To: The Clinical Research Committee of the College of Medicine of University of Cincinnati, and to Others Whom It May Concern

From: Robert A. Kehoe, M.D., Principal Investigator

Subject: INVESTIGATION OF THE METABOLISM OF LEAD IN THE HUMAN ORGANISM

Title of Present Phase of Investigation: The Fate of Inhaled Particulate Lead Compounds

Purpose of Present Phase of Investigation:

To determine the concentration of air-borne respirable lead, when distributed in the atmosphere of urban (and industrial) centers and of communities generally, which is compatible with the health and well-being of normal, healthy persons throughout their lifetime.

Present and Proposed Procedure:

The experimental procedure which has been employed during the past twenty-five years, during which the metabolism of lead in the human subject has been under investigation, and during the past fifteen years, in which the fate of inhaled, particulate, inorganic lead compounds has been examined, has been that of following the daily intake of lead in the food and beverages, and the daily output of lead in the feces and urine - essentially the technique of balance experiments (with certain omissions on both the intake and output sides of the balance, with respect to items of relatively small moment) - of healthy young to middle aged men, during a preliminary (control) period of observations which has extended through at least two seasons of the year; this preliminary period is followed by observations made when a subject enters and remains, according to a specified temporal schedule, in a respiratory chamber, designed as an office or laboratory, in the atmosphere of which a certain concentration of a specific compound of lead in a specified state of subdivision is maintained, in an adequate stream of inflowing and outflowing air.

In a series of observations involving 2 chambers and 2 subjects in parallel, now under way, lead sesquioxide in the concentration of 20 micrograms per cubic meter of air is dispersed in particles of the mean diameter of 0.05 micron, the largest of which are 0.18 micron in diameter. The concentration of lead in the chamber is checked by sampling the air within the chamber and determining its lead content, this being done once or twice per day of operation, dependent upon the duration of the period of exposure.

The duration of exposure, on a schedule of intermittency, is the variable factor in these observations. Since it is impossible to conduct these experiments in a continuous manner (24 hours per day on 7 days of each week over a period of months or years), the design of the experiment calls for the exposure of the subjects, within the chamber, on a graduated temporal scale beginning at 21 hours per week (3.5 hours per day on 6 days per week) over the period of, at least, 16 weeks, and continuing through 31.5, 42.0, 52.5, 63.0 and 73.5 hours per week, each for 16 weeks, or for such a period as will yield the maximum excretory response, if any. The two (2) subjects entered upon their first day of exposure within the chamber, after the preliminary observations, on October 17, 1966. The analytical data accumulated at this time are insufficient in number to be significant in terms of the response of the subjects.

Two subjects under observation in a previous experiment involving a similar schedule of exposure to lead in the concentration of 10 micrograms per cubic meter did not respond to the experimental exposure by a definite increase in the output of lead in their urine nor in the concentration of lead in their blood, and it appeared, therefore, that the dose of lead (as represented by concentration times the duration of exposure) was insufficient at any time to yield a detectable change in the status of the subjects, over and above that induced by the absorption of lead from the food and beverages in the alimentary

tract, plus that absorbed under ordinary (control) conditions from the atmosphere. This is not remarkable in view of the results of previous experiments. On the other hand, it was advisable to begin on the low side and work upward so as to detect the threshold of response, without exceeding it by more than the smallest possible margin. The basic experimental concept, tested partially by a preliminary experiment at a higher level of concentration of the same lead compound in the same dispersion, namely 150 micrograms per cubic meter of air, holds that it will be possible to extrapolate from four points on a smooth curve of response, the upward slope of which is determined by the increasing duration of exposure, to the effect of continuous exposure, i.e., 24 hours per day or 7 days per week over an indefinite period. A correlative thesis, verified in its essentials by extensive experimentation, holds that so long as the rate of the absorption of lead fails to induce a response on the part of the urine or blood, no appreciable quantity of lead will accumulate within the body of the subject, so that a dose in that category presents no hazard to the physiologically intact human organism.

The Potential Hazards of These Experimental Procedures:

(a) The present experiment involves no threat of intoxication to the experimental subjects from the absorption of lead, since it is being carried out at a level of dosage that will merely be sufficient to yield evidence of absorption in the form of increases in the urinary excretion of lead and, perhaps, in the concentration of lead in the blood. Earlier experiments involving the ingestion of dissolved lead were not so entirely devoid of the potentiality of yielding unexpected individual reactions, including certain histologic or functional deviations, such as changes in the formed elements in the peripheral blood, or biochemical changes in blood or urine indicative of alteration in the metabolism of hemoglobin (precursors of hemoglobin, as complex amino acids or porphyrins).

Even in the latter experiments, there was no likelihood of the occurrence of lead intoxication, in view of our extensive experience with the excretory response and the levels of the concentration of lead in the blood of individuals in industrial populations under known conditions of occupational exposure to lead, over more than three decades, and our persistent maintenance of a large margin of safety in our experimental subjects. (One is aware, of course, that an unexpected and improbable result may ensue, in almost any type of biological experimentation, and a sharp look-out for such a result is maintained. In this connection, a brief account of the present status of the criteria for the achievement of complete freedom from any incidence of lead poisoning in industry may be pertinent.)

An highly important criterion of safety, with respect to environmental conditions in the lead trades, since the time of Sir Thomas Legge and his associates, has been that of the concentration of particulate lead in the atmosphere of industria establishments, to which men were exposed during the work-day of (at that time) 48 hours per week. The standard of this type for the avoidance of occupational hazard due to the absorption of lead that has the widest, present, international application in this regard is that of the limitation of the lead content of the atmosphere to 150 micrograms of respirable lead (Pb) per cubic meter of air. (This is in relation to the present standard work-week of 40 hours.) An appreciable margin of safety exists here, as is indicated by the action of the American Standards Association in setting their standard at 200 micrograms of lead per cubic meter, and has been demonstrated by our experiments on human subjects under precise conditions.

A much more useful medical (physiological) criterion came into existence in our hands, as early as the nineteen-thirties, and has since been extended by ourselves and widely adopted in this and certain other countries. The present version of this criterion, in relation to inorganic compounds of lead, has

it that an individual workmen is in no danger of incurring lead intoxication so long as the concentration of lead in his blood does not reach the level of 80 micrograms of lead per 100 grams. Our initial expression of a physiological standard, in relation to the average rate of the urinary excretion of lead, set the threshold at a range (not a specific point, as in the blood) the low point of which is 0.15 mg. of lead per liter and the high, 0.20 mg. per liter. (The range derives from the physiological variation in the excretion of lead in the urine, induced by several factors, including, importantly but not exclusively, the throughput of water in unit time.)

Under experimental conditions, the exposure of subjects to lead in the air can be regulated within narrow limits, while the rate of the incidental ingestion of lead is being determined systematically and accurately. The experiments with human subjects have been characterized by a fairly wide margin of safety, in that no person has been subjected to experimental exposure to lead beyond the point at which the response approached the upper safe limit of the concentration of lead in the blood. Only one person has been permitted to come close to this limit, even fleetingly, this having been a subject of some years ago, to whom lead in solution was administered, orally, for 2 years in the dosage of 2 mg. per day, in addition to that in his diet. In the terminal month of this experiment, the concentration of lead in the blood of this subject ranged between 0.06 and 0.075 mg. per 100 grams. No other evidences of the absorption of lead above the usual levels were observed, but the experimental administration of lead was terminated at this point.

(b) From the aspect of the safety and well-being of each subject, as well as from that of the collection of base-line data that would yield standard values and physiological constants, certain clinical observations are made daily

(quantitative determinations of porphyrins and of delta-amino levulinic acid in the urine, and enumerations of the basophilic erythrocytic forms, including reticulocytes, in the peripheral blood); certain other observations are made weekly (interval account by the subject, of pertinent information, clinical examination comprising certain items, as weight, pulse, respiratory rate, blood pressure sitting and after "step" exercise, reflexes, dynamometric grip, erythrocytic, leucocytic and differential counts, hemoglobin determination, and clinical urinalysis), and at these or other times, such other regular or special observations of the clinic or laboratory are made, as are thought, by the supervising physician or the principal investigator, to be desirable or useful. In addition, determinations of lead in the urine and blood, the former daily, and the latter always once and sometimes twice weekly, serve to show the progress of the subject as to the absorption (indirectly) and excretion of lead. At longer intervals, as the analytical work progresses and as the data become available, the relationship between the intake and output of lead (insofar as these are determinable directly or by calculation) yield near approximations of the accumulation (retention) of lead in the body of the subject. Inasmuch as the "body burden" of lead is the product of the rate of retention of lead times time, the risk of intoxication must, perforce, find its ultimate expression, in these same terms, and such is the basic goal of this experimentation, despite the fact that it must be conducted in the laboratory so as always to be negative - that is, short of a toxic response, and yet as near thereto, for practical reasons, as the absolute preservation of the safety of the subject from any deleterious effect will permit. The responsibility for the current health and well-being of the experimental subject is vested in the senior physician in the Clinical Division of the Laboratory, who has the authority to terminate the experiment at any time at which, in his judgment, the health of the subject is in jeopardy, either from the experimental regimen or from extraneous causes.

Previous Work Done in This Area:

The procedures and certain of the results of previous investigations in this field in this Laboratory have been published, and are documented in the references below.

Method Used in Procuring the Consent of Subjects:

The subjects are not, in the usual meaning of the term, "volunteers." Rather they are selected for the purpose, and are engaged as experimental subjects, if they so choose, as regular members of the staff of the Laboratory, after a thorough inquiry into their physical and tempermental suitability, and after having been informed, fully and in detail, as to their duties and responsibilities, and advised as to the putative hazard involved in their acceptance of the position offered. Their task is likened, with suitable qualification, to employment in certain well-supervised lead-using industries, and the precautionary measures are discussed in detail, to show the highly favorable basis of the comparison. Each man is promised the fullest protection that is afforded by our knowledge and experience, and is familiarized with the purposes and goals of the experimental work in relation to industrial and public health. Each man is covered, as are other members of the staff of the Laboratory, with occupational compensation insurance, under the laws of the State of Ohio. Each man is given medical advice and care throughout the experimental regimen, and any medical procedures advised, in connection with the experimental program, are provided at no cost to the subject for services rendered by physicians or other professional personnel (e.g., dentists) outside the staff. As members of the functioning personnel of the Laboratory, each subject is given the same consideration as are our other colleagues, but is not regarded by ourselves or other members of the staff as being entitled to special regard, sympathy, or pampering. Indeed, in this Laboratory, in which it is fully recognized that all of us, as members of the

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public, as well as all workmen in our society, are being subjected, constantly and increasingly, to the stresses and hazards that are a normal product of modern technology, it is logical and appropriate that the effects of specific stresses and hazards should be investigated, environmentally and biologically, both in the Laboratory and in the community, and that fully controlled conditions provided in the Laboratory, involving observations on human beings, are wholly necessary as a means of interpreting and controlling environmental conditions.

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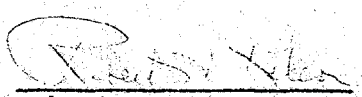
Signed: 

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