June 12, 1961

Mr. Sam Battista
Arthur A. Little, Inc.
30, Memorial Drive
Cambridge 42, Massachusetts

Dear Mr. Battista:

In the matter of the toxicity of the lead compounds to which you referred in your letter of June 1st, I must first know what you mean by "toxicity" before I can reply with any degree of responsiveness to your needs. If you mean that these compounds of lead may have a toxicity that goes beyond that relating to their content of lead, you are, I believe, entirely wrong, with the possible exception of lead chromate, which may owe some of its total toxic effect to its content of chromium. If, on the other hand, as I suspect, you mean to inquire as to the degree of limitation of the toxicity of the lead radical that is imposed by its union with the chromate or sulfate, because of the relative insolubility of these compounds and their low rate of absorption, that is another matter. That is not actually a lack of toxicity but a lack of absorption, and therefore, a failure to arrive rapidly at a toxic concentration in the vulnerable tissues. (I am not lecturing, but only defining the problem, for it is often misunderstood.)

So far as I know, there are no satisfactory answers to your question (which I will paraphrase into practical terms) as to the relative degree of danger that is associated with exposure to either the chromate or the sulfate (or the basic or acid sulfate or the persulfate), as compared with certain other compounds of lead. There is suggestive evidence that the chromate, in finely divided form in the atmosphere, is absorbed more slowly than are many other lead compounds, as for example, the oxides and the carbonate. There is much better but far from conclusive evidence that the sulfide is indeed poorly absorbed in the respiratory system. As to the normal sulfate and the other forms of sulfates, there is, so far as I know little or nothing. Nor is there any way of answering this question by simple means. The overall rate of the absorption of particulate solids, such as the dust or fume of a lead compound, is determined by (1) whether it reaches the large alveolar surface of the lungs or (2) whether it goes in part into the lungs and in part into the upper respiratory tract and thence into the alimentary tract (if it is separated out in the upper respiratory tract, much of it, perhaps most of it, may be swallowed). The rate of absorption, itself, is also determined by the size of the particles, and whether uniform or not (the small particles under 1 micron in diameter will reach the alveolar surface, and the still smaller particles, 0.01 - 0.10 micron in diameter, will be absorbed much more rapidly than those of 1 micron, but the smaller the particles, within limits, the more of them will escape from the lung in the exhaled air). The absorption in the respiratory tract (if the particles are soluble or if they are small enough) is rapid and

virtually complete, while that in the digestive tract is rarely more than 10 to 15 per cent, at best.

Now as to certain practical facts, the oxides of lead and the carbonate are readily absorbed from the lungs, and well enough absorbed from the alimentary tract. The question here is not one of relative toxicity, but rather the relative rate at which lead, absorbed as some inorganic salt or oxide or hydioxide, accumulates in the body. It is almost certainly converted to some other compound in the various tissues and structures of the body - in the skeleton, for example, it combines almost certainly with phosphate (as some compound with phosphate). In the blood it is combined with something (perhaps the organic phosphate) in the erythrocyte. Certainly it exists in the body in some loosely bound form or forms from which it is dislodged by the metabolic processes of the body, since it is being excreted steadily at a rate that depends mainly (but not solely) on the total quantity available in the body (the body burden).

As you can appreciate, therefore, toxicity, as such is not the problem at all. Rather the problem is by what means and at what rate, does lead enter the body. The radical to which it is bound may hinder or accelerate its entrance, speaking in relative terms, and much will depend upon the size of the particle that occurs in the respired air, so far as respiratory exposure is concerned, but the toxic effect with which we are concerned is that of lead, which is much the same regardless of how it gets into the body, so long as it is in inorganic form.

For the past 10 years we have been investigating the respiratory absorption of lead compounds systematically in human subjects, who spend variable periods of time per day and per week, for about two years, in a respiratory chamber in which a specific compound of lead in a specific state of subdivision, and in a specific concentration is dispersed in the air. The total intake and output of lead on the part of these subjects is being followed, so as to enable us to determine the loci and the rate of absorption, the excretion from the body and the retention, if any. This is being done in this laborious manner for the reason that no adequate information is available to answer the questions which you have raised, together with other pertinent questions. We need these answers, but we shall be a long time in obtaining them.

We have nearly completed our work with the sesquioxide, and the results, in part at least, are being published soon. We expect to study one of the sulfates sometime soon, but I am not sure now when we can begin. We shall not be able to use the chromate in human experiments because of the potential hazard of chromate cancer of the lung, but perhaps we can use animals. This is much more difficult and less satisfactory, but it may be possible to do it.

I'm afraid I have not answered your questions or provided the references you would like to have. If these questions could be answered otherwise, we should not be spending so much time (and money) in investigating them.

Cordially yours,

Robert A. Kehoe, M. D.