels at a rural site in Starke, Florida. Major findings of this study are as follows:
>
> - A downward trend in air lead levels has occurred at all sampling sites, except the highly rural location at Starke, Florida.
>
> - The annual average air lead concentration decreased by at least 25% from 1970-71 through 1975 for all locations except Starke, Florida. The air lead levels at Starke remained at an average of 0.10 $\mu g/m^3$.

- The highest monthly average air lead level at each site decreased by 36 to 46% from 1970 through 1975.

- There is a pronounced seasonal trend at most sites. The peak air lead values occur in the fall and winter months and the lowest values occur during the summer. The peak monthly air lead level for any year is usually at least twice as high as the low summer values.

  The seasonal trend in air lead levels measured at the six Du Pont sampling sites is also observed in air lead data reported by the California Air Resources Board.

- The seasonal trend in air lead levels is not associated with traffic activity or lead used in gasoline. In fact, the lowest air lead levels occur in the summer when vehicle traffic activity and lead usage in gasoline are the greatest. Air lead levels are lower in the summer because the air lead is more widely dispersed by better ventilation. Conversely, higher air lead levels are observed in the winter because of reduced ventilation."

Page 7-42, Lines 19-20

This should be corrected to read: "The average concentration of organic lead in the urine was 0.071 mg/l for workers in the tetramethyl lead operation and 0.063 mg/l for workers in the tetraethyl lead operation."

DETAILED COMMENTS ON CHAPTER 11, "BIOLOGICAL EFFECTS OF LEAD EXPOSURE"

Page 11-37, Lines 7-8

This statement ". . . accumulation of protoporphyrin has been taken to indicate physiological impairment relevant to human health.[146]" is attributed to the Center for Disease Control statement on lead poisoning. The CDC statement does not say this. This statement is incorrect and represents a conclusion not supported by fact.

Page 11-37, 2nd Paragraph

This paragraph reports results of a study by Sassa, et al. However, the statement ". . . the scatter observed when blood lead is correlated to erythrocyte protoporphyrin on a random basis is the result of fluctuations of lead caused by day-to-day variation and experimental error." is not a correct summary of the authors' study. First, blood leads don't fluctuate on a day-to-day basis, although the analysis results may fluctuate due to experimental error. The authors attributed the fluctuation both to a lag in response of blood FEP and to experimental error.

Page 11-38, 3rd Paragraph

This attributes, falsely, to Roels a blood lead threshold of 15 to 20 for elevated FEP in school children. In his paper, Roels himself clearly states that ". . . for FEP response, a threshold value is clearly observed at a Pb-B of approximately 20 ug/100 ml of blood." This observation is based on the author's regression of their FEP and blood lead data on exposed and unexposed children as illustrated in Figure 2 of Roels' paper.

EPA also erred in not carefully examining the procedure reported by Piomelli in deriving a blood lead threshold of 15.5 for elevated FEP in children. Piomelli has described his work in only a 20-line abstract.

Our analysis of the FEP and blood lead data from the Piomelli study found a threshold value for elevated FEP of 20 ug Pb/dl instead of the 15.5 ug Pb/dl reported by Piomelli and cited in the Criteria Document. The individual blood lead and FEP data from the Piomelli study were supplied to us by EPA. These data represent 'normal' blood lead levels, < 40 ug Pb/dl, obtained on samples taken in the New York City blood lead screening program during January, February, and March of 1976. The data were analyzed using the "hockey stick" regression model which is the most correct and suitable statistical model to evaluate the blood lead level for threshold of elevated FEP. The "Probit" analysis model, valuable in some cases for data analysis, is not appropriate for this current analysis since it is an unsatisfactory technique for evaluating a threshold effect level.

Our analysis of the Piomelli data used all of the data since we could find no statistical reason to reject any of the values nor did we find any lack of fit to the "hockey stick" function when all the data were used. Thus we conclude that all the data must be used, and when this is done, the value of the blood lead threshold for elevated FEP is 20. Piomelli in his analyses excluded blood lead values above 28 because in his view, these values are higher than 'normal'. We find no justification for this arbitrary elimination of data because the population selected was homogeneous and continuous.

Our analysis of blood lead and FEP data from several other studies of children found blood lead threshold values for elevated FEP higher than 20 ug Pb/dl, ranging from 23 to 28 ug Pb/dl.

Our analyses of the Piomelli data and other studies as contained in the Du Pont technical report PLMR-8-78, "Blood Lead - FEP Relationships" by Dr. J. M. Lucas.

Page 11-39, Lines 18-23

This analysis does not prove the absence of iron deficiency anemia! It only says there is no difference between the younger and older groups. This is a poor attempt to manufacture a clean set of data, but the logic of this reasoning is inaccurate. The fact remains -- the children in the Piomelli data group could have elevated FEP due to some iron-deficiency anemia and not to lead.

Page 11-42, 2nd Paragraph

This states that: "In children, a threshold level for anemia is about 40 ug Pb/dl, whereas the corresponding value for adults is about 50 ug Pb/dl."

Dr. J. J. Chisolm criticized this statement in his December 1, 1977 letter to Dr. Gordon Hueter as being incorrect. Dr. Chisolm states:

> "The use of the term 'anemia' in Table 13-2 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 on 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' is a more appropriate term scientifically than the term 'anemia'."

Page 11-43, 2nd Paragraph

This again states the blood lead threshold for elevated FEP incorrectly. The children blood lead threshold for elevated FEP is 20 as discussed in our comments on Page 11-38. The data on adults rest largely with another study by Roels in which he found female blood lead threshold for elevated FEP ranged from 20 to 25 ug Pb/dl, while the adult male blood lead threshold for elevated FEP ranged from 25 to 35 ug Pb/dl.

These corrected values are also recognized by the World Health Organization.

Page 11-43, 3rd Paragraph

Several statements in this paragraph attributed to the CDC and WHO have been twisted and are not correct.

The third sentence in this paragraph implies the WHO called elevation of FEP greater physiological relevance than increased urinary δ-ALA. Actually on page 127 of the WHO, Lead Criteria Document, it states simply that "... increased FEP is an indicator of impaired hematopoiesis."

The last sentence is attributed to CDC: "... this finding [elevated FEP] should be used as an indicator of a significant and worrisome body burden of lead." Actually, the CDC said: "... this should be used as an indicator of an increased lead exposure."

These mis-statements indicate the directional bias of this supposedly technical document. If the technical data are misquoted and extrapolated, then judgments for a safety margin will represent extreme excess.

Pages 11-146 and 11-151, Last Paragraphs

On page 11-146 EPA reports on a study by Fahim which has received much criticism. However, the critical review of this study is not given until five pages later on page 11-151. Again, this treatment does not appear to be technically objective.

Dr. J. J. Chisolm, consultant to the EPA Science Advisory Board Subcommittee on Lead Criteria in his review of the Third Draft has also criticized this study, but his comments have gone unheeded or unread. (Letter, Dr. J. J. Chisolm to Dr. R. O. McClellan, Chairman, EPA Subcommittee on Scientific Criteria for Environmental Lead, September 13, 1977.) Dr. Chisolm states that:

> "I note that some weight is given in Draft No. 3 to the study of Fahim, et al. These authors report an association between premature birth and premature rupture of membranes and mean Pb-B of 25-30 ug, which, if it could be substantiated, would give considerable cause for concern. Unfortunately subsequent studies to test this hypothesis have not been reported to my knowledge. Likewise, unfortunately, the report of Fanim, et al, does not provide sufficient data for critical analysis by the reader. Patients were apparently matched for age (group or pairs ?), economic status (annual income $7,000 to $10,000), but not for socio-economic status."

"They were also matched for residence. Although mean Pb-B data, together with the standard error of the mean are given, one would also like to know the distribution of Pb-B values in the various groups. One does not know for example whether these arithmetic mean values are disproportionately elevated by the presence of a few unusually elevated values. Race should be known, inasmuch as average birth-weights differ between caucasians and non-caucasians. Parity also influences birth weight and prematurity. One report suggests that there may be seasonal fluctuation in maternal and fetal blood lead concentrations. It is, for example, possible that the groups contain both students and non-student local residents who are from different socio-economic classes, but still of the same annual income. The population is drawn from Missouri, an area included in the "moonshine whiskey" belt (National Academy of Sciences, 1972, page 83). No comment about this is made; however, alcohol does increase suspectibility to lead toxicity. Thus, this study leaves a number of unanswered questions. Although these authors may be correct, one would like to know more about the data if it is to be given considerable weight, as it apparently is in Draft No. 3."

DETAILED COMMENTS ON CHAPTER 12, "ASSESSMENT OF LEAD EXPOSURE AND ABSORPTION IN HUMAN POPULATIONS"

Page 12-5, 3rd Paragraph

This states, correctly, the importance of the geometric standard deviation, but it fails to give guidance in what is acceptable. It identifies a value of 1.3 for the best studies, but fails to point out that most studies reviewed in the Criteria Document have geometric standard deviations for population blood lead levels of 1.4 to 1.7. All of these are not equally good. Some guidance should be given for acceptable or satisfactory and unsatisfactory or questionable studies.

In keeping with this, some comment should be made on the effect the dispersion has on the extreme ends of a log normal distribution as shown in Figure 12-2. This is very important in assessing the percent distribution of blood lead levels in a given population.

Page 12-9, Line 10

This phrase ". . . also includes method variance" complicates this whole description of variation in blood lead values as illustrated in Table 12-1. The within group variance should not include method variance. The method variance is derived from sampling and analytical error and should be described separately so as to know if method or selection of subjects (within group variance) causes variation. Including the two together ignores significance of different source of variation. The data as presented in Table 12-1 are not useable in analyzing a study.

This section should provide a means for an objective and quantitative estimation of the quality of blood lead data in a population study. The present version of this section attempts to show that an SGD of 1.3 indicates an acceptable population blood lead study. However, this is not supported by the data given in Table 12-1. Table 1 shows the Idaho and Houston studies have the same SGD of 1.3, but the measurement variance component of the Houston study is considerably larger than the Idaho study. Thus, the variation in the Idaho study is due mostly to within group make-up; the Houston study variation is due almost entirely to measurement variation. While the SGD may be useful, it is still necessary to consider each variance component to accurately evaluate the usefulness of a study.

The necessity of having to evaluate each variance component in a study will require a minimum of duplicate blood samples taken one day apart. Each duplicate sample should be analyzed in duplicate in separate operations. A suggested revision to this section is given below.

"Suggested Revision to 1st Paragraph, Section 12.2.1.3"

12.2.1.3 Variation in Blood Lead Values

The total variation in blood lead values for any study is composed of three variance components: (1) between group, (2) within group or individual, and (3) method variation. The method variance results from both sampling and analytical measurement variations. The within group variance is due to the difference in biological response among individuals with the same exposure as well as demographic differences in age, sex, race, socio-economic status, and environmental background in the individuals in a group. The within group variance is a measure of the homogeneity of people in a group and does not include method variance. The between group variance is due to the differences in the composition of people in a group, such as policemen or housewives, etc. In studying the effect of lead exposure on blood lead levels it is necessary to separate these sources of variation to know if the study results are meaningful. If the blood lead sampling and analysis error are large, any effects of different lead exposure may not be seen. In a similar manner, if the group chosen for a study is not homogeneous, the within group variance may be so large that the differences in blood lead values cannot be interpreted as due to exposure.

The sources of variations estimated for several studies are given in Table 12-1. These data show that a large portion of the total variation for all studies except Idaho is due to measurement variation. The measurement variation for the Johnson Southern California study was unusually large, suggesting that the results of this study should be used with caution.

A geometric standard deviation (SGD) can be computed for each variance component. The standard geometric deviation for the sum of the within group and method variance for selected studies is shown in Table 12-1 in addition to the value of each of the three variance components. This SGD has been

cited (1) as a useful measure of the quality of blood lead data obtained from a homogeneous human population. Most of the studies shown in Table 12-1 exhibited an SGD of about 1.3.

The SGD should be used with understanding and caution, however, since a large blood lead method variance can overwhelm any within group variance component. The sum of these variances may produce an SGD of ~ 1.3, but the method variance may be large enough to produce a negative within group variance. In this case the SGD really has little meaning. In such cases, it is more useful to examine the individual variance components. Such a case is shown by the Houston (7) study in Table 12-1.

SUGGESTED REVISED VERSION OF TABLE 12-1

TABLE 12-1

ANALYSIS OF VARIANCE OF BLOOD LEAD VALUES FROM SELECTED STUDIES

Study	No. of Subjects	Variance Components				
		Total	Between Group	Within Group	Method	SGD*
Idaho (1)	879	0.190	0.118	0.060	0.012	1.31
Azar (4)	150	0.148	0.049	0.050	0.049	1.33
Seven Cities Study (2)	1908	0.090	0.008	0.019	0.063	1.33
Johnson Southern California (3)						
Males	64	0.224	0.042	-0.035	0.216	1.53
Females	107	0.183	0.016	0.026	0.141	1.51
Houston (7)	189	0.182	0.113	-0.027	0.094	1.30

* SGD = Standard Geometric Deviation for Within Group + Method Variance.

Page 12-10, 1st Paragraph

Table 12-1 references data obtained from the Center for Disease Control which was used to calculate the Idaho study measurement variance. Since this is unpublished data, it should be more completely described and referenced. In addition, the published reports of the Idaho study do not indicate duplicate analyses were obtained at the time of the study. Thus, a complete variance analysis could not be made. It is extremely important to know when and how the Center for Disease Control data were obtained and whether these data include sampling as well as analytical measurement variation.

The Idaho measurement variance may be small because it includes only analysis error, and no sampling error. If so, this measurement variance is not a real value in the same sense as the other studies.

EPA notes the GSD for most of these studies was low, about 1.3. However, it should be noted most other studies reported have GSD of the mean of 1.4 to 1.7. A typical example is the data reported by Baker on a study of smelter town children cited on page 12-20. It is not the SGD of the future studies, but these already reported which need to be considered and no guidance is given in considering the acceptability of studies reviewed in this chapter.

Page 12-10, 3rd Paragraph

EPA has completely missed the point of the problem of "false exceedences". The main point is that in almost all reported studies, 80% of the total study variance comes from measurement error. This is an artifact of the experiment and is not a true variation. As such the GSD or dispersion of blood lead values is untruly large which causes large uncertainties in the extremes of a log normal distribution. Thus, if measurement variation can be reduced, by better technique, such as duplicate samples and duplicate analysis, then more correct assessment can be made of the population distribution of blood lead values.

Page 12-13, Table 12-3

EPA fails to show the most significant findings and data of the Seven Cities Study discussed and partly shown in Table 12-3. The difference between blood lead values of housewives between different urban areas was much greater than difference between urban and suburban areas. Since air lead levels were essentially the same, this implicates other sources of lead as major contributors to blood lead.

Page 12-13, 2nd Paragraph

EPA reports Nordman reported all populations he studied had a mean blood lead less than 13.5. The EPA incorrectly eliminated two groups of residents near living in Tikkwrela, near Helsinki, who had mean blood lead levels of 18.1 and 14.3.

Again this appears to be an attempt to select only the data from a study which proves EPA's position.

Page 12-14, Table 12-4

The blood lead data in this table were obtained using finger-prick sampling which has, except in a few well controlled studies, always given high blood lead values. Thus, these blood values should not be used to define absolute mean levels or for defining percent distribution.

Page 12-17, 2nd Paragraph

The EPA ignored a significant finding reported in the five-year study of blood lead levels in 6300 people at 23 Du Pont locations across the U.S. The five-year study showed the blood lead levels were not changing over a time period when lead sales were increasing and air lead levels were increasing. The results of this study show the blood lead levels of persons in these groups were not affected by a change in air lead exposure.

Page 12-19, 3rd Paragraph

The study by Joselow, et al, compared blood lead levels of children in Honolulu and in Newark, N. J. EPA ignores the basic part of the study, that is, selection of location of children. It fails to point out the influence of lead base paint in old Newark houses as a major source of lead exposure and probable source of higher blood lead levels in Newark children.

Page 12-20 and 12-21

EPA reports on several studies which show blood lead levels for children in or near lead smelters. There is no question of the problem of lead exposure in or near such plants, but great care should be exercised in interpreting the meaning or significance of this in relation to ambient air lead levels in typical suburban and urban areas.

First, the air lead concentration is usually many times higher near a smelter than experienced in urban areas. As noted in Chapter 10, page 5, these higher levels can cause greater effects than expected due to breakdown in body defense mechanisms. Thus, the findings at high level air lead exposure should not be extrapolated back to low level air lead exposure.

Second, the air lead emissions from smelters have a different chemical composition and physical particle size than air lead in urban areas. Again as noted in Chapter 10, these factors cause a greater difference in the gut absorption and lung deposition which govern contribution to body blood lead.

Finally, the selection of subject samples in these smelter town studies are usually not done in a manner to give a representation of the population exposure. Instead, they usually represent those at the extreme greatest risk.

Page 12-12, Lines 9-11

This reports results of an EPA study of effect of traffic on blood lead levels in Dallas, Texas. EPA fails to report that the groups of the study were not well matched, the groups were small, and finally that they could not find any relationship of blood lead levels to traffic activity.

Page 12-22

Again, all these blood lead values were obtained from blood lead screening programs which used micro blood samples. Thus, the blood lead values are not useful except in a relative sense within a given study. Blood lead values obtained with microtechniques are equivalent in the lab, but it has been shown that they always give high results in field studies, presumably due to contamination during sampling.

Page 12-30, Lines 23-24

This reports a study by Manton who attempts to determine the amount of air lead contribution to blood lead by measuring lead isotope ratio in air lead and in blood lead. EPA reports he finds automobiles supply 7 to 41% of blood lead.

A closer look at this paper shows the highly speculative conclusion of 7 to 11% of air lead contribution to blood lead rests on a questionable study. Manton studied 10 subjects and used data from four. No reason was given for the selection. It appears that selection of other subjects would have given a negative result. Again, it is very important for EPA to carefully review cited work to be sure the authors did not present biased conclusions.

Page 12-32, 2nd Paragraph

EPA should state that clinical studies dealing with few subjects are limited in their exact significance. The use of only a few test subjects minimizes its usefulness in extrapolating to population groups since a few subjects do not provide a full range of individual differences in biological response. This fact should be highlighted in discussions of clinical studies.

Page 12-52, Line 3

Reference No. 60 is incorrect. This is a reference which was written in 1972. Yankel and von Lindern did not measure the blood lead levels discussed here until 1974 and 1975.

Page 12-57, Lines 13-14, Table 12-22

This states blood lead in Yugoslavian populations increased with air lead levels. This is incorrect, since there are as many low blood leads with high air lead exposure as there are high blood lead and high air lead exposure. The best statement is to question the accuracy of the blood lead values and whether the air lead levels are representative of exposure.

Page 12-67, Line 6

EPA says the Azar model is incorrect by stating "The specific method can be argued, . . ." However, EPA fails to substantiate their case by not presenting any alternatives.

Page 12-70, 1st Paragraph

The results of the Goldsmith study should be treated with caution. The Goldsmith study is considered suspect because the blood lead samples were taken nine months prior to their analyses, the samples were not frozen in the interim period, and the samples were only single determinations. In addition, the air lead data used for comparison was from stationary samples and of questionalbe representation of the actual air lead exposure.

Page 12-75, Section 12.3.1.5
Blood/Air Lead Relationships

A complete review and update on Du Pont analyses of this subject is given in a Du Pont report, "Relationship Between Blood Lead and Air Lead," PLMR-10-78, by R. D. Snee, February, 1978.

Page 12-79, 2nd Paragraph,
Figure 12-8

Figure 12-8 is not from the paper by Azar, et al. This figure has been constructed by EPA and does not properly present the data from the Azar, et al study.

Page 12-79, 3rd Paragraph

The new model developed by Snee to fit the Azar, et al data provides a significant improvement in fit to the data. This was explicitly noted in the Du Pont report, "Evaluation of Studies of the Relationship Between Blood Lead and Air Lead," PLMR-8-77, April, 1977. EPA erred in this statement.

Page 12-90, 3rd Paragraph

This paragraph discusses CDC and EPA analysis of 1974 and 1975 blood lead-air lead data from the Yankel and von Lindern study at Kellogg, Idaho. This information reports high blood lead to air lead relationships which are basically not correct because all of the blood lead change between 1974 and 1975 was attributed to air lead. This is not correct since other lead exposures also changed and affected the blood lead.

We have completed a comprehensive analysis of these data and find the blood lead-air lead relation for this second year's blood lead and air lead data is the same as reported for the 1974 data. Our analyses are included in the Du Pont report PLMR-10-78, "Relationship Between Blood Lead and Air Lead," which is included as part of our record submitted to the EPA on February 15, 1978.

Page 12-92, Last Paragraph and
Page 12-125, 1st Paragraph

EPA states that the data on blood lead and air lead relationship vary over a range of 1 to 2 with children near the upper end. We feel the value of 2 for the relationship of blood lead to air lead for children is too high. We believe it should be 1.2 based on our analysis of the available data for children.

Our analyses were based on the three cited epidemiological studies on children: Johnson Southern California, Goldsmith, and Yankel and von Lindern. The data we developed and that developed by EPA for children and included in Table 12-28 of the Criteria Document are in agreement. These data are shown below in Table 1. Because of the different size of the studies and the differences in the uncertainty of the data from these studies, we used an acceptable statistical weighting procedure to compute an average value for the blood lead-air lead relationship. As shown in Table 1, the average value for the relationship of blood lead to air lead using all three studies is 1.2 with a 95% confidence limit of ± 0.4.

TABLE 1

BLOOD LEAD-AIR LEAD RELATIONSHIP FOR CHILDREN

Study	Subjects	Blood Pb-Air Pb Slope	
		Du Pont*	EPA**
Johnson Southern California	33 Male & Female	1.1 ± 0.4	-
Goldsmith	486 Male & Female	2.0 ± 1.3	2.3 1.7
Yankel - von Lindern	615 Male & Female	1.2 ± 0.7	1.16 to 1.37
	Average	1.2 ± 0.4	1 to 2 with children at upper end.

* Snee, R. D., Du Pont Report PIMR-8-77, "Evaluation of Studies of the Relationship Between Blood Lead and Air Lead," April 7, 1977. E. I. du Pont de Nemours & Co., Inc., Petroleum Laboratory, Wilmington, Delaware 19898.

** "Air Quality Criteria for Lead," EPA-600/8-77-017, (December, 1977) p. 12-80.

EPA chose to reject the Johnson study because of some uncertain blood lead values and their stated blood lead to air lead relationship ranged from 1 to 2 with children at the upper end. If data are to be eliminated on the basis of unacceptability, then the Goldsmith data should also have been excluded along with the Johnson Southern California data. This leaves only one study on children -- the Yankel, von Lindern study of children in Kellogg, Idaho, which we have repeatedly stated is the best and only suitable study to determine the blood lead-air lead relationship for children. Based on this study the blood lead contribution from a unit air lead exposure for children should be 1.2 to 1.4 over the range of expected ambient air lead exposure of 1 to 5 ug/m^3.

DETAILED COMMENTS ON CHAPTER 13,
"EVALUATION OF HUMAN HEALTH RISKS FROM
EXPOSURE TO LEAD AND ITS COMPOUNDS"

Page 13-11, 2nd Paragraph

This discussion of averaging-time considerations does not provide any information on FEP. FEP has a lifetime of ~ 120 days, thus an FEP elevation may not be derived from present blood lead level, instead it could represent an exposure earlier than 30 days ago. This problem was not considered in basing the health effect on FEP elevation and setting a 30-day average for the air lead standard.

ESJ/eaa

APPENDIX A

CITY OF BALTIMORE
WILLIAM DONALD SCHAEFER, Mayor

DEPARTMENT OF HOSPITALS
4940 Eastern Avenue, Baltimore, Maryland 21224

December 1, 1977

F. G. Hueter, Ph. D.
Associate Director
Health Effects Research Laboratory
U. S. Environmental Protection
Agency
Research Triangle Park, N. C. 27711

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

Chapters 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
Mr. Ernst Linde, EPA

Specific Errors and Other Comments Noted in Final Draft of Air Quality Criteria for Lead (December 1977)

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

December 1, 1977

Page No.	Line	
1-6	2	The value of 20 to 40 μg/liter for processed milk does not apply to canned evaporated milk, which should be identified separately as containing 200 to 400 μg Pb/liter.
1-15	14	"...essential nutrients such as calcium...protein..." This list should also include zinc.
1-15	4 lines up from the bottom	"...storage approaches 95%..." This sentence would be clearer if it read "...such storage in bone approaches 95%..."
1-32		The discussion of the "Billick data" from New York City should include the very strong possibility that the changes observed may be related to changes in the population screened. If I know conscientious public health nurses, they will seek out those children who are known to them to be at high risk first. When this is accomplished, they may well turn to lower risk children. This very real possibility could not, of course, be evaluated prior to an in depth analysis of the data.
9-17 to 9-18		On page 18 in which the procedure of Chisolm and Brown is briefly described, it is stated that "coproporphyrin employed as the standard." This is incorrect. Protoporphyrin is used as the primary standard. Coproporphyrin is used only as a secondary standard to adjust for instrumental drift. The same comment also applies to the methods of Piomelli and Granick, et al. Historically, the use of coproporphyrin as a primary standard was necessary because of the unavailability of protoporphyrin standard reference material. This fact and various instrumental considerations contributes importantly to interlaboratory variation. Now that protoporphyrin standards are available, this error should be corrected.
11-11	2nd para.	This paragraph summarizes work by Moore, et al. It might be of interest to add the Pb-B level at which the myocardial mitochondrial changes were observed and significant inhibition of cardiac ferrochelatase was found. These changes were observed at Pb-B = 53 μg.
11-18	bottom line	"...encephalopathy at a previous time." A more precise statement would be "...encephalopathy at a previous time and higher Pb-B."

12/1/77

Page No.	Line	
11-27	6	"...first reported by Nakao, et al...in 1968." This statement is incorrect. Nakao, et al and deBruin were not the first to observe that ALAD is inhibited by lead. This observation was made in the first published report on the purification and properties of δ-amino-levulinic acid dehydratase by Gibson, Neuberger and Scott (Biochem. J. 61:618, 1955) and shortly thereafter in 1956 by Drexel and Falk, as well as by Granick and Mauzerall in 1958.
11-29	1	"...ALAD activity may be used to estimate blood lead with a good degree of accuracy." This is incorrect from the methodologic point of view. In the usual assays depicting the ALAD Pb-B relationship, there is wide scatter about the regression line. Only if DTT and zinc are added to optimize in vitro assays can one get a reasonably close approximation of Pb-B by determining ALAD.
11-30	3	"Its use for this purpose..." The correct statement is "Its use in children for this purpose has, however, been rejected." This measurement has, however, been widely used in adults and indeed, in subsequent chapters, considerable use has been made of this technique in the development of dose-response data.
11-30		For reasons stated in my letter, I cannot accept the discussion of the Pb-B-ALAU relationship, as described on this and the next page.
11-39	8	"...a group in which iron-deficiency anemia is uncommon" The data gathered in the Ten-State Nutrition Survey, as well as a rather large body of data in the hematology literature indicate that iron deficiency is common in adolescents and adult females. In the case of adult females, the daily requirement for iron is higher than it is in males. In this and other areas in which the difference in the FEP response between adult males and females is discussed, it is appropriate to place emphasis on the difference in iron requirements rather than on hypothetical and as yet unproven hormonal factors.
11-62		On this and subsequent pages, the work of de le Burdé and Choate is listed together with others as a retrospective study. This is not true. The work of de la Burdé and Choate is the only prospective study on the question of neurobehavioral impairment that has been done. Mothers were followed during pregnancy and infants during early infancy. Only those considered normal at nine months of age were selected for study. The lady should receive credit for this fact. Although this study has its weaknesses, the fact that it is prospective is one of its great strengths. (In general, I consider the portion of the chapter on CNS effects in children as quite good.)

Page No.	Line	
11-79	6 lines up from the bottom	"...several with sickle cell trait." This is incorrect, and therefore misleading. Among the few case reports of clinically evident peripheral neuropathy in children, there is a striking clustering of patients with sickle cell disease (hemoglobin Types SS and SC), but not in those with sickle cell trait (hemoglobin Type SA). In several other places in the document, sickle cell trait has been included as a follow-up to this incorrect statement. The sickling diseases together occur in well under 1% of the black population.
11-139	6 and related material in the rest of this para.	"...first noted in acute lead poisoning by Wilson..." This is incorrect. Wilson and coworkers were the first to report the occurrence of hyperaminoaciduria in lead poisoning. Glycosuria had, of course, long been known. They did not note the occurrence of hypophosphatemia and hyperphosphaturia which, functionally, is the important component of the Fanconi syndrome. The first report of the full Fanconi syndrome is that of Chisolm, Harrison, Eberlein and Harrison (A. M. A. Am. J. Dis. Child. 89: 159-168, 1955).
11-146	5	"...stillbirths and abortions." This is incorrect. Lane's report concerns the occurrence of three stillbirths in 15 pregnancies carried apparently to term. He made no comment concerning abortions.
11-151	last para.	This paragraph concerns Fahim's studies in pregnant women. While emphasis is placed upon residence in a lead belt area, Fahim's data suggest that there is a relationship between preterm delivery and premature membrane rupture related to blood lead concentration, irrespective of residence. Similar elevations in Pb-B were also found in the control area.
11-152	3	The paragraph starting on line 3 concerning the case report by Palmisano should be omitted. Emphasis in this paragraph is placed upon lead data, but not on the fact that the mother was a chronic alcoholic. The findings in the infant fit quite well with the fetal alcohol syndrome, which on clinical grounds, was probably the major factor in this case.
11-171	1	"...yield values lower than the actual blood lead levels." This sentence carries the implication that polarographic techniques are not as accurate as dithizone and other techniques for the measurement of lead. There is a good deal in the analytical literature to indicate that electrochemical techniques, including polarographic methods, are inherently more accurate than dithizone and atomic absorption methods.
12-15	2	"...and 36 μg/dl..." Is this a typographical error?

Page No.	Line	
12-55	13	"... The lead levels were about 25,000 ppm..." This sentence is not clear. Did you mean the soil lead levels?
12-69	8	"...A consistent correlation between air and blood lead..." This sentence does not seem to agree with the data in Table 12-26 just below. Are there some typographical errors involved in the table or did you mean no consistent correlation?
12-98	8 lines up from the bottom	This paragraph cites studies by Sayre in Rochester, N.Y. These workers were able to make a distinction between old and modern urban housing. Lead values were higher in the old urban housing than in the modern urban housing. This point has been omitted from this paragraph.
13-13	(13.5.1.3)	The title of this section is "Effect of lead on δ-aminolevulinate dehydratase (δ-ALAD) and δ-aminolevulinic acid (δ-ALA) excretion". Discussion of δ-ALA excretion has been omitted from this section.
13-14	3	"...ALAD inhibition is virtually complete..." The scientifically correct statement is as follows: "ALAD inhibition, as measured by various in vitro assays in peripheral blood, is virtually complete..."

E N D

MICROPHOTOGRAPHER Taylor

DATE 8-23-75

MICROFILM SECTION

NAVY PUBLICATIONS AND PRINTING SERVICE OFFICE
BUILDING 157-2, WASHINGTON NAVY YARD
WASHINGTON, D.C. 20374