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The Potential Hazard Associated With The Introduction Of Tetramethyllead
As An Antiknock Agent Into Commercial Motor Gasoline, With Respect To The
Absorption Of Lead By The Handlers Of Such Gasoline.

- An Interim Report Made After Nine Months of Distribution -

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Introductory

Certain questions arose initially concerning the potential hazard of
lead absorption in connection with the distribution and use of gasoline containing
the antiknock agent, tetramethyllead. The primary factor which might give rise to
hazard through the substitution of this compound for tetraethyl lead in equivalent
concentration in gasoline (equivalent in terms of the proportional representation
of lead in the molecule, whereby, at the maximum, 2.05 ml. of TML are equivalent to
3.00 ml. of TEL), was that of the appreciably greater volatility of tetramethyl
lead. The practical question revolved around the extent to which this higher volatility
might operate with significant effect to contaminate the air with tetramethyl lead,
or whether this factor would be offset sufficiently by the high dilution of the
tetramethyllead in the gasoline, and, additionally and more pointedly, by the
movement of currents of air in diluting any such volatilized lead to insignificant
levels of concentration in the air breathed by those who would handle the gasoline
under the ordinary, as well as the possibly extraordinary (from time to time), conditions
of the commercial handling of the gasoline.

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This question, in so far as a comparatively short period of time and a specific set of conditions (regarded as uncommonly severe) of use were concerned, had been answered in the negative (See Report of The Kettering Laboratory of November 10, 1959). It was believed, however, that the matter was of sufficient importance to justify further investigation of the conditions associated with the gamut of commercial operations over a period of time sufficient to reveal any even slight increase in the occupational exposure of the handlers of such gasoline. (It has been shown that persons subjected to varying degrees of exposure to lead, in the course of occupations that follow approximately the normal schedule of 40 hours per week of employment in the U.S.A., reach a practical equilibrium with their environment, with respect to their absorption and excretion of lead, as demonstrated by the concentration of lead in the blood, and by the rate of the urinary excretion of lead, in from five to eight months, after which no further increase will occur so long as the conditions of exposure remain essentially constant.) Accordingly, a program of investigation, to be carried out over the period of one year, was designed along two general lines - one concerned with the periodic measurement of the lead in the air in the areas in which men were carrying on various relevant occupations, and the other involving the determination of the approximate rate of their urinary excretion of lead from time to time. (Determinations of the lead content

of the blood of the workmen were to be made at the beginning and at the end of the investigation, ^{as} not to ignore any evidence of the absorption of lead in any form. However, the absorption of tetramethyl lead cannot be detected by determinations of lead in the blood, but, rather, is revealed by the measurement of the lead in the urine. The latter, therefore, was to be followed at intervals of three months throughout the year, so as to assess in quantitative terms any degree of occupational exposure to tetramethyllead that might be incurred by individuals and groups.

Investigative Methods.

Inasmuch as a final report to this investigation is to be made in full detail on its completion, it may suffice for present purposes to deal briefly, ~~with~~ with the experimental design and the methods of procedure. A preliminary survey of the principal areas, ⁱⁿ in which gasoline containing tetramethyllead was to be distributed, resulted in the ²selection of the sites at which air analyses would be carried out systematically, and in the selection of various groups of employees, whose exposure to the potential hazard was regarded as representative of the ~~range~~ ^{range} of occupational exposure in this ~~and severe forms~~ ^{and severe forms}. ~~Certain details of the procedure~~ ^{Certain details of the procedure} ~~severe conditions of exposure. Certain methods of the environmental survey will be~~ described briefly, ^{of investigation, the procedure of} in the following Part 1 of this report, while the general ~~method~~ ^{method} ~~procedure with reference to~~ the employees is outlined in the following paragraphs.

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Men engaged at ~~various~~ various occupational sites were selected for periodic investigation, according to the numbers of such persons available, or in such numbers as would be representative of their occupation. When the total number of available persons was ample, every effort was made to select ^{steady} ~~these~~ employees whose service could be expected to continue uninterruptedly, ~~(stability and~~ ~~reliability)~~ as well as those whose work appeared to involve the maximum severity and duration of exposure. Table I, below, indicates the sites, the specific operations involved, and the types and numbers of personnel projected for investigation in the San Francisco area:

Sites	Types of work	Numbers of workers Members of work with significant exposure
Refinery		
1. Blending plant	Regular mixing of TML with gasoline	5
2. Tank Truck Loading Rack	Loading petroleum ^{products,} periods including gasoline containing TML. Approximately 60 drivers have irregular, intermittent exposure, but only the loaders, 12 in number, are exposed regularly.	12
3. Wharf	Loading barges, inspecting, sampling and testing contents	4
4. Barrel Filling Area	Workmen fill drums with gasoline containing TML. 2 are the regular employees and 3 others are available for relief.	5 (2 regular employees)
5. Chemical Laboratory	Testing and distillation of gasoline. of 12 persons there as engaged most continuously were selected	4 (2 regular employees)
Service Stations in S.F.		

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Sites	Types of work	Number of workmen with significant exposure
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Service Stations in S.F.
10 very busy and widely distributed in area

Regular dispensing of gasoline to consumers. *Some turnover of persons expected. Substitution, then to be made*

Approximately *30* ~~(Some turnover expected)~~

Severely possible (some turnover of persons expected) (no investigation)
Comparable (somewhat smaller) numbers of persons employed in the foregoing

categories, with the exception of barrel filters (no such operation was carried out

at the refinery in the Los Angeles area, were selected. The actual numbers of

and type of employment
persons in the various groups will be shown later in the tabulation of the analytical data.

Each individual in these groups ~~were~~ examined by a physician associated with the medical department of the oil company concerned. The details of these examinations will be reported later after the *second and final (later on)* ~~final~~ examination has been carried out. The examination consisted of a medical and occupational history, a complete physical survey, a hematologic examination and certain other laboratory procedures according to routine or as required in specific instances. At the initial examination *samples* of blood for analysis for lead were obtained, together with a sample of urine, collected in containers supplied by The Kettering Laboratory and in accordance with the instructions of the Laboratory. All of such samples were forwarded to The Kettering Laboratory for analysis.

Additional samples of urine were collected at intervals approximating

three months and forwarded to The Kettering Laboratory. A terminal series of

samples of urine is to be collected in May ^{and} June of 1961, at which time a

second and final series of samples of blood will be obtained. ~~(in terms of the~~

~~findings up to the present time, there is no reason to suppose that the~~

~~observations will need to be extended beyond the year postulated in the original~~

~~plan of the investigation).~~

*See findings obtained by the analysis of the urine of the subjects
of the above named cases, all of which will be dealt with in a
general summary.* ~~Part 2 of this report.~~ ~~While the analytical results of the blood of these persons~~
~~of considerable interest in another relationship, they have little significance~~
~~to present time for the purpose of this report. As all the necessary samples~~
~~and the terminal series of samples had been obtained and analyzed, therefore~~
~~the available data relative to the blood are not presented at this time.~~

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In general, the data as presented in the foregoing tables give a clear answer to the question which led to their collection. With a few exceptions, so few indeed as to be regarded as fortuitous or irrelevant, the concentrations of lead in all of the samples of urine of all of the subjects are so consistently within normal limits as clearly to demonstrate that the groups of persons, regardless of their specific occupations, sustained no appreciable absorption of lead during the period of approximately nine months during which they were subjected to periodic investigation.

When all of the analytical results obtained from the investigation of all of the subjects were assembled and separated only with respect to the three periods of sampling, no valid statistical evidence of any ~~xxx~~ abnormal absorption of lead on the part of the ~~entire~~ group could be found in any period of the observations. The data distributed themselves statistically in strict accord with comparable types of data obtained from entirely normal persons devoid of occupational or other unusual exposure. There was some variation in the data of the three periods, but the variations showed no consistent trend with the lapse of time, and they were well within the limits of physiological variation, as these have been observed in other data involving samples of urine of small volume. A few individual findings deviated appreciably from the general trend of the results and could be

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as a whole. For this reason, and also because the combined data were composed of results from inhomogeneous groups of employees, the findings were rearranged for more detailed study, according to the occupations and the geographic distribution of the employees.

After exploring every relevant combination, ^{relationship, with a negative outcome,} they were reassembled into the tables represented above (Tables 7,8,9 and 10) in which all of their characteristics can be seen readily. Only a few comments are called for.

The few aberrant results, four in all, are in no wise remarkable. Samples collected with the most minute care are contaminated from time to time. These ~~results~~ results could be discarded as being irrelevant on the basis of their departure from the statistical universe represented by the other data. However, they have been included in the ^{data of} tables, and have also been examined individually and in their specific relationships. The facts concerning them are as follows:-

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In Table 8, under "Loaders^a of Tank-trucks", ~~the~~ result of 0.11 mg. per liter (which is not entirely beyond the extreme upper normal limit of the concentration of lead in a ~~sample~~ sample of urine of small volume). *is obviously aberrant in the statistical sense and is* ~~may well be regarded as aberrant and~~ probably invalid, because of the results obtained by the analysis of the first and third samples of this same person, 0.015 and 0.03 mg. respectively, per liter. (The value of 0.07 mg. per liter which occurs in the same table is not to be take too seriously, from the aspect of any physiological meaning which it might have otherwise, because of ~~its~~ ^{the} small volume, by which the analytical error is magnified. It is not, of course, remarkably high, but it stands out by comparison with the other values in this table.)

In the same table, under "Barrel Fillers", is a result of 0.12 per liter. This was sufficiently unusual, especially in this small group of men engaged in an occupation that might (under certain unusual circumstances) ^a give rise to/significant degree of exposure, that a further sample was called for and obtained, ~~and~~ ^{it} on analysis yielded the value of 0.02 mg. per liter. The prior and subsequent samples may be seen to have been 0.025 and 0.02 ~~mg.~~ respectively, ~~mg.~~ per liter. This relatively high finding can be dismissed from further consideration.

In Table 9 is a single result, obtained in the first round of

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observations, of 0.15 mg. per liter. This result in a service station attendant could not, by any stretch of the imagination, be regarded as evidence of a dangerous occupational condition, and the aberrant character of this finding could be inferred from its unique relationship to the others in the same category. Accordingly it was not checked by obtaining a further sample within a short time. The results obtained in the second and third samples from this same subject were 0.025 and 0.045 mg. respectively, per liter.

Essentially the same situation as that above is repeated in Table 10, in which a result of 0.20 mg. per liter, obtained on the first round of sampling, was followed by the finding of 0.015 and 0.02 mg. respectively, per liter, in the second and third samples from the same man. One additional comment may serve a useful purpose in relation to the urinary findings. The idea has been advanced and has gained credence evidence in certain circles, that samples of urine of small volume, such as those voided ^{at one time,} ~~on one occasion,~~ do not convey valid information concerning the general level of the urinary excretion of lead. This is true only of ^{small} samples that are of quite small volume because of the unavailability of suitable quantities of water within the body of the person who supplies the sample, or of samples of unusually large volume voided at a time when the

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throughput of water is unusually high. (Assuming, of course, that the renal function is essentially normal.) In short, ~~an highly unusual~~ a ~~essentially~~ highly concentrated sample of urine will contain an unusually high concentration of lead, while a highly dilute sample will yield the opposite result. Attempts have been made to correct the analytical result to a standard specific gravity, or a standard concentration of some allegedly invariable or less variable constituent of the urine. Thus far, no such correction factor can be held to be valid, even though it may move the aberrant result somewhat closer to the mean or medium value of a related group of results. The correction is especially questionable in dealing with the extremes of concentration, and it cannot be counted on to do more than artificially to reduce the variability of a series of results. This fictitious and often misleading procedure has not been considered for application to the results presented herein. Rather, we have relied upon a broad experience with a wide variety of results obtained by methods comparable to those employed in this instance, which, without artifice, have supplied the background for the differentiation of "normal" from "abnormal" results. Finally it should be said, that the comparison of a series of samples of urine of small volume, with samples of

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large volume from the same individuals, shows the former to be somewhat more widely variable at both ends of the spectrum, i.e., the small samples make a wider universe, but there is little difference, otherwise, in the distribution and the statistical characteristics of the two sets of results. For the purposes of this investigation the lower incidence of contamination of small samples collected under supervision and instruction, greatly outweighs the advantage which might otherwise be gained from samples of large volume, while the *variances of variability* in the case of individual samples are blotted out by resort to multiple samples just the same as is done by numbers of individual samples obtained from reasonably homogeneous groups of persons.

Summary

The principal facts obtained in this investigation, as carried out thus far, are summarized under the two main headings indicative of the dual character of the investigative approach.

1. Lead in the air at the occupational sites.

(a) The highest levels of concentration of tetramethyllead are

being encountered in the areas in which the antiknock compound is mixed with gasoline, at the domes of tank cars, ^{which the original lead} ~~when first opened~~. ^{transition to the minimum, when these domes are first opened.} Occasional concentrations up to 35 micrograms per cubic foot were found. This situation is fleeting, and it involves no necessary or likely exposure of the operators at these sites. The average levels of concentration at these points in the blending areas in the vicinity of Los Angeles and San Francisco, respectively, were 5.44 and 1.53 micrograms of lead per cubic foot of air. The lead in the air at other locations in the blending areas averaged less than 2 micrograms per cubic foot.

(b) The levels of lead concentration in the ^{at the filling} ~~air at~~ filling stations averaged 0.132 microgram per cubic foot of air in Los Angeles, and 0.26 microgram per cubic foot in San Francisco. The higher level of concentration in San Francisco derives from the relative nearness of the sampling apparatus to the tanks of the cars during their filling. In consonance with this factor, approximately 55 per cent of the total lead in the air at filling stations in San Francisco was organic lead; in Los Angeles, the

organic lead approximated but 35 per cent of the total lead in the

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air at the filling stations.

(c) Samples of particulate matter collected in central

commercial sections of the two cities contained average quantities

of lead amounting to 5.3 micrograms per cubic meter of air in

Los Angeles, and 1.9 micrograms per cubic meter in San Francisco.

These levels are somewhat lower than those reported in investigations carried out in both cities during 1954.

2. The significance of the occupational exposure of the personnel.
~~approach.~~

(a) Groups of individuals engaged in the several occupations

involved in the preparation and distribution of gasoline containing

tetramethyllead as an antiknock compound, failed to give any

evidence of their absorption of lead in the course of their regular

performance of their duties over a period approximating nine months.

(The response to occupational exposure to lead in even low and

hygienically insignificant levels of severity occurs promptly in

the form of an increase in the concentration and output of lead

in the urine. The failure of such a response is indicative of

a negligible degree of exposure.)

(b) The numbers of persons engaged in certain of the occupational

groups was too small to provide data for statistical treatment. 45

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that comparisons must be made of the ^{individual} findings, ~~on the~~

~~individuals~~. In no instance was there a progressive increase

~~(or any increase)~~ beyond the level of strictly normal variability) in the concentration

of lead in the urine of ~~an individual member~~ / ~~these small groups~~.

(c) The statistical comparison of the levels of lead concentration

in the urine of the two groups of service station attendants

(in San Francisco and Los Angeles) ^{found out} ~~revealed~~ certain inconsistent

differences. These differences, while of statistically significant

magnitude in some instances, cannot be regarded as of physiological

significance in relation to the hygienic question under investigation,

because of their erratic occurrence in time. Moreover, all of the

differences noted are within the range of normal or incidental

variability, and, therefore, ~~they~~ must be accepted as being

within the range of ^{the} deviation ^{associated with} of the general methods of investigation.

(e) The statistical comparison of the data obtained at the three

stages of the investigation from each of the two groups of filling

station attendants also reveals certain differences within the

individual groups. These differences have the same characteristics

as those referred to above, and, therefore, are of no significance

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Conclusions
Summary and Conclusions

The results of the surveillance of the industrial and commercial activities associated with the handling of an antiknock compound containing tetramethyl lead in a petroleum refinery and with the distribution of gasoline containing this compound of lead, as carried out over a period approximating nine months, ^{have been summarized above.} ~~are summarized briefly below.~~ These results coincide with those of an earlier and less prolonged investigation of this problem, in demonstrating that the exposure to lead, specifically to tetramethyl lead, under the conditions which ~~prevail~~ prevail in association with these activities, is negligible. The quantities of lead which escape into the atmosphere during the performance of the relevant operations are small, and the contamination of the atmosphere therewith is intermittent and is regarded as of insignificant proportions in terms of occupational hazard. ~~This view~~ the insignificance of the occupational exposure to lead is fully confirmed by the lack of any evidence of the absorption of lead by the persons who have been engaged in the performance of the various operations. No individual in any of the categories of employment represented in this survey has manifested any physiological response to the environmental conditions of his work in the form of a demonstrable increase in the rate or magnitude of ^{the} ~~this~~ excretion of lead in his urine. Inasmuch as such a response can be

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of occupational exposure to lead in any form, the non-occurrence of such exposure in these relationships is clearly evident.

~~The facts in support of this general statement were summarized~~

~~under two headings:~~

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