What happens to tetraethyllead (TEL) in the body ?

Report of progress, 1953-58

The work during these years has been concerned primarily with devising analytical methods for the detection of TEL and of triethyllead ion and of diethyllead ion in tissues. These methods have been applied to animals exposed to TEL. Fairly conclusive evidence was obtained of the presence in liver of TEL after its inhalation. This was published in the Journal of Pharmacology and Experimental Therapeutics in 1956. Development of methods for the ethyllead ions followed. Triethyllead ion was first sought and was found in extracts of livers removed from intoxicated animals a day after they had inhaled TEL. Diethyllead ion was then sought. It was not detected in the livers of animals similarly exposed and killed. However, triethyllead ion was again found, and this by a technic of isolation rather different from that used in the earlier identification. This is the point now reached in the main line of this work.

Publication of the work on the detection of TEL has been made as noted above. A manuscript intended for publication of the work on the ethyllead ions is being prepared. These two papers cannot, of course, incorporate most of the ancillary observations that have been made. These include data on: solubility of TEL in water, persistence of TEL in vivo for several days, preparation of pure ethyllead derivatives, methods of extraction of triethyllead ion as chloride, as benzoate and as dithizonate, methods of extraction of diethyllead ion as benzoate and as dithizonate, spectra of several ethyllead compounds in various solvents, their solubilities, formation of chelates and their solubilities and spectra, stabilities of various of these ethyllead compounds in several solvents, behavior of ethyllead ions in various extraction procedures, failure of TEL to affect myoneural transmission and cholinesterase, etc. This material has been detailed in my weekly and annual summaries of the work.

KF 0003446

The work ahead, beyond completion of the material intended for our next publication, might be aimed in any of several directions, for example:

(1) to detect diethyllead ions in tissue at lower concentrations than present methods will detect,

(2) to discover in what chemical combinations triethyllead and diethyllead ions are held in tissues and in excreta,

(3) to discover which, if any, enzymes are involved in decomposition of TEL in the body,

(4) to develop methods for separate measurement of TEL, of triethyllead ion and of diethyllead ion in urine, blood, tissues, etc.,

(5) to measure rates of formation of triethyllead ion and of diethyllead ion (if formed) from TEL in organisms,

(6) to measure rates of excretion of TEL, of triethyllead ion and of diethyllead ion (if formed) in bile, urine, feces, etc.,

(7) to determine where triethyllead ion and diethyllead ion (if formed) are formed in the body and in cells, what their distributions among tissues are, and how rapidly they are formed and decomposed, or otherwise eliminated,

(8) to search for the factors that may be important in influencing any of the above processes or phenomena.

In more general terms, the work is: (a) to detect, (b) to discover products of, (c) to determine, (d) to measure rates of metabolism of, and (e) to establish enzymatic or other mechanisms of metabolism of TEL and of each of its decomposition products in the various regions of the body (excreta, organs, tissues, cell fractions, molecular constituents).

KE 0003447

To exemplify in more detail what each of the eight suggestions listed above might involve, consider the first one: detection of diethyllead ions at lower concentrations in tissue. This might be undertaken by methods of analytical chemistry or by histochemical technics. Methods of analytical chemistry thus far employed have been limited by the inefficiency of methods currently used for following diethyllead ion through the extraction and isolation procedures needed. More specifically, difficulties arise from:

(a) sensitivity of infrared equipment on hand in this laboratory,

(b) lack of specificity of the dithizone reaction for diethyllead,

(c) instability of diethyllead dithizonate,

(d) firmness of attachment of diethyllead ion to tissue, making extraction difficult and incomplete,

(e) paucity of information on the chemistry of the organolead ions.

Attempts to surmount these difficulties might be made in various ways, e.g.:

(a) Micro absorption cells and adapters for the infrared spectrometer could be obtained. They should increase the sensitivity of detection by several fold.

(b) Countercurrent distribution studies, including chromatography, might lead to practical technics for separation of the various dithizonates from each other. The absorption bands of the dithizonates might be sufficiently sharpened at low temperatures and in particular solvents to make the differentiation of diethyllead dithizonate possible. Or, synthesis of dithizones carrying various substituents on the aromatic ring might yield reagents which would prove more useful for the differentiation of the ethyllead and inorganic lead ions.

(c) Systematic investigation of diethyllead dithizonate in various solvent systems under various conditions might indicate the causes of its instability and, possibly, ways of avoiding them. Greater stability might be found in substituted dithizonates such as those suggested above.

KE0003448

This expectation follows from observation of the great differences in stability of various salts of diethyllead such as the benzoate, the bromide and the dithizonate.

(d) A more intensive investigation of the extraction of diethyllead ion from tissues might include the use of various solvents in conjunction with a variety of chelating and complexing agents, i.e., an extension of one facet of the work in which we have already made some effort.

(e) Preparation and study of diethyllead and triethyllead complexes, including salts, might be undertaken systematically to provide data of possible use in the analytical problems. The fact that only 27 salts of diethyllead have ever been reported suggests the need for basic data.

Many other approaches might also be suggested, e.g., the use of isotopically labelled C, H, and Pb atoms in the diethyllead. This could make its detection and measurement in tissue fractions and extracts more certain than present methods permit.

No one has attempted to detect any ethyllead ions histochemically, to my knowledge. They do form insoluble sulfides, as does inorganic lead, but whether these might prove as useful in histochemistry as lead sulfide can scarcely be anticipated from the scant information now available. Diethyllead chromate has apparently never been prepared, - lead chromate being the analogous inorganic salt used in histochemistry.

It is possible, of course, that diethyllead is formed in larger quantities at a later stage in the intoxication by TEL. We have limited our work with few exceptions to tissues removed one day after inhalation of TEL; the animals were all suffering with marked tremors at that time.

KE 0003449