February 22, 1962

Memo to: Dr. Robert A. Kehoe

From: T. Sterling

Subject: Analysis of California TML Study

The changes observed in the excretion of lead and in the blood picture of workers (who switched from handling TEL containing products to those containing TML) are of such consistency and magnitude as to preclude any chance factors. The pattern of results would ordinarily force only one conclusion on the investigator; namely, that underlying changes in physiology or body chemistry had taken place during the period subjects handled TML. It is true that the data were collected in a somewhat haphazard and cavalier fashion. However, the most important findings are based on laboratory analyses of urine and blood samples and may be above reproach.

It is a great misfortune that the medical follow-up data turned out to be useless. The results available now would make it appear desirable to complete the collection of all the data and do it in the form originally planned as well as to extend the follow-up on the laboratory analyses for an additional year.

Lead Levels in Urine and Blood

1. Data on lead in blood and urine were almost complete. Five urine samples were obtained during the year of study while two blood samples were taken, one in the beginning the other at the end of the study. These data are presented in a series of tables at the end of this memo. Consecutive examinations are identified as "Rounds" one to five. The number of samples are given in the second column of each table. Statistical evaluation of differences observed between consecutive rounds are based on Analyses of Variance. The statistical analysis is made extremely complex by the fact that, while most measures were made repeatedly on the same subjects, not the same number of subjects was tested each round. The analyses are not reproduced here. When the probability of finding, by chance, a variation among means as large as the one

observed was smaller than .05, asterisks were placed on the table. (For example, the means on Tables 1, 2, 3, and 4 differ with acceptable statistical reliability. This is indicated by placing asterisks on each side of * Table *, * Table *, etc.)

2. Levels of lead in urine and blood as well as urine volume and specific gravity are given in Tables 1 to 5 for all workers combined, in Tables 6 to 10 for workers in San Francisco, and in Tables 11 to 15 for workers in Los Angeles. There is an obvious, consistent and statistically significant decline in the lead content of blood and urine. This conclusion is reinforced by the progressive decline in urine lead, over the period of the study, toward a new stable state. Such a progression would be expected, on basis of the lead chamber studies, whenever the burden of environmental lead decreases. (Statistical significance among urine volumes for "All Data" is not accompanied by any systematic increase or decrease and may be discarded as spurious.)

3. Three occupational subgroupings were singled out, who would have relatively uniform exposure. These were service station attendants in San Francisco (Tables 16 to 20), service station attendants in Los Angeles (Tables 21 to 25) and Blenders (Tables 26 to 30 - all Blenders are located in San Francisco). Again lead in urine and blood decreases for all occupations. It is interesting to note that the decrease appears to be most pronounced for Blenders.

Blood Analyses

1. A series of laboratory tests on red and white blood cell counts were made. Not all counts were repeated so that comparison data are lacking for:

Hematocrit - Per Cent
Reticulocytes - Per Cent
M.V.C.
M.C.H.
M.C.H.C.
Polys - Metamyelocytes
Morphology
Platelets

Comparisons of the counts listed above could not be made.

he data were complete for comparisons on the following blood ell counts:

Red Blood Count	(Table 31)
Hemoglobin - grams	(Table 32)
Color Index	(Table 33)
White Blood Count	(Table 34)
Polys-Neutral Total Per Cent	(Table 35)
Polys-Filamented Per Cent	(Table 36)
Polys-Nonfilamented Per Cent	(Table 37)
Lymphocytes	(Table 38)
Monocytes	(Table 39)
Easinophiles	(Table 40)
Basophiles	(Table 41)

The blood cell count increases consistently (except for Lymphocytes) ~~which is to be expected~~. Not all increases are statistically significant; however, since all increases are in the same direction, there can be no doubt as to the over-all change in the blood count.

One very interesting fact emerges from the inspection of cell counts. In each case the change is from a low normal to the mean of the distribution which defines normal blood cell count. In the case of Lymphocytes the change is from a high normal to the mean.

The blood data are too fragmentary to permit further breakdown by city or occupation.

Some Conclusions

The consistent changes demonstrated by the data lead, without dispute, to the conclusion that they reflect fundamental changes of physiology or body chemistry engendered by the change in leaded gasoline. The total pattern of results is such that even if none of the changes would have reached an appreciable magnitude of statistical significance the former conclusion would have to be reached. There is no question, therefore, of statistical magic or manipulation on which conclusions are based.

Two basically divergent interpretations of these findings appear to be possible. (The alternatives were derived through discussions with Horton, Cholak and Grupp.)

A. TML provides lead which ~~is~~ deposited in soft tissue in excess ~~of excretion~~. The rise in blood cell count may be a compensatory

highly speculative

reaction, as for example, to interference with blood oxygenation across the lung tissue as a reaction to organic lead deposited there.

B. Because of the increased volatility of the gasoline, lead is either inhaled in smaller, or exhaled in larger amounts. The body burden of lead being decreased the amount found in urine and blood declines to a new stable state and the increase in blood cell count represents the reaction of the bone marrow to the decreasing amount of lead in surrounding tissue and blood supply and a return to a more normal (if such an expression can be used) state of the blood cells.

lead compounds in the

Also speculative & probably unwarranted

Since hypothesis A would indicate heightened toxicity to relatively small occupational exposure one would expect that this increase in toxicity would have been spotted during the manufacture of TML, where workers are exposed to much higher concentrations of lead in the atmosphere than are the occupations present in this study. However this was not the case in the plants of the Ethyl Corporation. Hypothesis B appears more reasonable and there is then substance to the conclusion that TML presents less of a lead hazard than does TEL under normal procedures of handling. This is unfortunate. It is more likely that the absorption by the personnel is entirely negligible, and that the changes in the fundus derive from other totally different environmental factors. The changes are in no case of clinical significance, so that the attempted interpretation of them is highly speculative, and a bit facetious.

KE 0066043