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RE 0012394

March 15, 1966

Robert E. Eckardt, M.D.
c/o American Petroleum Institute
1291 Avenue of the Americas
New York, New York 10020

Dear Doctor Eckardt:

I am sending herewith a revised copy of the proposal made to the International Lead Zinc Organization for such action as may be taken in connection with this project by the American Petroleum Institute. Pages 1 and 2 are unchanged (so as to keep this portion of the record as it was in August 1965), while pages 3 and 4 have been altered to bring matters up to date.

I trust that this will be satisfactory for your purposes.

Sincerely yours,

Robert A. Kehoe, M.D.

RAK:wp

enclosure

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date
3-11-66
RAK

PROPOSAL TO INTERNATIONAL LEAD ZINC ORGANIZATION FOR
CONTINUATION, THROUGH THE YEAR 1966, OF THE FINANCIAL
SUPPORT OF THE PROGRAM OF RESEARCH OF THE KETTERING
LABORATORY, IN THE DEPARTMENT OF ENVIRONMENTAL HEALTH*
OF THE COLLEGE OF MEDICINE OF THE UNIVERSITY OF CINCINNATI,
ON THE PROJECT "HUMAN EXPOSURE TO PARTICULATE LEAD
COMPOUNDS IN THE AIR UNDER EXPERIMENTAL CONDITIONS"

On October 3, 1962, the general experimental procedure of this project, together with the details of a specific experiment to be carried out in 1963, were described in detail. Further proposals, relating to the continuation of the work, were made on September 4, 1963 and on September 10, 1964. The work has gone on in essential accordance with the purposes and procedure described in these proposals, and is to be continued in the year 1966 along similar lines indicated herein.

The immediate goal of the experimental work in 1965 was that of defining, through human experience, the maximum concentration of ideally respirable and absorbable (i.e., pulmonary absorption, exclusively) particulate lead in the ambient atmosphere to which normal, healthy, human subjects might be subjected, continuously and for indefinitely prolonged periods of time, without incurring the potential risk of a demonstrable degree of accumulation of lead in their bodily tissues.

The experimental principle involved the exposure of two human subjects, in parallel respiratory chambers, to air containing lead (approximately 10 micrograms of Pb, as lead sesquioxide, per cubic meter) dispersed in minute particles (ranging in diameter from less than 0.01 to 0.18 microns, with the mean diameter of 0.05 microns), on an intermittent schedule of increasing duration (3 hours per day every other day for approximately 16 weeks, i.e., 10.5 hours per week; 6 hours per day every other day for approximately 16 weeks, i.e., 21.0 hours per week; and so on to 31.5, 42.0 hours, etc.) until the effect of the exposure became evident through a slight (statistically demonstrable) increase in the output or concentration of lead in the urine, presumably (as judged by earlier experiments) without demonstrable increase in the concentration of lead in the blood, of the subjects.

During 1965, these observations have continued as scheduled, except for necessary adaptation of the periods of exposure to the tolerance of the subjects for disruptions of their daily lives. That is, when the schedule reached the point of requiring the subjects to spend more than 12 hours per day in the chamber (on alternate days) it became necessary to shift to daily periods of exposure. Obviously, also, the continuation of the family life of the subjects required, at least, one day per week of freedom from exposure. The result was a new schedule, involving the proper number of hours of exposure per week subdivided into equivalent periods on six of the seven days of each week. At this time (August 1965), one of the subjects (N.K.) is spending 63 hours per week in the

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* Officially changed, as of July 1, 1965, to that above.

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chamber, while the other (S.S.) (who was taken on late as an experimental subject, as reported previously) is spending 52.50 hours per week.

Inasmuch as neither of these subjects has yielded the slightest response to the graduated levels of experimental exposure, the experiment is to continue as long as possible at the present level of lead concentration in air. It is not anticipated at present that it can go far beyond 12 hours per day on 6 days per week, with due regard for the comfort and convenience of the subjects. If then no response shall have been obtained, the concentration of lead in the chamber will be increased by a small increment, and the incremental increases in the duration of exposure will be rescheduled, beginning at a level of intensity (time x concentration) that will not duplicate that of previous steps. It will be necessary, obviously, to obtain a response, and such response must be graduated from the least demonstrable intensity through at least three levels in excess of the minimum, in order to provide data for extrapolation to the effects of continuous exposure (24 hours per day on 7 days per week). Accordingly, the experiment may be expected to continue through the entire year 1966.

It is conceivable that the experimental regimen can be modified so as to shorten the time required to obtain definitive results. The means of so doing are under consideration at present, and the entire situation will be explored critically at the end of this calendar year. There is some risk, however, in any radical alteration of the original design of the experiment, in that too sharp an increase in the exposure may yield an excessive response, and threaten, thereby, the further usefulness of the subjects. It was for this reason that the initial level of the concentration of lead in the chamber was set at 10 micrograms per cubic meter - a level which could be counted on (from indirect but satisfactory evidence) to yield negative results at first, with the possibility that there might be a positive response as the time factor progressed toward continuity.

With the present facts and anticipations in mind, the cost of the experimental program in 1966 is expected to be similar to that of 1965. Some economy may be affected, since it seems unnecessary, in future experiments, to analyze duplicate samples of the food of the subjects. (The correlation between the lead in the food, day by day, with that in the feces, day by day, is so satisfactory as to enable the former items of data to be eliminated, apparently without introducing an error that is greater than the sampling error. Further statistical work will be necessary to substantiate the facts in this regard with certainty, and this feature of the design will be examined critically at the end of the current year (1965).

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The foregoing proposal, with its budget and its statement of the sources of funds and the amounts expected to be available from such sources, was made on August 18, 1965. Since that time, certain changes in experimental procedure, and in the funds and their sources, have come to light, and in the interest of clarity for all concerned the proposal should be modified.

First, with reference to the experimental results now available it can now be said that one of the subjects (N.K.) completed the desired period of exposure, 16 weeks, to air containing 10 micrograms of lead (under the experimental conditions described in detail previously) on February 20, 1966. (The other subject, for reasons explained previously, will not reach this point for some 20 weeks.) There being no significant evidence of a response to this exposure to 10 micrograms (approximately half of each 24-hour period), it is evident that the concentration of lead in the chamber will have to be increased, and that the experiment will have to go on for somewhat more than a full year from the middle of this year in order to provide the points on a curve from which an extrapolation can be made to the effects (on the urinary excretion of lead and on the lead content of the blood) of exposure for 24 hours per day every day. Just when this new experimental regimen can be inaugurated is somewhat uncertain at this time, because of the uncertainty of the willingness of the two present subjects to continue for an additional period of eighteen or more months (as required). This matter is being worked out. (It will be considerably easier and less costly to proceed with the same subjects, than to go through the preliminary observations on two new subjects, with their period of indoctrination and critical supervision. There is hope that this can be avoided.)

Second, it is now somewhat uncertain, for several reasons including the availability of funds, whether the renewal of the application to the Public Health Service will be approved and activated. The expectation is that this will be the case, but the expenditure of funds is being scrutinized so as to maintain the solvency of the experimental program if this should not come about. For this reason, plus the expectation that a share of the expenditures (as indicated) will likely be assumed by the American Petroleum Institute, a new budget of expenditures is submitted at this time, together with a statement of the sources of the expected funds. Curtailment or some degree of acceleration of expenditures will be affected in accordance with the outcome of the financial negotiations now under way. (In this connection, the economy that may be realized, if necessary, by eliminating the analyses of food and beverages, has been referred to above. Recent consideration of the direct usefulness of the information obtained as to the food of the country, have convinced us that these analyses should not be abandoned unless it becomes necessary to do so, for the lack of funds.)

The following budget is recommended for 1966, on the basis of the expenditures made in 1964 and 1965, and of those now visualized:

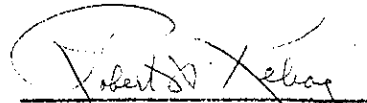
For personnel and services (direct and indirect costs)	\$85,000	
For special reagents, supplies, allowances for food, etc.	5,000	
Overhead (proportional share of cost of operating the Laboratory)	34,000	
Total		\$124,000

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On the assumption that funds will be available for the support of this work, the costs would be allocated in round numbers, as follows:

Ethyl Corporation	\$25,000	
E.I. du Pont de Nemours and Company	25,000	
International Lead Zinc Research Organization	25,000	
American Petroleum Institute	25,000	
U.S. Public Health Service	<u>24,000</u>	
Total		\$124,000

Should the Public Health Service grant be discontinued, every effort will be made to stay within the limits of \$100,000.


Principal Investigator
Robert A. Kehoe, M.D.
Kettering Laboratory

Date: March 11, 1966

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