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IN REPLY REFER TO

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Washington, D.C. 20460

Dear Dr. Newill:

This is in response to your letter of May 31, 1972. I beg your indulgence for my delay in answering. I shall comment on those of the many questions you posed upon which I can best comment.

With respect to question number (1) (Goldsmith-Hexter equation), I will make only a general comment. When dealing with very low levels of exposure from a variety of sources, it seems almost impossible to sort out the relative contribution of each individual source through a human epidemiologic approach. I presume that you have had response from competent biostatisticians on the actual equation.

Question (2). It would appear to me that whole blood lead concentrations do not provide an adequate index of total body lead burden. On the one hand, the Tri-City Study indicates in living persons, no increase in whole blood lead concentration with age. On the other hand, autopsy studies do indicate an increase in bone lead concentration, but not in the concentrations in the soft tissues. To my knowledge, serial blood lead and bone biopsy studies (uncontaminated with bone marrow) have not been done. I believe that the NAS document adequately summarizes the information on relationship between blood lead concentration and the "mobile" and "poorly diffusable or non-mobile" fractions of the total body lead burden. It would be helpful in one's thinking to divide the bone lead pool into "incorporated" and "adsorbed" fractions. Whether lead stored in bone is totally physically "inert" would probably depend upon the presence of conditions which affect the rate of dissolution of bone. It seems likely that only disorders associated with rapid dissolution of bone might be associated with significantly rapid mobilization of lead into soft tissues. Whether such things occur in human populations would have to be studied to determine whether the rate of mobilization of lead from bone would be sufficiently rapid to be harmful. Appropriate subjects for study might include those with "renal rickets," hyperparathyroidism,

Paget's disease of bone, high-dose long term corticosteriod therapy and possibly other groups of diseases. With respect to young children, the issue might be more appropriately studied in weanling animals. It is my opinion that the following statement in your letter is incorrect: "We know that chelation therapy of children with elevated blood leads can result in acute clinical symptoms of lead poisoning as a result of mobilizing lead from bone." In my opinion, the background for this statement has found its way into the medical literature largely on the basis of experience prior to the use of chelating agents and that today, such apparent occurrences are more often due to inadequate and/or inappropriate use of chelating agents in children with very severe illnesses and blood lead concentrations that ordinarily are well above the 100 µg Pb/100 g whole blood level. My thinking on this point is given in the attached reprint. I know of no evidence that lead incorporated into bone is removed by chelating agents. Unfortunately, most of the animal data on this point have been obtained in acute experiments, which are not suitable to answer this question.

With regard to question (3), I know of no additional evidence besides that cited in the NAS report relative to the amount of air breathed per day. Suffice it to say that one would anticipate some variation in respiratory exchange in relation to body size, metabolic rate and physical activity.

With regard to question (4), it is my opinion that it is not entirely appropriate to extrapolate industrial threshold limit values to the general population, inasmuch as the industrial population is likely to be selected and is unlikely to include individuals who may show increased susceptibility to certain occupational levels of exposure to lead. In particular, those with iron deficiency states due either to deficient intake or chronic increased blood loss chiefly from the G.I. tract may be more susceptible as was pointed out in NAS document. In this regard, the recent report of Six and Goyer on experiments in iron-deficient weanling rats is appropriate. (J. Lab. and Clin. Med. 79:128-136, 1972, The influence of iron deficiency on tissue content and toxicity of ingested lead in the rat). The data in this study indicate that absorption of lead from the gastrointestinal tract may be greater in the iron deficient experimental subjects. With regard to the occurrence of clinical symptoms attributable to plumbism in humans, one should note that where such episodes have occurred in individuals with blood lead concentrations in the 50-80 µ Pb range, such individuals are generally found to have moderately severe anemia – usually of the iron deficiency type.

With regard to question (5), I recently forwarded to Dr. Bridbord some comments on the occurrence of increased lead absorption in children in the Smeltertown area of El Paso, Texas. With regard to the lead content of dust and soil in urban areas, there is no data known to me which identifies the relative contributions of automotive exhausts on the one hand, and lead from paint derived from the weathering and demolition of old buildings to which lead-based paints have been applied, particularly on the exterior. Relatively speaking, the direct ingestion of lead paint flakes by young children provides a far greater dose of lead than does exposure to dust. It is certainly true that intake of lead from all sources is additive with respect to the total dose assimilated. However, the dose provided by the repetitive ingestion of small flakes of paint appears far greater than all other sources combined, if one excludes such things as moonshine whiskey and

improperly lead-glazed ceramicware and other unusual sources. EPAs proposed reduction of lead emissions may help to reduce the incidence of minimally elevated blood lead concentration in young children, but it is unlikely that it will have a measurable effect on the occurrence of the sort of clinical disease associated with definite residual deficits, as seen today in children. At issue is the question of whether blood lead concentrations in the 40-60 µg range sustained over a period of two to three years or longer in early childhood is associated with adverse effects on function, development and growth in young children. At the present time, it can be stated only that measurable adverse metabolic effects in the form of increased ALA excretion in urine and increased levels of protoporphyrin in blood may be found in a significant proportion of such children. Whether these metabolic observations are associated with significant developmental and functional defects is not known and is difficult to determine because the affected children are also subject to many other sorts of environmental deprivation which, in turn, may adversely effect them. I cannot agree entirely with those who say that all lead poisoning in young children is not due to the ingestion of leaded paint chips in deteriorated urban areas. It has been my experience that housing inspectors do not always make a sufficiently thorough search for flaking paint. While it is certainly desirable to reduce the lead content of dust and dirt, the hazard of lead and old paint is certainly a far more concentrated and hazardous source of exposure. Appropriate studies with respect to housing area and source of exposure and particularly to the El Paso group of children might provide more definitive answers to your questions.

In view of the likelihood that we may never obtain epidemiologic data in humans which can provide clearly defined limits, it would appear appropriate to limit exposures from various sources so that total assimilation in the general population is such that blood lead concentrations are maintained at 40 µg Pb/100 g whole blood or less. This probably would provide due allowance for susceptible individuals factors known and unknown.

Yours sincerely,

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

JJC:ov
Enc.
cc: Dr. Paul F. Wehrle, Chmn.,
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