SECRET

MEMORANDUM ON THE LEAD ALKYL COMPOUNDS

The compounds in this series that have been studied with respect to their toxicity consist of lead tetra ethyl, lead tetra methyl and the tri, di, and mono configurations of these two radicals. The formulae, the densities, and per cent of composition of lead in the molecule, the vapor pressure at 25° C, and the toxicities of these compounds administered orally upon the skin are given in the table below. The data on oral toxicity demonstrate that these compounds have a toxicity of the same order of magnitude, varying to some degree probably in accordance with their ease of absorption from the alimentary tract; with the exception of tetra methyl, they are absorbed through the skin to such a degree as to produce fatalities. For some reason which is not clear, tetra methyl is absorbed only slightly and not in sufficient dosage to cause fatalities in experimental animals. This is not the consequence purely of its volatility, since its application to the skin even under conditions that have prevented volatilization have not produced acute illness and death.

From the point of view of inhalation, the lethal concentration of lead tetra ethyl for 12 to 18 hours of exposure is of the order of magnitude of 0.12 mgs. (expressed in terms of lead) per liter in air. Concentrations of much lesser magnitude of lead tetra ethyl will produce fatal results on prolonged exposure. A concentration approximating 0.18mgs. per liter will produce fatal results after three exposures of 6 hours per

day on successive days. (Experimental animal here is the rabbit.)

The study of inhalation exposures in the case of the other compounds has been limited, but the indications are that they are all of the same order of toxicity when the concentration is expressed in terms of lead. (Pb)

From this fact alone one would assume that the toxicity of these compounds is referrable to their content of lead. However, other experimental evidence justifies this conclusion still more strongly. In particular, the distribution of lead in the organs in acute intoxication is that of a fat soluble compound. High concentrations are found in the brain, liver, muscle, and fatty depots, with negligible quantities in the skeleton. The concentration in the brain which coincides with fatal poisoning is of the same general order of magnitude, regardless of the compound employed. (Reference here is made only to the compounds listed in the first sentence, since these are the only ones in the alkyl series that have been investigated.)

These organic lead compounds are decomposed in the body, the first result of this decomposition being that volatile lead compounds can no longer be reclaimed from the tissues after a few hours following their administration. A further decomposition takes place as shown by the fact that within about 14 days of the administration of a sublethal dose the distribution of lead in the tissue corresponds to that of water soluble lead compounds rather than to that characteristic of tetraethyl lead.

The clinical picture of tetraethyl lead intoxication, as well as that produced by the other compounds mentioned previously, is that of an acute central nervous system intoxication

with hyperreflexia and agitation, which progresses into convulsions and coma. This picture can best be described in terms of the fatal human cases of poisoning. In such cases the clinical picture is the same substantially, regardless of the length of time required in terms of exposure to produce toxic concentrations in the body. Even in those cases in which exposure to small concentrations has occurred over a period of months, the clinical picture has been the same. Chronic lead poisoning has never been seen in association with exposure to these organic lead compounds. No microscopic changes occur in the cellular elements of the blood. That is to say, there is no stippling, no anemia, and no evidence of disturbance of the bone marrow. The intoxicated individual develops mental abberations characterized by a dream-like state with wild representations, confusion, personality distortions, and hallucinosis. As the intoxication develops, the confusion increases and the state of acute mania may ensue, followed by convulsions, exhaustion, coma, and death. In mild cases the mental symptoms predominate and may develop and disappear without the more serious manifestations of chemical intoxication. Even in the most acute cases the evidences of organic intoxication are limited largely to circulatory manifestations in which there is a very low systolic and diastolic blood pressure, slow pulse and hypopyrexia.

Following exposure there is a long lag in the appearance of symptoms. Varying with the dosage this lag varies from 24 hours to 7 or 8 days. By reason of this lag in relation to an incident of exposure and by reason of the bizarre clinical picture,

the diagnosis of lead poisoning has never been made by any physician who has not had first-hand experience previously.

From the point of view of chemical warfare tactics, insofar as the writer has any familiarity with previous concepts, it would seem that this group of compounds offers little or no promise. From the point of view of dosage, large quantities of material would be required to produce an effect. Moreover, the time lag between exposure and the induction of symptoms is so great that disability would be greatly delayed. It is apparent that if effective concentrations could be obtained and maintained in a combat area, a very considerable amount of incapacitation of sizable numbers of men would be brought about. However, the quantities of material that would be required to produce this situation would be very great indeed.

No experience has been had with the higher homologues of the compounds referred to in this memorandum. Actually such compounds as have been synthesized even in small quantities, have merely been the subject of scientific curiosity with respect to their physical and chemical properties. No commercial uses have been found for them, and therefore no effort has been expended on studies of their toxicity and mode of action. Judging from the facts available, one would assume that the toxicity of such homologues would be of the same order of magnitude as those that have been investigated, and that their properties as chemical warfare agents would be less rather than more satisfactory.

The reference above to the quantities required to produce an effect is considered in a relative sense. Obviously,

the less material that has to be handled the more effective should be the results, all other factors being similar. In this connection the extremely high toxicity of ricin comes to mind, in that only the lowest concentrations of this material need be available to produce prompt and highly dramatic effects. As compared with such a material lead tetra ethyl and its homologues must be regarded as very tame substances.

Robert A. Kehoe, M.D.

December 12, 1944

Toxicity and Certain Properties of Alkyl Lead Compoun

Compound	Density	Lead Content Percent	Mm. Hg. at 25°C	Approximate M.L.D. in mgm/Kg as Pb				Sa indef
				Intrav.	Sub.q.	Oral	Percutaneous	
d tetraethyl	1.66	64.0	0.5	17.0 rabbit	70.0 rabbit	40 to 110* rabbit	750 rabbit	0.2 p
d tetramethyl	1.99	77.5	30.0	40	65-70 rabbit	20 rabbit	not absorbed with fatal results	
dimethyl-diethyl	1.79	70.2	3.0			10 rabbit	150 rabbit	
trimethyl-ethyl	1.88	73.7	10.0			15 rabbit	210 rabbit	
triethyl-methyl	1.71	67.0	1.0			25 rabbit	150 rabbit	

ion apparently result of carrier.

Toxicity and Certain Properties of Alkyl Lead Compounds

ity	Lead Content Percent	Mm. Hg. at 25°C	Approximate M.L.D. in mgm/Kg as Pb				Concentrat	
			Intrav.	Sub.q.	Oral	Percutaneous	Safe for indefinite time	Lethal
66	64.0	0.5	17.0 rabbit	70.0 rabbit	40 to 110* rabbit	750 rabbit	0.2 per cu.m.	
99	77.5	30.0	40	65-70 rabbit	20 rabbit	not absorbed with fatal results		4.5 pe rab
79	70.2	3.0			10 rabbit	150 rabbit		
88	73.7	10.0			15 rabbit	210 rabbit		
71	67.0	1.0			25 rabbit	150 rabbit		

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d tetraethyl	1.66	64.0	0.5	17.0 rabbit	70.0 rabbit	40 to 110* rabbit	750 rabbit	0.2
tetramethyl	1.99	77.5	30.0	40	65-70 rabbit	20 rabbit	not absorbed with fatal results	
d dimethyl-diethyl	1.79	70.2	3.0			10 rabbit	150 rabbit	
d trimethyl-ethyl	1.88	73.7	10.0			15 rabbit	210 rabbit	
d triethyl-methyl	1.71	67.0	1.0			25 rabbit	150 rabbit	

Variation apparently result of carrier.

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