

January 12, 1960

MEMORANDUM:

TO: Dr. Robert A. Kehoe

FROM: Biometrics

SUBJECT: Modification of Design of Lead Study

1. The experimental design proposed in the memo of August 25, 1957 (Design of Lead Study) has been modified as follows:
 - a. The present experiment will not vary the level of lead in air concurrently with the length of time periods the subject remains in the chamber. Dose differences will be defined solely by differences in the length of experimental exposures. The concentration of lead will be .150 mg/m³.
 - b. The subject will spend three different time periods in the chamber instead of the eight different time periods proposed previously. Experiments will consist of 4, 8, and 10 hour sessions. Four hour sessions will start in the morning or in the afternoon in mixed order. Ten hour sessions will occur once every four weeks. (The time periods of 4, 8, and 10 are only approximate. The actual durations will be chosen on the basis of practical considerations of preparing the chamber, the food, by the toilet needs of the subject, etc.) A copy of the daily time periods for the first 72 weeks of the experiment is appended.
2. The changes were generated predominantly by the impressions gained from past experiments by Dr. Kehoe and Mr. Schafer that differences in increments of excreted lead, following small differences in doses, were too trivial to be detected over relatively short time spans. If this should be true it would be extremely difficult to reduce the necessary number of eventual experimental subjects by recovering individual dose-response curves.

However, it was demonstrated that cumulative effects of successive exposures, although extremely small, can be isolated by the elimination

KE 0004419

of random variations. It was proposed, as a reasonable statement, that not all the lead entering through the lungs would be eliminated over a 24 hour period. The excretion of lead should then increase constantly over the weekly experimental days (i.e. from Monday to Friday) and constantly decrease during the weekend (i.e. over Saturday and Sunday.) By eliminating some of the random variation about the days of the week it was indeed demonstrable that urinary excretion of lead increases constantly from Monday to Friday and then drops again during Saturday and Sunday. (The observed trend was based on 80 experimental weeks and the statistical significance of the differences was tested by Analysis of Variance.) Random variations were eliminated in a very crude fashion and one can hope with good reason that more powerful numerical analyses will be efficient in recovering even smaller increments for fewer observations.

3. The final action of the experiment appears to be:
 - a. The experiment will be a pilot attempt to recover a dose-response curve from a single subject and to make crude predictions of the effects of unobserved dose levels. (Dose is here defined simply as variation in time for fixed levels of lead in air.)
 - b. Whether or not time of exposure, rest between exposures, and level of lead in air (and perhaps even particle size) will be varied concomitantly in future single subject experiments will depend on the success with which the proposed analyses can isolate differences in excretion and storage between 4 and 8 hour doses and the utility of such increments in prediction effects of the 10 hour dose level.
 - c. The analyses of the data will proceed as outlined previously, taking cognizance of changes introduced in the experimental design. As suggested then, only part of the accumulated information will be used to derive the desired estimates and prediction equations, the remainder will serve as check for reliability of the procedures.
 - d. Mr. Schafer is working out techniques that will measure directly the amount of lead remaining in the lung of the subject after a stated period of exposure.
 - e. Mr. Cholak has agreed to report blood and urinary lead levels to three decimals.
 - f. A detailed schedule of experimental conditions will be given to Mr.

KE 0004420

Creech, who will supervise the compliance of the subject with experimental conditions. A detailed calender of events will be given to the subject, to Mr. Creech, and to whoever will monitor all phases of the experiment as soon as the starting date of the experiment is determined. This calender will consist of the daily regimen and include the following information:

- i. The hour at which the subject is to enter the chamber
- ii. The hour at which he is to leave
- iii. A reminder of the starting hour of the following day
- iv. A reminder of blood samples, examinations, etc. that are to take place that day.