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February 8, 1966

To: All Members of the LIA-ILZRO Lead Health and Safety Committee

Attached is a copy of a paper written at our request by Dr. Haley and designed to be published in the AMA Archives of Environmental Health. I would be most interested in having your reactions, comments, and criticisms of the work. You will remember that several people at our recent Committee meeting expressed interest in seeing this paper.

Very truly yours,

Don C. Fowler

DCF:sw
attachment

A TOXICOLOGIST'S VIEWPOINT ON SUPPOSED CHRONIC LEAD INTOXICATION FROM ENVIRONMENTAL CONTAMINATION

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This article was supported by Contract AT(04-1) GEN-12 between the Atomic Energy Commission and the University of California.

INTRODUCTION

Recently a geochemist has suggested that the people of the United States are being subjected to chronic lead insult from industrial sources with the result that there are functional shifts in higher nervous activity. (1) He also stated that the lead levels in the literature should be set aside. This does not make sense to the toxicologist so it is necessary to reevaluate the past and current use of lead in the United States; the sources of the lead entering the human body; the metabolism of lead including lead balance of the body; the manner in which bone seekers (such as lead, strontium, etc.) are discriminated against by physiological mechanisms and last, but by no means least, the overall toxicology of lead.

USES OF LEAD

Examination of the total uses of lead for the periods of 1925 to 1929, 1952 to 1956 and the years 1960 to 1964 inclusive reveals only a slight increase in consumption of lead in the United States (Fig. 1). Such applications as ammunition, bearing metals, solder, casting metals, weights and ballast and so forth have seen slight fluctuation and, in some cases, actual decrease in total yearly usage of lead. Figure 1 shows the actual decrease in the use of lead pigments and building materials, i.e., lead pipe. These changes have been brought about by the development of substitutes such as titanium pigments and copper or galvanized as well as plastic pipes. By far the greatest increases in the uses of lead have occurred in storage batteries and lead alkyl gasoline anti-knock compounds. Thus, although large amounts of lead continue to be used, those applications, i.e., paints and plumbing, which were involved in inadvertant toxicity in the past have been almost eliminated at the present time. Decreases in the use of lead-containing insecticides have also occurred as a result of the introduction of the chlorinated hydrocarbons and phosphate insecticides. Lead insecticides utilized in 1930 were 6000 short tons, in 1944 were 25,957 short tons and in 1959 so low that definite figures were not given (2).

ANTI-KNOCK LEAD ALKYLS

In view of the increase in usage of lead alkyls and their indictment as a general cause of chronic lead insult to the general population (1) it is now necessary to examine the overall picture in more detail. Figure 1 shows the increase in lead alkyl usage for the years 1925 to 1964 inclusive and this reflects the increase in application of the automobile as the principal means of transportation in the United States. The prime question is not the increased burning of lead alkyls by the internal combustion engine with the subsequent release of lead compounds into the air but the type of compounds released, the area of release, the particle size and solubility of these compounds and their overall availability to the public. Hirschler et al (3) have shown that tetraethyl lead decomposes into $PbCl{\cdot}Br$, $\alpha\text{-}NH_4Cl{\cdot}2PbCl{\cdot}Br$, $\beta\text{-}NH_4Cl{\cdot}PbCl{\cdot}Br$, $2NH_4Cl{\cdot}PbCl{\cdot}Br$, $PbSO_4$, $PbO{\cdot}PbCl{\cdot}Br$, H_2O and in the presence of phosphate additives $Pb_3(PO_4)_2{\cdot}PbCl{\cdot}Br$. However, the distribution of the various compounds depends on both the automobile and its method of operation.

A mixture composed of the ammonium-lead-halide complexes appears predominantly under city driving conditions; whereas Pb·Cl·Br appears at full-throttle accelerations. Moreover, the former complexes are most often formed in dual-exhaust systems which operate at lower temperatures. Comparison of clean versus dirty exhaust systems indicates that the former emits 20 per cent of the lead burned while the latter emits up to 60 per cent. Severe service tends to clean the exhaust system. The range of particle sizes emitted range from 0.01 micron to several millimeters in diameter with those smaller than 1 micron, although more numerous, accounting for only 5 per cent of the emitted lead. City-type driving results in the emission of 27 per cent of the lead as particles 5 microns and larger while acceleration increases this emission to 39 per cent. The particle size distribution and composition are independent of the amount of lead alkyl in the gasoline. The inorganic compounds under discussion are relatively insoluble and the ammonium-lead-halide so unstable that even the water in the exhaust gases can cause it to decompose to more of the inorganic lead compounds. It is well known that the larger particles, above 5 microns, have a tendency to settle rapidly and those that are inhaled are trapped in the external nares. Particles in the lower size ranges are removed by two mechanisms: entrapment in the bronchcolar mucous secretion as a result of centrifugal action produced when the air stream reaches the various bronchcolar bifurcations and direct precipitation on the mucous secretions. In both cases ciliary action removes the particles from the lungs and allows them to be expectorated or swallowed and excreted via the gastro-intestinal tract. The particles below 1 micron can reach the depths of the alveoli and be absorbed directly or phagocytized by the tissue macrophages. In either event the total amount absorbed via the lungs is only a small proportion of the daily lead intake compared to that absorbed from food and water.

BODY LEAD CONTENT

In discussing automobile exhaust, it becomes quite apparent that the lead compounds released are rather insoluble and thus can only be small contributors to the lead content of the body. Only 0.03 mg of the daily lead intake comes via air-borne material; whereas food and liquid intake contribute 0.3 mg to the total lead intake of 0.33 mg (4). Kehoe (5) has shown that almost every food stuff and beverage contains some lead as a natural constituent of its total mineral composition. This is not surprising because most soils in this country contain between 15 and 20 ppm of lead which is taken up by plants and transferred to animals eventually ending up in the human food chain. Similar conditions apply to the water supply where weathering and leaching of rocks add lead to the water supply. Lead as Pb^{210} is constantly released from the earth's crust as a result of decay of the uranium series of nuclides. Maynecord et al (6) have shown that this alpha emitter is taken up by grasses and other plants which are eaten as forage by animals which in turn become part of the human food chain. Hill (7) has shown that the lead-210 which escapes into the atmosphere is returned to earth with rain and adds to the natural radio-activity in the food chain. Burton and Stewart (8) found that the mean residence time of lead-210 in the atmosphere is about 4 weeks, sufficiently long enough for mixing to occur but short compared to this nuclide's half-life of 21.4 years. Water supplies also contain lead-210 as a result of rain or from leaching of the earth's crust by river water (9). The total amount of lead-210 is small compared to stable lead but these nuclide measurements again point to the daily food and liquid consumption as the most important sources of lead intake by the human. Kehoe (5) has pointed out that, although

lead contamination of food and drink can occur during harvesting and processing, it is remarkable that such contamination is of such a low order as to contribute very little to the overall lead intake. Lead excretion follows a definite pattern with feces containing 0.3 mg per day and urine containing 0.03 mg per day. Thus the average individual is in lead balance and not accumulating excess lead to add to his total body burden. Changing environmental conditions can change both the intake and excretion pattern but the body adjusts to maintain its normal lead balance. Distribution of lead in the body reveals a low order of concentration of the element in the soft tissues other than the liver with 0.04 to 0.26 mg/ 100 gm and the kidney with 0.015 to 0.16 mg/ 100 gm.

The largest lead depot in the body is in the skeleton where the amount varies with different types of bone, being 0.21 to 1.11 mg/ 100 gm in flat bone and 0.67 to 3.59 mg/ 100 gm in long bone (5). Recent studies of 150 cases by Tipton and Cook (10) pointed out that there was a wide variation in the lead content of all body tissues but the values obtained were in agreement with those Kehoe et al (11) reported 23 years earlier. Similar results have been obtained by Nusbaum et al (12) for bone samples obtained in the Los Angeles area. They found no correlation between lead concentration and time of residence in the area and no correlation between concentration and age in the 175 cases analyzed. Comparison of their results and those obtained by others is given in Table 1. It can be seen that there has been little change in bone lead concentration over a period of 31 years when the use of lead alkyls has shown such a large increase (see Figure 1). Thus, again the unavailability of the lead compounds in automotive exhaust is apparent. Furthermore, Holtzman (16-18) has shown that lead-210 from the food-chain also appears in the human skeleton as well as the soft tissues.

LEAD TRANSPORT AND METABOLISM

After absorption mostly via the gastro-intestinal tract, lead is carried to various tissues by the blood. The distribution of lead in the blood stream has been shown by Kehoe (5) to be: plasma, 0.0015 mg/100 gm; erythrocytes, 0.024 mg/ 100 gm or a total of 0.027 mg/100 gm for whole blood. Recently the United States Public Health Service conducted a survey of blood and urinary lead among groups of individuals in Cincinnati, Los Angeles and Philadelphia. (19) Mean blood levels were: Cincinnati, 0.023 to 0.025 mg/100gm; Los Angeles, 0.019 to 0.021 mg/100gm and Philadelphia, 0.013 to 0.026 mg/100 gm. Urinary lead values were: 0.026 to 0.028 mg/L; 0.014 to 0.021 mg/L and 0.020 to 0.033 mg/L respectively. These data served to confirm those obtained earlier by Kehoe (5). Experimental ingestion of lead at a constant level of 0.3 mg per day produced no detectable elevation of blood lead in 420 days. After 4 years of ingestion of 1 mg of lead daily the blood lead reached 0.046 mg/100 gm. When the daily dose was raised to 2 mg for 2 years the blood value was 0.065 mg/100 gm and when ingested lead was increased to 3 mg daily for 4 months the blood level reached 0.05 mg/100 gm. Experimental inhalation of air containing 0.15 mg of lead/M^3 for 37.5 hours per week for 102 weeks increased the blood level to 0.45 mg/100 gm. Obviously both experimental ingestion and inhalation increase blood lead levels but there was also a concomitant increase in urinary lead amounting to 0.034 to 0.11 mg/L after ingestion to 0.74 mg/L after inhalation. Here again the body was adjusting to increased lead intake by increasing lead excretion via the kidney (20). There is also increased lead in the feces, the

principal route of excretion, and this partially explains why even with a controlled experiment it is very difficult to increase the body burden of lead.

Another mechanism exists for decreasing the amount of lead in transit, namely, deposition in bone. MacDonald et al (20) have shown that both lead and strontium are bound to bone by adsorption or ionic exchange at the surfaces of bone salt crystals or combined with the sulfate in the organic matrix. Bone seeking elements such as lead and strontium are also discriminated against by the kidney. MacDonald et al (21) have shown that when both calcium and strontium are available for skeletal retention, the kidney preferentially excretes the latter.

LEAD INTOXICATION

In the previous discussion the various means whereby lead enters and exits from the body have been covered. In no instance has frank lead intoxication been discovered in the thousands of cases discussed. This is probably, as has been shown, due to lead balance in which excretion has kept up with ingestion. When this balance breaks down, three forms of lead intoxication can result: primary intoxication, characterized by intestinal tract dysfunction, loss of appetite, constipation, colic and general malaise and weakness; secondary intoxication, characterized by weakness and some atrophy or even paralysis of the forearm extensor muscles; finally, the lead encephalopathy frequently seen in infants and children. In all three instances changes in hematopoiesis with basophilic stippling of the erythrocytes and reticulocytes are seen. The main causes of lead poisoning in the population are industrial exposure, burning of battery cases, eating of lead based paint, ingestion of lead insecticides, etc. Dangerous exposure to lead give blood lead values ranging from 0.07 to 0.2 mg/100 gm and urinary values ranging from 0.08 to 0.4 mg/L. Fleming (23) has pointed out that the application of good industrial hygiene practices has prevented any cases of lead intoxication in the manufacturing of lead alkyls in the last 30 years. Similar exemplary records have been compiled for the other segments of the lead industry. Even cases of inadvertant poisoning by lead have been reduced to very low figures, but no one can guarantee absolute prevention of acute lead intoxication in the population. However, the development of chelation therapy has prevented lethality and decreased the possible damaging effects of lead. Chronic lead intoxication from inhalation of the breakdown products of lead alkyls has not been demonstrated in the 2300 individuals covered in the tri-cities survey conducted by the United States Public Health Service during the period June 1961 through May 1962 (19). Thus, again it becomes apparent that to cause either acute or chronic intoxication the toxic agent must be in a form that can be readily absorbed and transported to its target organs. This has not been demonstrated for the decomposition products of lead alkyls.

SUMMARY

It has been shown that the population of the United States is in lead balance and the old causes of acute and chronic lead intoxication have been reduced to very low levels by changes in technology. There is no such entity

as natural lead body burdens because the population has been exposed to approximately the same amount of lead in the solid and liquid components of the diet since very early in time. The earth's crust contains the lead which eventually enters the body via the food chain and it has been shown that, although people have been exposed to increased concentrations of lead compounds, these are not available and the body burden has not increased over the last 30 years.

TABLE 1

LEAD CONCENTRATION IN BONE

Micrograms per Gram of Ash

Year	Flat Bone	Long Bone	Calvarium	Rib	Reference
1933	50-55	55	---	---	13
1956	-----	76-540	---	25-63	14
1957	-----	---	76 M 65 F	39 M 33 F	15
1961	32	89	---	---	5
1964	-----	---	74 M 63 F	75 M 80 F	12

M = Male F = Female

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