

June 21, 1973

Mr. R. J. Sherwood
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Abingdon, Berkshire OX13 6AE
England

Dear Mr. Sherwood:

Your letter of June 15 to Mr. J. Cholak of this Laboratory, was referred to me for a reply, after talking the matter over with me. First, let me answer your request of Mr. Cholak, in relation to methods of analysis of the urine, especially in relation to the form in which lead may appear in the urine. This is strictly in Cholak's province, since I, a physician, am no chemist, in the sense of dealing with or employing analytical methods. He provides me with two reprints to send you in which the methods of analysis of urine for lead are described. You will note at once that no effort is made to identify the compound or compounds of lead which may appear in the urine. Rather, the effort made is that of destroying any chemical linkages which would, or might, mask the quantity of lead (Pb) in the specimens. The matter of the diagnosis of the type of lead which induced the poisoning is left to the physician to determine, essentially, on the basis of the clinical type of the illness. This may not always be feasible, but it is generally, and is preferable in our view to measures of analysis that do not measure all of the lead being excreted. We have not carried out investigations which would enable us to differentiate the compounds which may have been absorbed in the first instance, nor do we believe that this would be feasible under ordinary clinical situations.

When such compounds as the alkyl lead compounds have been absorbed, some degree of decomposition of the compound may occur in the body. Tetraethyllead decomposes to triethyllead - and probably on through diethyl and monoethyl compounds, as it does in vitro, under appropriate conditions. The alteration then, as you know, doubtless, proceeds to the inorganic form of lead (Pb^{++}), slowly. To what extent all of this occurs in the body, we do not know, nor do we know the extent to which time is required for the processes (if it occurs).

When, however, the alkyl lead compounds are absorbed (i.e., tetraethyl- and tetramethyl-lead) in sufficient quantities to cause illness, the clinical syndrome from the onset, differs from that of the absorption of inorganic lead, chiefly because, as it seems, the fat soluble lead is absorbed promptly into fatty tissues, including the brain, with the result of inducing mental symptoms as the outstanding pattern of the illness. Moreover, the lead does not mount in the blood (erythrocytes), as it does in poisoning by inorganic lead, because, no doubt, the lead offered to the blood stream is not in such form as to diffuse readily into

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e blood or to be absorbed into the erythrocytes if it does penetrate the capillary wall. There is here, much that is unknown, of course, but the fact is that the lead content of the blood in tetraethyllead poisoning is low (rarely exceeding 0.05 mg/100 grams) despite the high concentration of lead in the urine (which may be as much as a large fraction of 1 mg. per liter, or even more). We have never seen tetraethyllead poisoning as the result of a long period of absorption at a low level of exposure, and so the problem of (chronic cumulative) tetraethyllead poisoning has never appeared.

I hope this discussion will be of assistance to you, but if you have further questions, I shall be glad to attempt to answer them.

Cordially yours,

Robert A. Kehoe, M.D.
Professor Emeritus of
Occupational Medicine

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15th June 1973

Dr. J. Cholak,
Kettering Laboratory,
University of Cincinnati,
College of Medicine,
Eden & Bethesda Avenues,
Cincinnati, Ohio, 45219

Dear Dr. Cholak,

I am writing to seek your advice on the analysis of lead in urine with particular reference to the chemical form of the lead.

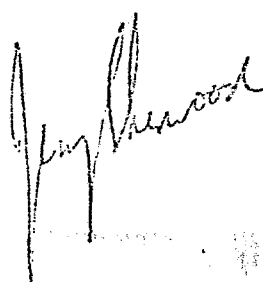
In a recent situation we had a serious need to distinguish between inorganic and organic lead poisoning, as diagnosis had been made of chronic lead poisoning from alkyl lead exposure. I think we can expect to find some of the lead present in urine after alkyl lead inhalation in the trialkyl form as shown by Bolanowska in rats, and should be able to distinguish chemically from inorganic lead.

I should be most grateful for your advice on whether this has been studied, and if so, where is it published? If not, I would be grateful for your advice on possible analytical procedures, and on the likely form that inorganic lead appears in urine - can it be conjugated as glucuronide, or is there some other mechanism involved in elimination?

Finally, I would be glad to know the technique you currently use for routine analysis for lead in urine.

My apologies for troubling you with these questions; I shall certainly appreciate your comments.

Yours sincerely,



RJS:MG