BEFORE THE
ENVIRONMENTAL PROTECTION AGENCY

TESTIMONY OF DR. EDWARD B. McCABE

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

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My name is Edward B. McCabe. I am a practicing pediatrician in Madison, Wisconsin. I am also an Assistant Clinical Professor of Pediatrics at the University of Wisconsin Medical School. I have served as a medical consultant to the International Lead Zinc Research Organization since 1972. I have been asked by the Lead Industries Association to comment on the proposed EPA Ambient Air Quality Lead Standard. In May of 1977 I was asked to serve as a consultant to the staff of the Health Effects Research Laboratory, EPA. The staff members of the Health Effects Research Laboratory, with the assistance of a large number of consultants, had the responsibility for the development of the document entitled, Air Quality Criteria for Lead. Without question, the Health Effects Research Laboratory staff, under Dr. Gordon Hueter's direction, performed a monumental task in producing the final document which was made available on December 12, 1977. The individuals' sincere and tireless efforts are recognized. Based on the contents of the

Air Quality Criteria Document, EPA proposed an Ambient Air Quality Standard for Lead which was detailed in the Federal Register of December 14, 1977. I wish to comment, today, on several medical issues derived from the Air Quality Criteria Document that were noted as key points in the development of the EPA ambient air lead standard. I will restrict my comments to those areas that pertain to the effects of lead on human health, and will attempt to focus mainly on those health issues that EPA has depended upon to support the proposed ambient air lead standard of 1.5 ug/cubic meter of air. Regarding several key areas, EPA has emphasized a number of studies that have been either poorly designed and flawed by obvious methodological inconsistencies, or studies based on incomplete and/or unconfirmed data. The most notable example of this latter objection involves undue emphasis on a 25-line abstract which was supplemented by unpublished and unconfirmed raw data.

In preparing an ambient air lead standard of 1.5 ug/cubic meter of air, EPA argues that the identification of at-risk groups of individuals within the general population is a major consideration. To this end, young children, pregnant women, and the fetus are singled out. The Air Quality Criteria Document emphasizes one study in particular, that of Fahim, et al., in support

of the notion that relatively low blood lead levels in pregnant women pose an increased risk for premature deliveries or premature rupture of fetal membranes at term. Careful review of the Fahim publication reveals a large number of curious and unexplained findings. For example, in comparing the women from the lead-belt area of Missouri and their controls, those from a nonlead area, one might expect to observe some differential in terms of blood lead levels. In fact, no differential existed for any of the groups examined, and in one case the blood lead level was highest in a woman from the control area. Another unexplained finding of the Fahim study is the large difference in all cases examined between maternal blood lead levels and the corresponding cord blood levels. There are at least eight studies in the recent literature that document the finding that there is a close correlation between the maternal blood lead level and that in the fetus, as determined by umbilical cord blood samples. Again, Fahim offers no explanation for this discrepancy. Analytical error involving the blood lead analyses appears to be the likely reason for these discrepancies, and as such, this study is seriously weakened. These obvious discrepancies were pointed out to the authors of the Air Quality Criteria Document by several observers on a number of occasions, and yet the study is given considerable emphasis in Chapters 1, 11 and 13.

Two of the most thoroughly studied effects involve the lead-induced changes in ALA-dehydratase activity and the presumed effect of ferrochelatase inhibition, resulting in an accumulation of free erythrocyte protoporphyrin (FEP) in erythrocytes.

The Air Quality Criteria Document correctly notes that the activity of ALA-dehydratase, a mitochondrial enzyme, is inhibited by lead levels that fall within the normal range, from 10-30 ug/dl, presumably by interference with the enzyme's sulfhydryl groups. This effect has been repeatedly documented for a number of years, and it has generally been accepted that this initial effect on ALA-dehydratase at these lower blood lead levels has no functional significance, and accordingly, suggests no adverse health effect. EPA agrees with this point.

On the other hand, the EPA document places great significance on a very similar lead associated effect, the inhibition of ferrochelatase, another sulfhydryl-containing mitochondrial enzyme that catalyzes the incorporation of the iron molecule into protoporphyrin to form heme. The resultant effect is an accumulation of protoporphyrin in erythrocytes. Whereas the EPA agrees with the consensus that early lead-induced ALA-dehydratase changes represent no adverse health effect to an individual, the proposal goes so far as to state

that the similar effect of lead on ferrochelatase activity, as indicated by an early change of FEP concentration, represents the pivotal adverse health effect from which is derived the ambient air lead proposal. The EPA proposal states that the threshold value of lead, above which FEP begins to increase exponentially, is 15 ug/dl. The acceptance of this value by EPA is the key point in a rather arbitrary line of reasoning that then leads to the proposed 1.5 ug/m^3 of air lead standard. There are a number of key points in this regard that the EPA proposal emphasizes that are highly questionable or are outright incorrect.

The EPA places undue emphasis on a report by Piomelli in which he summarizes the results of a study of 1,770 children whose blood lead levels ranged from 2-28 ug/dl. This report appears as a 25-line abstract, and as such lacks sufficient details for critical review. In this brief report, Dr. Piomelli states that the no-effect threshold for blood lead concentration and the effect on FEP elevation is 15 ug/dl. He further states that this threshold is an indication of a dose-effect relationship indicative of metabolic toxicity in children. Beyond that statement, no evidence supporting such a belief is offered. To my knowledge, this no-effect threshold of 15 ug/dl of lead has not been documented by other

investigators. The proposed Ambient Air Quality Standard incorrectly cites a study by Roels, et al., as also showing a no-effect threshold of 15 ug/dl. A point in fact is that these investigators noted a threshold value of approximately 20 ug/dl as stated in their publication. A number of other published studies have either failed to identify a no-effect threshold or have shown one between 25-30 ug/dl.

In addition to the objection of overemphasizing one abbreviated report, the issue of the biologic significance of early statistically significant changes in FEP has to be critically evaluated. As previously noted, similar statistically significant changes in another heme-synthesis enzyme, ALA-dehydratase, are generally accepted as not relevant to human health at low blood lead levels. Additionally, inhibition of ferrochelatase activity and the resulting accumulation of FEP at blood lead levels less than 40 ug/dl has never been shown to affect the synthesis of heme. In other words, inhibition of heme synthesis resulting in a decreased production of hemoglobin appears to be the critical adverse health effect of interference with this enzyme and this has not been shown to occur at blood lead levels below 40 ug/dl. This notion is confirmed in a study cited in the EPA document by Sassa, et al. These authors state the following in their summary:

interpretation of blood lead data appears sound. The available data indicate that the maintenance of a population geometric mean of no more than 20 ug Pb/dl whole blood would provide adequate protection and that the vast proportion of people would be maintained at blood lead concentrations of <35 ug Pb/dl whole blood. Using data from Idaho, von Lindern and Yankel[11] have in fact calculated that 98 percent of the population would have a blood lead concentration <40 ug Pb/dl whole blood when the geometric mean for the group is 24 ug Pb/dl whole blood. They used a geometric standard deviation of 1.3, just as EPA has done in the Air Quality Criteria for Lead document.

In summary, the blood lead "threshold" of 40 ug Pb/dl whole blood is an apparent threshold for the first detectable decrease in hemoglobin concentration; but, it is not a threshold for anemia. Erythrocyte protoporphyrin concentration is elevated in both nutritional iron deficiency and in increased lead absorption. In the calculation of the blood lead threshold for that part of the increase in erythrocyte protoporphyrin concentration due to increasing lead absorption, the influence of iron deficiency has not been taken into account adequately. Unfortunately, measurements relevant to iron status have not been included in most of the studies on

the blood lead-erythrocyte protoporphyrin relationship. There is, however, one published report which includes all of the data necessary to calculate statistically the relative influence of iron and lead absorption status on erythrocyte protoporphyrin concentration in children with blood lead concentrations <30 ug Pb/dl whole blood. Use of these data would permit a sounder estimate of the blood lead threshold for the erythrocyte protoporphyrin response. Appropriate statistical compensation for nutritional iron status would probably reveal that the blood lead threshold for the erythrocyte protoporphyrin response lies in the 21-30 ug Pb/dl whole blood range for women and children. Maintenance of geometric mean blood lead concentration in the population at no more than 20 ug Pb/dl whole blood would provide an adequate margin of safety against the functional adverse health effects of lead.

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