MEMORANDUM

On the Objectives of An Investigation of the Toxicologic Characteristics of Tetramethyllead.

When it became evident, recently, that tetramethyllead was to be employed as an antiknock agent along with or as a partial substitute for tetraethyllead, certain toxicologic investigations were initiated promptly. This compound, as well as the others of the series of ethyl-methyl compounds of lead had been examined in a preliminary manner by Machle (at that time, Associate Director of the Kettering Laboratory) ~~years before~~, when the use of these compounds came first under consideration. At that time, certain differences were noted in the biological behavior of tetramethyllead as compared to tetraethyllead (the principal difference being the virtual inability of tetramethyllead to kill small experimental animals when applied upon their skin), but the similarities were the outstanding basis for the tentative judgment that tetraethyllead and tetramethyllead, when absorbed, acted in much the same manner, and that these and the other compounds were possessed of the same general type and degree of toxicity.

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Tetramethyllead had, by this time, been handled by a number of persons who had synthesized the compound, and had examined it in a

number of experimental [redacted] procedures, and such experience had indicated that it had no immediate properties that should render it inordinately dangerous to handle in moderate quantities and over comparatively short periods of time. The property which had provided the obstacle to its use as an antiknock agent was the very property which made it technically desirable - namely, its volatility. It was feared that this property, which could be expected to contribute significantly to the rate and extent of the vaporization of the lead compound out of commercial gasoline, might create an uncontrollable hazard for the handlers and users of leaded gasoline. Since a great deal of costly investigation would have been required to establish the facts without which this compound could not be exploited for commercial purposes (in motor fuels), and since the prospect for a satisfactory outcome of such investigation was believed to be poor, the projected use of tetramethyllead was dismissed, or as it has turned out, postponed. Recently, a degree of need for a volatile compound of lead developed in the petroleum industry, and with the completion of a preliminary field investigation (in a taxicab garage in San Francisco), which demonstrated that the volatility of tetramethyllead did not, in fact and

in practice, pose a serious problem (in the quantitative sense) of cumulative absorption for the handlers and users of commercial gasoline containing appropriate concentrations of the compound, the way was cleared for its use. Moreover, the enthusiasm with which the availability of this compound was greeted by certain refiners and distributors of petroleum products, gave every assurance that tetramethyllead would be manufactured and distributed in an appreciable quantity. This assurance created the necessity for a thoroughgoing investigation of the effects of prolonged human exposure to tetramethyllead. Preparation for the field investigation, had required that tetramethyllead be manufactured in commercial quantities and in full-scale plant equipment. This was achieved without apparent injury to the personnel of the manufacturing plants. Moreover, the commercial production of tetramethyllead has continued now for about two years, and the product has been distributed commercially for eighteen months without incident. The conclusion might thus be arrived at, on practical grounds, that this development had followed the pattern of the successful manufacture and distribution of tetraethyllead, that the lead alkyls of the ethyl-methyl series are all of one piece in terms of toxicology and industrial hygiene, and that there is no further

necessity for the continuation of a detailed toxicologic investigation. The situation, however, may be otherwise, and it is essential therefore, to establish certain facts at the earliest possible time. Fortunately, this state of affairs, from the aspect of the toxicologic approach to tetramethyllead, had been anticipated from the outset of the renewed interest in the compound, and toxicological work has in this Laboratory (and to a lesser extent in others) been under way for some time. There are pertinent data to be examined, interpreted and reported on their own merits and also in relation to the more important questions to which answers must, if possible, be obtained.

In order that an adequate appraisal may be made of the significance of the experimental results obtained thus far, and in order to visualize clearly the direction and scope of any future program of investigation, the practical questions at issue, translated into a statement of the objectives of the investigative program, should be set forth:

I. Comparison of Immediate Intoxication Induced by Tetraethyllead With That Induced by Tetramethyllead.

(a) On the basis of the response of experimental animals to the immediate absorption of toxic quantities of these two materials, there is a general similarity, in that the effect on the central nervous

system is the outstanding feature of the intoxication in both instances. One observer, however, in the Haskell Laboratory, credited tetraethyllead with a stimulatory (excitatory) effect, and tetramethyllead with a depressant effect, upon the central nervous system. Whether these responses represent different stages or degrees of the same general effect, or whether these are expressions of different effects or effects mediated differently, needs to be determined. (It has been noted that tetramethyllead (presumably poorly absorbed percutaneously) is much less dangerous than tetraethyllead when kept in contact with the skin of animals. The differences in the lethal dosages of the two compounds, when administered by various methods in parallel experiments, may also be of some consequence in making approximate comparisons of the concentrations which exist in various tissues - the brain, in particular - in relation to the type, sequence and severity of the effects).

(b) The locus, type and extent of the injury sustained by general and specific organs and tissues of animals fatally poisoned by the two compounds also requires elucidation. In view of the fact that the lesions of acute intoxication vary with the severity of poisoning, with the length of the survival of animals (whether they expire promptly or suffer

are completely reversible and others irreversible, the gross and microscopic pathology of acute intoxication induced by the two compounds should be explored fully. (This is made the more imperative because of certain differences in cerebral histopathology which have been attributed by a pathologist in the Haskell Laboratory to the different actions of the two compounds. Whether these differences were real or only apparent, or whether they represent stages or degrees of severity of the same process, are matters of some consequence.)

(c) An important characteristic of human intoxication induced by brief, rapid absorption of tetraethyllead is involved in the foregoing paragraph (b).

This disease, as seen in man, has had the quality (somewhat surprising in an intoxication of such intensity) of leaving no demonstrable evidence of residual damge in survivors. Persons who have recovered from the most serious manifestations of such intoxication (excellent medical records of scores of cases disclose no exception), have sustained no residual effects. Apparently, there has been no irreversible damage to the human central nervous system, or such damage has been too slight to have significance, or has been confined to silent areas of the

brain.

There have been no reported cases of tetramethyllead poisoning, and it is not possible, up to this time, to observe either a parallelism with, or divergence from, tetraethyllead poisoning in man. This is an important matter, however, which intensifies the interest of the investigator in the pathology of the acute form (or forms) of intoxication induced in animals by the alkyl lead compounds. (It may be, and one hopes that it shall be, the case, that human cases of tetramethyllead poisoning will be too few in number to provide a definitive answer to this question.

2. Comparison of the Effects of Prolonged Exposure to Tetraethyllead and Tetramethyllead.

(a) The best information as to the outcome of the absorption of tetraethyllead over prolonged periods of time, is that which has been obtained in the course of the medical (clinical) and physiological (analytical laboratory) supervision of men engaged in the manufacture of tetraethyllead and anti-knock compounds containing tetraethyllead, over the period since the year 1926, when commercial production assumed large and increasing proportions. In addition to this most important source of information, workmen engaged regularly in the transportation of antiknock

compounds in national and international trade, and those engaged regularly or intermittently in repairing and cleaning gasoline storage tanks, have incurred dangerous types of exposure from time to time, with the result that there has been a low but significant incidence of cases of poisoning, which on investigation have yielded useful information concerning the nature of tetraethyllead intoxication. Of particular importance, was another series of cases of poisoning which developed during World War II out of conditions of employment which were capable of inducing intoxication only after some weeks of exposure. The clinical information obtained from these sources, and from the study of other cases of poisoning which have resulted from brief periods (minutes or hours) of exposure to tetraethyllead, has revealed only one form of human intoxication. No "chronic" form of the disease has been seen, or, at least, described. The clinical pattern is that of varying degrees of severity of toxic irritation of the central nervous system. There has been no case of peripheral neuritis, paralysis, or hematological abnormality. In fact, this type of intoxication bears no resemblence to any form of classical lead intoxication, except the acute encephalopathic type seen not infrequently in infants and small children. Lead encephalopathy due to the absorption of inorganic lead by

the adult man usually has distinctly different characteristics.

The characteristic form of tetraethyllead intoxication is interpreted (after the fact) as being due to the properties of the degradation products (in the animal organism) of tetraethyllead. That inorganic lead compounds are not well represented in the human body at any time among these degradation products, is demonstrated by the fact that the concentration of lead in the blood (i.e. in the erythrocytes) is never high in tetraethyllead poisoning (or when tetraethyllead has been absorbed in appreciable but not unduly dangerous quantities over prolonged periods of time. The proportional representation of various (potential) degradation products of tetraethyllead in the bodies of exposed persons is not known in relation to any set of conditions of exposure or any temporal sequence, but the presumption is reasonably assured that the inorganic component(s) of these degradation products is never represented in high concentration in the body. Thus, it is not too remarkable that the disease induced by tetraethyllead differs from that due to inorganic compounds of lead, since the chemical differences in the biologically active component (s) of the two agents can hardly fail to result in differences in the site (s) and type(s) of the biological effects.

(b) By reason of the sequence of the early events in the history of the tetraethyllead industry, and because of the state of the art and science of industrial toxicology at that time, as well as the inexperience, at that time, of the persons responsible for such investigations, there is a dearth of the type of toxicological information which might have been obtained from animal experimentation, and which now could serve as bases for comparing tetraethyllead and tetramethyllead with respect to their biological behavior. Men were being exposed to tetraethyllead from the year 1923 on, and it appeared to be more urgent and pertinent to supervise these men and to investigate their clinical and physiological status, as means of contributing to their safety, than to resort to ~~the study of~~ investigation of animals. The case of tetramethyllead is different, in that there is a degree of urgency in determining whether tetramethyllead can be expected to behave, in all essential respects, as does tetraethyllead. Accordingly, parallel experiments had to be devised initially, and will probably have to be extended in specific directions in the future, to determine the similarities and, more importantly, any differences which may exist between these two compounds in their initial and eventual behavior and fate in the complex animal organism. How do such things as their solubility, volatility,

the rate and character of their metabolic degradation in the body, and their ultimate fate therein (with respect to the distribution of their metabolic components in the body, their retention in various tissues, and their excretion from the body). With such information at hand one may come to conclusions with respect to the degree of safety of men engaged in the manufacture and the handling of tetramethyllead. Human experience has shown infinitely more clearly than any type of experimentation with laboratory animals could do, the important facts concerning tetraethyllead and human safety. Human experience with tetramethyllead will be required to prove the case for tetramethyllead. If, however, the latter compound behaves like tetraethyllead, or in an analogous manner with essentially quantitative, rather than qualitative, differences, one can gauge the safety of men with reasonable assurance and establish guides for the industry. In the event that there are significant or imponderable differences in the two materials, as revealed by animal experimentation, one can be forewarned, and in time, in all likelihood, be forearmed. The most important aspect of the question at issue here relates to the safety of men who will be engaged in the manufacture of tetramethyllead.

These men, inevitably, will absorb tetramethy lead in the course of their employment. The lead content of their tissues, as represented in tetramethyllead and its degradation products, will be elevated. How much can they be elevated without prejudice to their health, well-being and length of life? Some reasonable answer to this question should be obtained by indirect means (from the study of experimental animals). If this work is done well enough, it is likely that any favorable conclusions arrived at by this means will be confirmed by human experience.

3. The Problems of Therapy.

A better understanding of the behavior of tetramethyllead, as well as that of tetraethyllead, would aid in the therapy of poisoning. Accidents and irresponsible acts may be expected to result in some cases of poisoning and some fatalities. It would be advantageous to be able to establish an effective therapy for this disease. There is reason to believe that the study of both compounds will contribute more to our knowledge than would the study of one of them.

1. The relative hazard of the exposure of workmen to tetramethyllead, as compared with that of exposure to tetraethyllead, under conditions of the same type in the two manufacturing operations, has been investigated over the period of more than one year during which tetramethyllead has been in production. The comparison was the more valid, in view of the chemical and toxicological similarities of the two compounds, because of the long period of symstematic observation of the environmental conditions and the reaction of workmen thereto, in the manufacture of tetraethyllead.

Despite the fact that the twenty-one (21) workmen in the area of the tetramethyllead operations were subjected to somewhat more than twice the concentration of lead (Pb as tetramethyllead) that had prevailed in the area of the tetraethyllead operations (Pb as tetraethyllead) during the previous period, of at least two (2) years, of their employment therein, all remained in good health throughout the entire period, and sustained no abnormalities in their blood pressure or in the structural composition of their blood. There was, moreover, no significant change in the concentration of lead in their urine or blood (this is a phenomenon that finds its explanation in animal experiments). It seems evident that the hazard associated with the

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absorption of tetramethyllead is no greater - and is probably less - than that associated with the absorption of tetraethyllead.

2. The comparative toxicology of tetramethyllead and tetraethyllead has been under investigation in parallel experiments with animals for somewhat more than two (2) years. The two compounds, when absorbed by rats and dogs, induce the same general type of symptomatic response, involving the central nervous system, and their toxicity, as represented in terms of lethal dosages, is in the same general range of magnitude. There are, however, certain differences in their toxicity, and these differences appear to be associated with differences in their metabolism, as between themselves in the same species of animal, and as between animals of different species. These features of the behavior of the two compounds are under investigation in experiments involving prolonged exposure of animals to relatively low concentrations of vapor of tetramethyllead and tetraethyllead in air.

3. The field investigation of the potential hazards associated with the use of tetramethyllead as an antiknock agent in gasoline, as described in an Interim Report dated March 23, 1961, was completed in August of 1961. All of the data have been collected and examined, and the final report is being assembled for distribution. The results and tentative conclusions arrived at in the Interim Report have undergone no change. It is evident that the potential hazard associated with the greater volatility of tetramethyllead (as compared with that of tetraethyllead), is insignificant. The quantities of organic lead contributed to the atmosphere in the breathing zone of the men engaged in the occupations represented in this survey, were found to be too small to bring about a measurable increase in the absorption of lead by the workmen.