SUMMARY OF PRELIMINARY TOXICOLOGIC INVESTIGATION OF THE LEAD ALKYLS

The toxicologic behavior of tetramethyl lead and certain of the other lead alkyls was investigated at The Kettering Laboratory some years ago. Although these studies were limited in scope the information obtained has been reviewed and constitutes the subject of this report.

For the most part, rabbits were employed as the experimental animals in these investigations, which consisted primarily of attempts to obtain information as to the lethal dosages of tetramethyl lead, dimethyl-diethyl lead, trimethyl-ethyl lead, triethyl-methyl lead and a mixture containing tetraethyl lead and the other alkyls in definite proportion. In order to point up possible differences in the toxic responses induced by tetramethyl lead and tetraethyl lead, comparisons with the latter material have been made so far as data were available. Certain of the chemical properties of these materials are listed in Table 1.

SUMMARY OF INVESTIGATION AND RESULTS

The investigation of tetramethyl lead included observations of the toxic manifestations resulting from its administration to rabbits intravenously, subcutaneously, orally, upon the intact skin, and by inhalation; determination of the approximate lethal dosages by each

route of administration, as compared to tetraethyl lead; analytical determinations of the distribution of lead in the blood and body tissues, at various intervals after the administration of the compound; and, demonstration of the pertinent gross pathologic changes produced in the body tissues. Similar observations were made with the other alkyls except that the intravenous and subcutaneous routes of administration were omitted.

The data relative to the lethal dosages, as summarized in Table 1, suggest that there are certain differences in the toxicologic behavior of tetraethyl lead and tetramethyl lead, which can be accounted for in part (but not entirely) by differences in their chemical composition. It will be noted that, when the two compounds are introduced directly into the blood stream of rabbits, deaths occur at a lower dosage of tetraethyl lead than of tetramethyl lead. The gross pathologic lesions (multiple infarction in the lungs) of the animals injected intravenously with tetraethyl lead indicate that the early deaths were the result of the immiscibility of the compound with blood. Conversely, when these two materials (TEL and TML) were administered subcutaneously (as a 20 per cent solution in almond oil), tetramethyl lead appeared the more toxic, a reversal of the relationship noted after intravenous administration.

The results obtained, following the oral administration of tetraethyl lead and tetramethyl lead, reveal another striking difference, which deserves comment. Tetramethyl lead administered orally, was lethal at one-half the lethal intravenous dose, e.g., it was twice as

toxic, via the oral route. On the other hand TEL was found to be less lethal, when administered orally, than intravenously, a phenomenon which may be explained in part on the basis of its immiscibility with blood, as noted above.*

Observations made following the application of the several compounds upon the intact skin of rabbits demonstrated highly divergent results. Whereas the lethal effect of the application of tetraethyl lead upon the skin of the rabbit was evident and uniform at a suitable dosage (750 mg./Pb per kilogram), no fatalities were produced by tetramethyl lead under comparable or even much more severe conditions, i.e., contact of the skin of the rabbit with as much as 7000 mg./Pb per kilogram, for periods up to 3 hours. This discrepancy can be explained, in part, at least, by the high volatility of tetramethyl lead, whereby the quantity on the skin decreases progressively following its application. Support for this opinion is provided by the fact that 500 mg./Pb per kilogram (as TML) applied under a glass cell cemented to the skin produced illness which was followed by slow recovery. It would seem that this dose (500 mg./Pb per liter for 1 hour) is not far from the lethal range when the liquid is confined to prevent its becoming volatilized.

The inhalation for 1 hour of pure tetramethyl lead, in air, under

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* This is not the entire explanation, for the earlier observations on tetraethyl lead demonstrated its appreciably greater toxicity when administered intravenously, than when given orally, even under conditions (in emulsion) which eliminated pulmonary infarction. It was evident that the absorption of tetraethyl lead from the alimentary tract was comparatively slow and incomplete.

conditions in which 4.5 mg./Pb per liter (as TML) were delivered into the respiratory chamber (after this concentration had been achieved) produced deaths, whereas the concentration of 2.3 mg./Pb per liter, delivered similarly, was not lethal. Exactly comparable experiments with tetraethyl lead are not available, and strictly parallel experiments will have to be carried out in order to make satisfactory comparison. The available information, which is neither sufficiently precise nor sufficiently definitive of the minimum lethal concentration, in relation to specific periods of exposure, indicates that the concentration of tetraethyl lead which is lethal, following 1 hour of exposure, is lower than that of tetramethyl lead.

When deaths occurred from 12 hours to 7 days after the administration of tetramethyl lead by any route, analyses of the tissues demonstrated quantities of lead of the same general order of magnitude, and distributed in the tissues in much the same manner, as those found previously, following the administration of tetraethyl lead. Liver, kidneys, bone and brain consistently showed the highest concentrations of lead. When deaths occurred within the first 24 hours, the levels of lead concentration in the blood and blood-containing organs (heart, spleen, kidneys) were elevated well above normal values.

The most consistent features of the illness which followed the absorption of tetramethyl lead were weakness, diarrhea, weight loss, irritability, tremors and convulsions. Pathologic findings included congestion of lungs, liver, brain and kidneys, in most instances, regardless of the route of administration.

It can be seen from Table 2 that, following the oral administration of the individual lead alkyls and of the mixture of all of them, the lethal dosages were of the same approximate order of magnitude (in mg.of Pb per kilogram) as that of tetramethyl lead. Comparison of the lethal dosages of the several compounds applied upon the intact skin, suggests that there is a close resemblance between trimethyl-ethyl lead and tetramethyl lead, in that respect, in all likelihood because of their similar volatility. The percutaneous absorption of dimethyl-diethyl lead, triethyl-methyl lead and the mixture of the alkyls produced deaths only when the dosages applied upon the skin were increased two to three times higher than that of tetraethyl lead. The triethyl-methyl derivative, as well as the mixed alkyls, were lethal, following 1 hour of exposure to air containing approximately 4.0 mg./Pb per liter. Trimethyl-ethyl lead was lethal at approximately one-half of that concentration (2.0 mg./Pb per liter).

When deaths resulted from the administration of these compounds, analyses of the tissues demonstrated the presence of lead in quantities, and in manner of distribution generally comparable to those found following the administration of tetramethyl lead. The gross pathological changes induced by the absorption of the various methyl-ethyl derivatives, and the mixture thereof, were of generally similar type. A much more detailed analytical investigation of the tissues of animals subjected to various experimental conditions with respect to compound, dosage and interval of time after the administration of the compound, in a specific manner, would be required to disclose any significant

consistent differences in the extent and the pattern of distribution of the organic lead compounds and their metabolic (degradation) products. These matters will require further investigation if justification is afforded for such further investigation by the technological or commercial utilization of these compounds.

From The Kettering Laboratory in the Department of Preventive Medicine and Industrial Health, College of Medicine, University of Cincinnati, Cincinnati, Ohio.

Experimental Work by:

Willard F. Machle, M.D.
1935,1936,1937

Report by:

Albert A. Brust, M.D.

Approved Robert A. Kehoe
Robert A. Kehoe, M. D.
Director

Date: June 18, 1959

Table 1

Compound	Formula	Density	Per Cent Lead	p-25°C
Tetraethyl lead	$(C_2H_5)_4Pb$	1.66	64.0	0.5
Tetramethyl lead	$(CH_3)_4Pb$	1.99	77.5	30.0
Trimethyl-ethyl lead	$(CH_3)_3(C_2H_5)Pb$	1.88	73.7	10.0
Dimethyl-diethyl lead	$(CH_3)_2(C_2H_5)_2Pb$	1.79	70.2	3.0
Triethyl-methyl lead	$(CH_3)(C_2H_5)_3Pb$	1.71	67.0	1.0
Alkyl Mixture*		1.795	67.0	6.2

*This mixture contained the following amounts of the lead alkyls (expressed in moles per cent): tetraethyl 5.4; tetramethyl 7.5; trimethyl-ethyl 24.0; dimethyl-diethyl 35.5 and triethyl-methyl 27.6

Lethal Dosages of the Lead Alkyls Following Their
Administration to Rabbits

Compound	I.V. (mg.Pb/kg.)		Subcut. (mg.Pb/kg.)		Oral (mg.Pb/kg.)		Cutane Applica (mg.Pb/
	Not Lethal	Lethal	Not Lethal	Lethal	Not Lethal	Lethal	Not Lethal
Tetraethyl lead							
20% in almond oil	15	17	250	(1)	-	-	-
pure compound	-	20(4)			20	40	500(3)
Tetramethyl lead							
20% in almond oil	30	40	50	70	-	-	-
pure compound	30	(1)	-	-	10	20	7000 500(3)(5
Trimethyl-ethyl lead	-	-	-	-	10	15	2100(1 hr
Dimethyl-diethyl lead	-	-	-	-	7	10	1200
Triethyl-methyl lead	-	-	-	-	15	20	700(1 hr
Alkyl Mixture	-	-	-	-	20	25	1700

(1) Not carried to lethal level.
(2) Comparable information not obtained.
(3) Contained in glass cell cemented to skin; duration of exposure 1 hour.
(4) Deaths accompanied by embolism, not necessarily associated with, or indepen
(5) Animal became ill but survived.