Lead Alkyls

Report, 1960-1961

During the past year, two papers touching on the organolead ions have been noted that may have some application in biological work. These are the papers of Snyder and Henderson on the determination of lead in air and in antiknock blends by the dithizone reaction (Analytical Chemistry 33: 1172-80, Aug., 1961).

We have just submitted for publication a brief communication on the solubility of tetraethyllead (TEL) in water. About 0.25 mgm. of TEL dissolves in a liter of water at 0° to 40° C., a rather low solubility. By way of comparison, it may be noted that TEL is only ten times more soluble than metallic mercury (estimate of Walter Hughes, 1957). Our values will be the first to be published; the solubilities privately reported in the literature of Ethyl Corporation are 50 to 60 times as great. The measured aqueous solubility emphasizes the probability that TEL will associate with lipid materials in the body. Consideration of Hildebrand's solubility parameters suggests that some sterols may closely resemble TEL in solubility, but other factors as well as solubility are doubtless important in determining the distribution of TEL among tissues and cellular components.

If TEL is to be eliminated as such from the body, it will probably be dissolved in lipid, e.g., via the intestinal tract in mineral oil.

If TEL is not eliminated as such from the body, it is decomposed. The first decomposition product we have identified as being formed in vivo is the triethyllead ion. This is formed exclusively in the liver, presumably in the microsomes of the liver cells, according to Cremer (1959). Perhaps the diethyllead ion is also formed, but of this there is little evidence as yet. The organolead ions must be formed as complexes with chemical groups presently unidentified. Because the organolead ions are capable of combining more firmly than TEL with bodily constituents, and because they are formed from TEL to a rather large extent, and because they persist in the body for days after their formation, and because, although formed in one organ, they are transported throughout the body and thus affect other organs, these ions warrant our attention.

Because the organolead ions are presumably brought into existence as complexes in the cells, and because they probably exist in the body in combinations somewhat resembling those of the inorganic lead ions, and because they may be expected to exert their influences on bodily functions through their combinations with various chemical groups, it is important to determine the affinities of these ions for the various chemically functional groups with which they may come into contact in the body. In other words, the stability constants of the organolead ions with various ligands are of

concern in discovering what happens to TEL in the body. The stability constants of such complexes are far from being the sole determinants of the fate of the organolead ions in the body, as considerations of solubility, molecular shape and other properties will at once suggest. Study of the complexes may, nevertheless, be important in suggesting likely alternatives concerning the sites of action of the organolead ions in cellular metabolism, the mechanisms of transport of the organolead ions into and out of cells and in the blood stream, the kinds of reagents that may be useful in detecting, and in extracting the organolead ions from tissues, and the ligands that may decrease the toxicity of the organoleads.

One group of complexes of the organolead ions with which we have worked is the group of dithizone complexes, as our publications have recorded. The analytical work we have done with the dithizonates has been based upon spectrophotometry. From this experience and from observing that a number of the complexes of inorganic lead have been the subject of spectrophotometry over the past thirty years, we began our work on the organolead complexes with spectrophotometric observations. Spectra of a number of organolead complexes were obtained. Gradually, it became evident that these spectra, obtained on the Beckman DK instrument, were unreliable. We changed to the Cary instrument, in the Chemistry Department. Although reliability was increased, the relative inaccessibility of the instrument and various problems of technic that had at first seemed

unimportant, together with an increasing realization of some of the limitations of the methodology (confirmed in the literature, e.g., on page 50 of Rossotti and Rossotti's book, 1961), led us to turn from spectrophotometry to the potentiometric measurement of the stability constants in complex formation, as a way of approach.

The potentiometric measurements show clearly the existence of complexes of the organolead ions in aqueous solutions at body temperature. In general, the diethyllead ion forms stronger combinations with ligands than does the triethyllead ion; of the three ions, the inorganic lead ion forms, so far as we have determined, the strongest, most stable complexes. The strongest complex we have observed is that of EDTA (Versene, ethylenediamine tetra-acetic acid) with inorganic lead. EDTA also complexes with the diethyllead ion, contrary to published report, but a complex of the triethyllead ion with EDTA is barely detectable by the technic we have used. These observations not only suggest why EDTA may fail to counteract the toxicity of triethyllead (as reported for slices of brain, by Cremer) but indicate that the analogy between the organolead ions and inorganic lead may be pushed too far. In EDTA, the complexing groups are the carbonyl groups and the nitrogen atoms. We have examined the complexing strength of these groups in other molecules, e.g., acetate, benzoate, aminoacetate. And we have examined molecules containing other types of groups, e.g., thiols, phenolic

hydroxyls, phosphates, singly and in various combinations. The thiols are, next to EDTA, the strongest complexers we have noted.

In one of these thiols, BAL, we encountered impurities that seriously interfered with our measurements. At least one of these impurities, trithiopropane, was recently found (J. Am. Pharm. A., 1960) to be responsible for undue toxicity in BAL. With the analytical division, we are currently endeavoring to see if the methods of gas chromatography can be used to determining the impurities in BAL, as an aid in preparing BAL for our measurements.

We have supplied triethyllead chloride and other ionic organolead compounds that we have synthesized to others in the laboratory.

At present, we are continuing to explore the chemistry of the complexes of the organolead ions and of inorganic ions.

As before, my research in cancer is continuing; a paper on this was published in Experimental Cell Research 20: 645-50 (1960).

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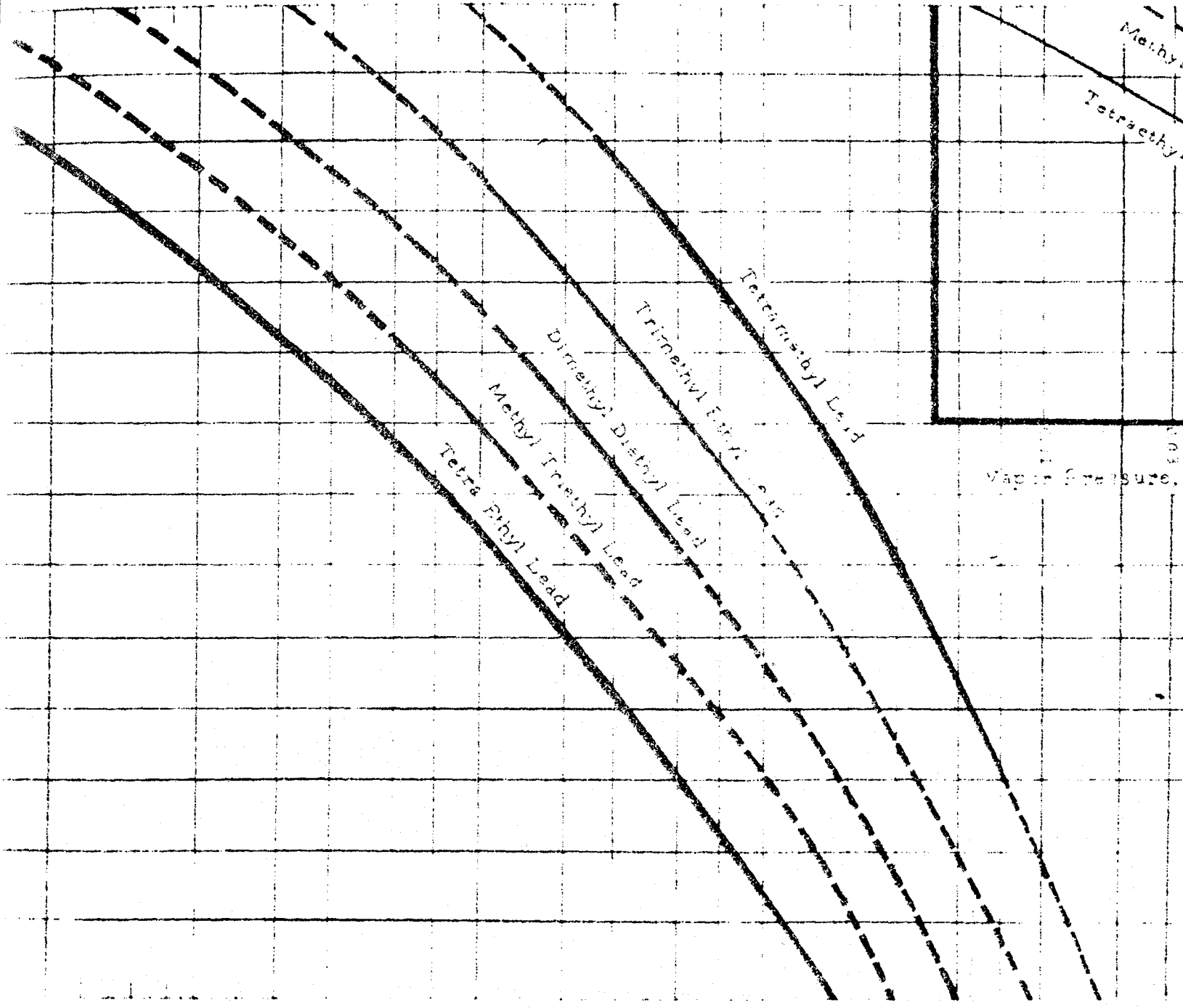
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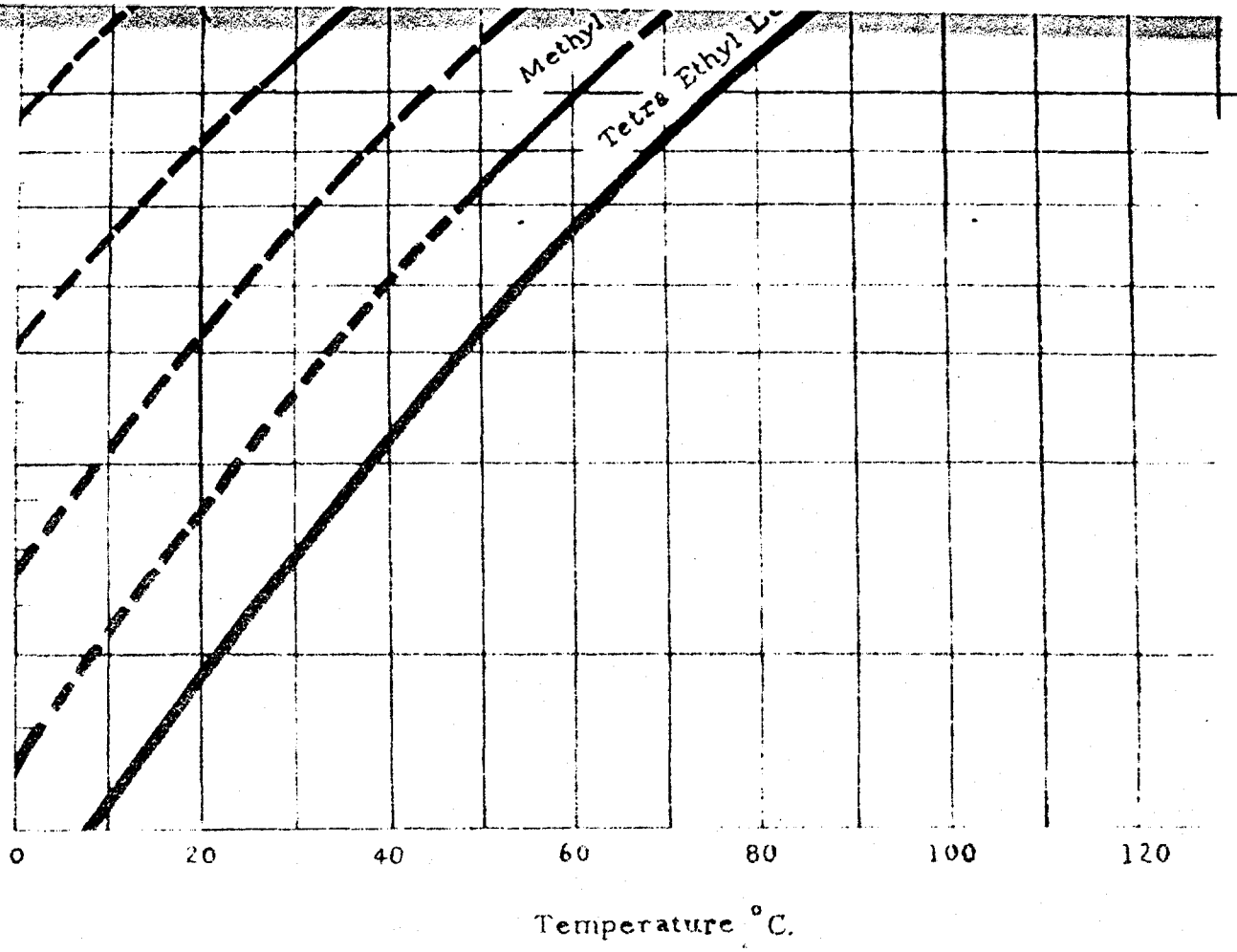

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