BEFORE THE
ENVIRONMENTAL PROTECTION AGENCY

TESTIMONY OF DR. J. JULIAN CHISOLM, JR.

ON THE PROPOSED NATIONAL AMBIENT AIR
QUALITY STANDARD FOR LEAD
DOCKET OAQPS 77-1

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I am Dr. J. Julian Chisolm, Jr., Associate Professor of Pediatrics at The Johns Hopkins Medical School and Senior Staff Pediatrician at the Baltimore City Hospital. A copy of my Curriculum Vitae is attached to this statement. I have been asked to testify today by the Lead Industries Association. I participated in the development of the Air Quality Criteria for Lead which was issued by EPA in December 1977, as a consultant to the Science Advisory Board of EPA. Members of the Science Advisory Board and consultants were asked to give their individual endorsement of the final draft document. Although the final draft document contained many good points, I was not able to endorse it without serious reservation. These reservations were set forth in my letter dated December 1, 1977, to F. G. Hueter, Ph.D., Associate Director, Health Effects Laboratory, U.S. E.P.A., Research Triangle Park, N.C. A copy of this letter is attached. My substantive reservations

are concerned with the failure of the document to present the quantitative aspects of various dose-effect relationships between lead and the metabolic indices of disburbance in porphyrin metabolism. Basically, it appears to me that the document does not differentiate between small, but statistically significant differences and biologically significant changes. Major emphasis is placed in it on the blood lead "threshold" for the erythrocyte protoporphyrin response; however, EPA has failed to compensate adequately for the influence of nutritional iron deficiency which is also associated with an increase in erythrocyte protoporphyrin concentration.

The major adverse effects of lead are its effects in the hematopoietic system, the nervous system and the kidney. There is general agreement that the critical or earliest adverse effect of lead occurs in the erythroid cells in the bone marrow.[1,2,3,4] That is to say that the disturbance in heme synthesis in the bone marrow occurs at lower blood lead levels than demonstrable effects in the nervous system and kidney. The Air Quality Criteria for Lead issued by EPA in December 1977 is in agreement on this point with the other reports just cited. I agree that the available data in man support the view that the erythroid cells in the bone marrow are the first cells affected adversely by lead. The earliest detectable reduction in hemoglobin, which is the functional consequence of

disturbed porphyrin metabolism in the erythroid cells in the bone marrow, has been reported at blood lead levels of 50 ug Pb/dl whole blood in adults. In children, some reports note an increased frequency of reduced hemoglobin when blood lead concentration exceeds 40 ug Pb/dl whole blood,[5,6] while studies in different groups of children indicate a somewhat higher blood lead "threshold" for beginning reduction in hemoglobin or hematocrit.[7,8,9]

It is important to note that both the Air Quality Criteria for Lead document and the World Health Organization statement lists the blood lead threshold for anemia at 40 ug Pb/dl whole blood. This is not, in fact, the case. What is found at this blood lead concentration is the earliest detectable decrease in hemoglobin. In the case of adults, the changes observed are still within the broad range of normal variation in hemoglobin concentration. This then would appear to be a very conservative estimate of the threshold for the earliest detectable decrease in hemoglobin. Decrease in ALAD activity, increase in d-aminolevulinic acid and coproporphyrin in urine and increase in zinc protoporphyrin in circulating red blood cells serve as early metabolic indicators of this effect which can apparently be compensated by normal body mechanisms until blood lead concentration exceeds at least 40 and 50 ug Pb/dl whole blood in children and adults, respectively.

The blood lead "thresholds" for nervous system effects are somewhat higher, as noted in the Air Quality Criteria for Lead document. The only studies in which an increased frequency of minimal cerebral deficits have been found have been limited to young children with blood lead concentrations in excess of 50-60 ug Pb/dl whole blood. Maintenance of blood lead concentrations in the population at <40 ug Pb/dl whole blood will provide a margin of safety against such effects. The Center for Disease Control uses a blood lead concentration of 30 ug as a cutoff point in the screening of children for the prevention of lead poisoning. One may view this as an action level so that steps can be taken before poisoning occurs in the case of children whose blood lead concentrations may be rising due to continuous abnormal ingestion of lead. I am also in agreement with this approach.

I must take issue with the blood lead "threshold" for the erythrocyte protoporphyrin (EP) response contained in EPA's December 1977 Air Quality Criteria for Lead document. Analysis of data from New York City in two to seven year old children included in this document suggests that the blood lead "threshold" for this response is at 15 ug Pb/dl whole blood. European studies[1,3] suggest that the blood lead threshold for the erythrocyte protoporphyrin response in women and school-aged children is at a blood lead concentration of 20 to 25 ug Pb/dl whole blood. I

take issue because the EP response is not specific for lead. None of these studies have taken into account, satisfactorily, the fact that erythrocyte protoporphyrin is increased in iron deficiency as well as lead poisoning. None of these studies has included separate measurements on iron status. The necessary raw data can, however, be found in the report of Stockman, et al.[10] who have measured blood lead concentration, mean corpuscular red cell volume, serum iron and total iron binding capacity. The title of this report, "The measurement of free erythrocyte porphyrin (FEP) as a simple means of distinguishing iron deficiency from beta-thalassemia trait in subjects with microcytosis" may have misled the staff of EPA, since it does not include the term "blood lead." Nevertheless, the blood lead data are there, as I repeatedly pointed out to EPA. Stockman, et al., have shown that there is a clear association in children with blood lead concentrations <30 ug Pb/dl whole blood between the erythrocyte protoporphyrin concentration and the ratio of serum iron to total iron binding capacity or the percent iron saturation. Erythrocyte protoporphyrin was elevated only in those children with a percent iron saturation <15 percent. When the percent saturation (serum iron - total iron binding capacity) is <15 percent, iron deficiency is present. In persons with normal nutritional iron status and

increased lead absorption, the opposite occurs: Serum iron and percent iron saturation are normal or elevated -- not decreased. The evidence in these children with blood lead concentrations <30 ug Pb/dl whole blood is that increased erythrocyte protoporphyrin is due primarily to iron deficiency. With the raw data from this study, it would be possible through polynomial regression analysis to calculate statistically the contribution of iron deficiency to the erythrocyte protoporphyrin response in these children. Iron deficiency could then be factored out statistically. If both iron status and blood lead concentration are taken into account in the appropriate statistical analysis, it should be possible to arrive at a sounder scientific estimate of the relationship between blood lead concentration and erythrocyte protoporphyrin in children with blood lead concentrations <30 ug Pb/dl whole blood. Inspection of Stockman's report would suggest that the blood lead threshold for the erythrocyte protoporphyrin response is in the 21-30 ug Pb range and probably at about 25 ug Pb/dl whole blood. I would strongly suggest that EPA request the raw data and that EPA staff undertake the necessary statistical analysis. It might then be possible to apply the necessary statistical corrections to the New York City data upon which the report relies so heavily. When developing dose-population

response curves, it is absolutely essential that other factors which influence the biochemical indicator of response be factored out (erythrocyte protoporphyrin in this case).

Nutritional deficiences and increased lead exposure are likely to occur in the same populations. There is now abundant experimental data which indicate that calcium, magnesium, iron, zinc and possibly other dietary trace metal constituents influence the absorption and retention of lead. The experimental observation that dietary calcium intake enhances lead absorption has been confirmed in children. Furthermore, it is suspected that iron deficiency may be an important etiologic factor in a minimal brain damage. The quality of the data indicating this effect of iron deficiency is about the same as the quality of the data which indicate that lead causes minimal brain damage. Nutritional deficiencies deserve correction on their own merits, and should be ameliorated through appropriate public health policies. Improved public health nutritional policies provide another societal option for the maintenance of health, particularly in populations at increased risk for lead poisoning.

For standard-setting purposes, the log normal distribution of blood lead concentrations and the use of geometric means and geometric standard deviations in the

> "The moles of protoporphyrin found in the circulation at a chronic blood lead concentration of 0.06 mg/100 ml is only 1/3000 of the moles of heme present in hemoglobin. Because the mean corpuscular hemoglobin concentration is not appreciably affected it is probable that the insertion of iron into protoporphyrin to form heme is scarcely interfered with at this blood lead level."

Doctor Zielhuis, a noted European authority on the biological effects of lead, agrees with this opinion. In a statement prepared in 1975 for the European Economic Community he stated the following:

> "Increase of protoporphyrin denotes a disturbance of porphyrin metabolism but as such is not linked to sub-clinical signs or symptoms of disease or of impaired functional capacity. It mainly serves as a warning signal that the capacity of some biological systems to cope adequately with lead is beginning to be exceeded."

These authors point to the important distinction between measurable changes that are widely noted in human physiology and changes that can be shown to be deleterious to human health.

Finally, the elevation of FEP is non-specific and is undoubtedly widely affected not only by Pb exposure, but also by iron deficiency, a common nutritional deficiency in children. There is no indication that the Piomelli report or the Air Quality Criteria Document has taken into satisfactory consideration the contribution to increased FEP

production by iron deficiency. The majority of published studies that have measured FEP levels for children with blood lead levels less than 40 ug/dl have demonstrated large variations in FEP values, a finding likely related to iron deficiency. Stockman, et al., noted in a study of a large number of children in 1975 that the FEP is probably increased in the earliest phases of iron deficiency, before any detectable change in the hemoglobin or hematocrit becomes apparent. Thus, in attempting to relate lead exposure and heme synthesis, it appears that the EPA has placed great emphasis on a non-specific metabolic change, increased FEP production, without taking into due consideration the fact that the same change takes place with the common childhood condition of nutritional iron deficiency.

There is no doubt that the development of sensitive analytic techniques for measuring FEP levels in blood represents a useful means for monitoring both lead exposure as well as iron deficiency in children. FEP is a normal constituent of erythrocytes. The FEP concentration, as well as certain fluctuations in concentration, has been shown to be dependent on a number of variables such as lead exposure, iron deficiency, and some infections. Other variables, including trace metals and biofeedback mechanisms within the heme synthesis pathway are likely to be found to have bearing on the FEP level.

With these considerations in mind, it seems inconsistent with sound public health practices to attempt to set an ambient air lead standard on mere statistically significant changes that are without concomitant physiologically significant reduction in heme production. The EPA's argument for a specific ambient air lead standard based solely on FEP changes within the normal physiologic range at low lead levels is scientifically unjustified.