October 28, 1962

Dr. Richard A. Prindle, Medical Director
Deputy Chief, Division of Air Pollution
Public Health Service
Washington 25, D.C.

Dear Doctor Prindle:

Please accept my thanks for your letter of October 10th in which you point out the unsatisfactory spots in the subject investigation as reported. I cannot say that I am actually "disturbed" by the defects in the investigation or the report, but I agree that some further observations should be made so as to be able to answer any question which exists. Inasmuch as I am able to keep myself informed as to any difficulties that might conceivably arise, I am disposed to postpone the further observations until an appreciably longer experience has been fulfilled. In my view, certain periodic observations will be required from time to time, and I expect (so long as I am on the job and have any influence) to see that the industry keeps itself informed.

I am sending two (2) copies of the final version of the report, with the request that you replace the earlier copies and have them either returned to me or destroyed. The latter is simpler, of course, and I merely wish to get them out of circulation. The final version differs from the earlier copies in that a few sentences have been deleted (as a matter of professional courtesy), a few clarifying additions have been made, and a number of typographical and printing errors have been corrected. If you wish to have additional copies, just let me know.

We had some earlier correspondence about the Harben Lectures, and I am not sure that you have received such copies as might be useful. I shall be pleased to send cloth-bound copies to such persons as you may designate, on the basis of need or special interest.

Sincerely yours,

Robert A. Kehoe, M.D.

Encl: 2 copies of report

RAK:ss

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DEPARTMENT OF HEALTH, EDUCATION, AND WELFARE
PUBLIC HEALTH SERVICE
WASHINGTON 25, D. C.

BUREAU OF STATE SERVICES

Refer to: AP:OC

October 10, 1962

Dr. Robert A. Kehoe
Kettering Laboratory
College of Medicine - Eden Avenue
Cincinnati 19, Ohio

Dear Dr. Kehoe:

Thank you for your letter of 18 September relative to our telephone conversation of 17 September.

As I expressed in our conversation, I find myself concerned with the two items in the report on the investigations of the use of tetramethyl lead on the West Coast. These items relate to the incompleteness of the clinical investigations and to the changes in the blood hemoglobin and erythrocyte count observed on the subjects.

As you indicated in your letter, one cannot help but be disturbed by this incompleteness and although it, in itself, may prove nothing "pro" or "con", it tends to leave one with less solid ground upon which to stand. The change in the erythrocyte count and hemoglobin may or may not be related to effects of tetramethyl lead on the erythropoetic system. However, in an investigation of this type, it is desirable to have a reasonable explanation.

In view of these problems, it would appear most desirable for further study to be undertaken as a continuation of this project, perhaps with

augmentation of both study procedures and subjects. I would hope, therefore, that your organization might continue such work and provide the additional information.

Again, let me express my appreciation for the opportunity of reviewing this material and discussing it with you.

Sincerely yours,

Richard A. Prindle, Medical Director
Acting Chief
Division of Air Pollution

September 13, 1962

Air Mail

Dr. Richard A. Prindle, Medical Director
Deputy Chief, Division of Air Pollution
Public Health Service
Washington 25, D.C.

Dear Doctor Prindle:

Following our telephone conversation of September 17th, I came to the conclusion that it would not be inappropriate for me to make a few comments on certain features of the report which I supplied to you and your colleagues on the investigation of certain aspects of the use of tetramethyllead on the West Coast. There were two points in this report which could be expected to receive special attention, and it was to these, unerringly, that you directed your remarks to me. I refer of course, to the omission of the detailed data of the final clinical survey, and to certain hematological findings.

I would expect any experienced investigator of population groups to be disappointed and, in some degree, frustrated, as I was, by our failure to complete the work represented in the orderly design of this experimental program. It is a shock to one's logical and even aesthetic sensibilities to encounter such a void, and especially to be a party to it. On the other hand, from either the practical or the strictly factual consideration of the weight of evidence, this is not a serious defect in the investigation in this instance, and for a very excellent reason. It is, in fact, comparatively unimportant that the effects of the exposure to, and the absorption of, lead on the part of these men, were not examined in minute detail, since the incontrovertible evidence is available to demonstrate that they absorbed no lead in the course of 16 months of their employment (or so small an amount, if any, as to be masked completely by some other environmental factor which actually reduced their over-all exposure to, and absorption of, lead). One can argue in and around this point, and through a variety of strategic questions and answers, but he cannot get away from this compelling fact. What matter, therefore, that the clinical observations are incomplete? The matter is that neither you nor I, nor any of us, like the appearance of an abandoned scheme of study. It suggests to us things that we do not put into words. However, as a cautious industrial physician, I am constrained to acknowledge, despite my irritation over this matter, that, aside from the niceties of an experimental program fulfilled to the letter, my medical colleagues in Standard Oil Company of California - who are good responsible internists, but not epidemiological investigators - had fairly good justification for their conclusion, that the repetition of the detailed examination would be an utter waste of time.

This brings me to consider again the apparent modest increase in the average numbers of erythrocytes and in the concentration of hemoglobin which occurred during the 16 months of these observations. Is this related to the absorption of lead? The answer is an unequivocal negative, and this is the point of the issue. Why is it unequivocal? Because of the evidence obtained by the analysis of the blood and urine. It is clear that the negative findings in the blood do not prove that no tetramethyllead was absorbed (they do prove that no significant quantity of inorganic, airborne lead, in excess of that being absorbed prior to the introduction of tetramethyllead into the gasoline, was being absorbed); the negative findings in the urine, however, do prove that no significant quantity of tetramethyllead was being absorbed during the period of the observations. However, there is another factor here to be considered. Even if tetramethyllead had been found, by other means, to have been absorbed, it would not have produced the hematological results observed. It has been established that the absorption of the organolead compounds, tetraethyllead and tetramethyllead, does not exert an erythrogenic function and that it does not alter the metabolism of hemoglobin so far as such effects can be discerned by ordinary clinical observations on the peripheral blood and by analysis of the urine for various prophyrins. Here again, we are disturbed (our statisticians are unhappy) by this unexplained pair of findings, and we speculate on what may lie behind it. This suggests the desirability of further observations, and I shall feel better about the matter when such observations have been made and recorded. But without being swayed toward an improper regidity of opinion, I think it unlikely that further observations will explain these related phenomena, unless one makes a sharp issue and a major project out of a further investigation.

I am not discrediting, in any manner, the procedures of careful clinical investigation. As you are aware, I am sure, I have long been an exponent of the careful and ever more careful and complete collection of clinical data as the subject matter of the epidemiological work in this field. I cannot ignore the fact, however, that the physiological data in this situation are of much greater significance than are even the most exacting clinical observations. It is because of the sound background of information which implements the interpretation of these data that I have a strong sense of security in the position that I have taken in this matter.

Sincerely yours,

Robert A. Kehoe, M. D.

RAK:ss

cc: Dr. W. Clark Cooper