FUNDAMENTAL STUDIES TO ESTABLISH A SUITABLE MAXIMUM ALLOWABLE CONCENTRATION OF LEAD IN INDUSTRIAL AIR

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In order to recommend a suitable maximum allowable concentration (M.A.C.) of lead in air in industries, the fate of lead introduced into the body, and the nature of the resulting symptoms, must first be clarified by experiments with humans and laboratory animals.

AN EXPERIMENT ON THE ORAL ADMINISTRATION OF LEAD IN MAN

Three healthy Japanese male adults were chosen; to two of them lead was given, while the other served as a control. The experiment was continued for nine months, from October 1952 to July 1953, and the experimental period was divided into four stages of two, two, two and three months respectively. The method used to administer the lead in each stage of the experiment is shown in *Table 1.*

Table 1

Stage number	*Administration method*
1: (61 days) (Oct. 5 – Dec. 4, 1952)	3 mg of lead acetate (Pb: 1·64 mg), orally, taken every morning
2: (60 days) (Dec. 5, 1952 – Feb. 2, 1953)	6 mg of lead acetate (Pb: 3·28 mg), orally, taken every morning
3: (67 days) (Feb. 3 – Apr. 10, 1953)	Lead administration discontinued
4: (98 days) (Apr. 11 – Jul. 17, 1953)	Therapeutic stage

The total amount of lead administered was about 300 mg.

The lead content of the subjects' daily food and drink, and of their whole blood and daily urine and faeces was measured by the mixed-colour dithizone method. Frequent examinations were made during the experimental period of the number of erythrocytes, leucocytes, stippled cells, and reticulocytes, the haemoglobin content, haemogram, the amount of urinary coproporphyrin and liver function, all by the usual methods.

The lead content of the whole blood showed considerable fluctuations in the course of the experiment, ranging from 14 to 108 μg/100 g for the lead consumers, and from 9 to 59 for the control. For the lead consumers, 31 and 29, respectively, out of the 75 quantitative determinations showed the lead content of the blood to be greater than 50 mg/100 g. Such concentrations were encountered in only 5 out of 74 determinations for the control. The lead content of the whole blood of the lead consumers during Stage 2 showed but a slight increase over that during the first stage in spite of the fact that the lead intake was doubled.

The amount of lead excreted in the urine showed remarkable variations ranging from 20 to 613 μg/day for the lead consumers and from 10 to 202 for the control. An increase in the lead excretion in the urine of the lead consumers was observed 1–3 days after administration of lead began, and, after increasing gradually for two weeks, it reached a peak. In Stage 2, where the lead intake was doubled, the excretion of urinary lead showed only a slight rise, and no significant difference was observed between the amount excreted in Stages 1 and 2. There was no sharp decline in the amount of urinary lead for Stage 3, during which no lead was administered.

The amount of lead in the faeces of the lead consumers increased suddenly on the 2nd day of the experiment. From the beginning of Stage 2, in which the lead intake was doubled, the lead content in the faeces of the lead consumers increased about two-fold compared with the value during Stage 1. On the other hand, when the lead intake was discontinued in Stage 3, the amount of lead in the faeces showed a marked decrease of about 25 per cent compared with the previous stage. The amount of lead in the faeces comprised about 80–85 per cent of the total lead excreted in Stages 1 and 2.

The number of erythrocytes and the haemoglobin content of the lead consumers decreased and did not return to normal even after the administration of lead was discontinued. No increase in the number of erythrocytes or of the haemoglobin content was seen in this experiment, even during the early period of lead administration. Some increase in the number of stippled cells and reticulocytes was observed during the course of the experiment, but the increases were neither large nor regular. Neither the number of leucocytes nor the differential count of leucocytes were significantly different for the lead consumers and the control.

The amount of urinary coproporphyrin of the two lead consumers reached to 120–160 μg/day during the course of the lead administration, while the amount for the control was about 80 μg/day, *i.e.*, within the normal upper limit.

The liver function tests on the lead consumers were almost normal.

This experiment has proved that the amount of lead in the blood, and the quantity of lead excreted in the urine and faeces of the lead consumers, exceed that of a normal control subject. These amounts of lead, administered orally, do not result in any distinct change in the physiological conditions of the lead consumers except for a decrease in the number of erythrocytes and in the haemoglobin content. An abnormal increase in the amount of urinary coproporphyrin is observed during administration of lead, in spite of the absence of manifest clinical symptoms.

AN EXPERIMENT ON THE ORAL ADMINISTRATION OF LEAD IN LABORATORY ANIMALS (DOGS)

In an attempt to clarify the symptoms caused by administration of lead, a daily dose of 30 mg of lead acetate (Pb: 16·38 mg) was administered orally to two adult female dogs (" A " and " B ") over a period of 60 and 98 days respectively. The amount of lead administered totalled 984·3 mg for " A " and 1609·4 mg for " B ". Another dog (" C ") was used as a control.

An increase in the amount of lead excreted into the faeces and urine, and an increase of urinary coproporphyrin, were the earliest and most notable signs. These symptoms were followed by the appearance and increase in the number of stippled cells and reticulocytes in the peripheral blood stream. The number of erythrocytes dropped sharply from around the 30th day of the administration period in both experimental animals. The fluctuation of the haemoglobin content for " A " and " B " tended to parallel that of the number of erythrocytes. In the final stage of lead administration, the haemoglobin content dropped to about 50 per cent of the value observed before the administration began.

Most of the lead administered was excreted in the faeces, and a small amount of it in the urine. The total lead excreted was 86·5 per cent and 89·6 per cent, respectively, of the lead originally administered. It is assumed that about 10 per cent of the lead administered remained in the body.

Of the lead remaining in various tissues of the experimental animals, about 97 per cent was found in the bones and teeth.

AN EXPERIMENT ON THE ADMINISTRATION OF RADIOACTIVE LEAD (RADIUM D) TO LABORATORY ANIMALS (GUINEA PIGS)

Full grown, healthy, male guinea pigs weighing 400 to 500 g were employed as test animals. Lead acetate was given to the animals until they developed clinical signs of mild lead poisoning. A solution of radium D was then administered to the lead-poisoned animals in three ways; hypodermically, orally, and intratracheally. Subsequently, a daily examination was made of the amount of radium D excreted in the urine and faeces. Sometime between the 3rd and 20th day after the administration of radium D, the animals were killed by bleeding and the amounts of radium D in the blood and organs of the animals were measured.

The concentration of radium D in the whole blood reached a maximum several hours after each administration, and decreased rapidly 24 hours later. The radium D concentration in the blood after an oral administration was lower than that after parenteral administrations; it was found mostly in corpuscles, and only rarely in the plasma and serum.

Most of the radium D administered was deposited in hard tissues such as teeth and bones, and only a very small amount was found in soft tissues.

The amount absorbed in the body of the experimental animals, on the 20th day following the administration, was about 32 per cent after intratracheal administration, 24 per cent after hypodermic administration, and only 5 per cent after oral administration.

It seems that the amount absorbed is related to the amount excreted in urine. Consequently, it is considered that if the urinary lead excretion is measured, then the amount of lead absorbed in the body can be estimated approximately.

Concerning the recommendation of a suitable M.A.C. of lead in air in industries, it has been a matter of great importance to study the maximum amount of lead in the blood, urine, faeces, and tissues of a normal body.

A STATISTICAL STUDY OF THE UPPER LIMITS AND AVERAGES OF THE AMOUNT OF LEAD IN BLOOD, URINE AND FAECES OF HEALTHY JAPANESE INHABITANTS IN URBAN AND RURAL AREAS

It is clear that the content of lead, both in blood and urine, follows a normal logarithmic distribution curve. As the frequency distribution of the results obtained follows a statistical law, the results from the author's specimens may be applicable to larger groups of the population.

Lead content	*Area*	*No. of specimens*	*Upper limit (5% sig.)*	*Mean*	σ
Lead in whole blood (μg/100g)	Urban	244	32	11	1·90
	Rural	122	32	12	1·82
Lead in urine (μg/day)	Urban	78	159	36	2·81
	Rural	135	107	36	1·92
Lead in faeces (μg/day)	Urban	31	—	240	—
	Rural	62	—	236	—

A STATISTICAL STUDY ON THE UPPER LIMITS AND AVERAGES OF LEAD IN BLOOD, URINE AND FAECES OF LABORATORY ANIMALS

Lead in small specimens was analysed by a spectrochemical method using an Adam Hilger E_3 spectrometer. The results obtained are summarized below.

The frequency distribution of the amount of lead in the whole blood of 312 rabbits followed approximately the distribution of a normal logarithmic type, its mean value being 35 μg/100 g and the upper limit being 104 μg/100 g with the significance level equal to 5 per cent.

The frequency distribution of the amount of lead in faeces of 322 rabbits followed approximately a normal distribution type; the mean value being 164 μg/10 g, and the upper limit 269 μg/10 g, with the significant level equal to 5 per cent.

OTHER INVESTIGATIONS

A study of the lead content in Japanese daily food

The lead content was studied of those daily foods which are considered to be the principal sources of the lead found in the tissues, including blood, urine or faeces, of normal, healthy, Japanese people apart from lead workers.

Fresh meat, fruit and vegetables contain comparatively large amounts of lead. The lead content decreases to some extent after washing the food with water. A fairly large amount of lead is found in the intestines of some kinds of small fish. A large amount was detected in canned and bottled foods. The lead content in each whole meal in a menu was determined directly after reducing a specimen meal to ashes. From these studies the lead taken orally by adults in Japan has proved to be approximately 200–300 μg/day. Thus, a normal, healthy Japanese adult takes in lead through his respiratory and digestive tracts to the extent of approximately 200–400 μg daily.

Studies on the M.A.C. of lead in air*

A study was made on the change of the physiological conditions, and on the development of clinical symptoms, due to lead, using the same method as in the poison tests. The symptoms were surveyed with reference to the concentration of lead in the air, on the basis of a statistical analysis. It is considered that, for the Japanese male adults who engage in lead work requiring moderate physical exertion for 8 to 8½ hours a day for more than one year, the safety limit for the average lead concentration in the air, in order to protect them from any significant harm, is approximately 0·05 mg/m^3.

A study on a combination method of diagnosis of mild or latent lead poisoning (an application of the statistical discriminant function)†

The early detection of cases of mild or latent poisoning is necessary for the control of the health of lead workers. While such methods as the lead line, the count of erythrocytes and stippled cells, the haemoglobin content, lead in blood and urine, and coproporphyrin in urine, *etc.*, have been used for diagnosis of lead poisoning, none of them provides a clear indication which can be used for the diagnosis of mild or latent cases. Although diagnoses have been made by clinical tests based on the methods mentioned above, they are rather difficult for the average practitioner. For these reasons a combination method has been devised for the diagnosis using the statistical method of discriminant functions with the results of several examinations.

The following relationship was established:

$$Z = X_1 + 81{\cdot}19X_2 - 69{\cdot}95X_3 - 2{\cdot}55X_4 - 9{\cdot}14X_5,$$

where X_1 = erythrocyte count ($\times 10^4$/cm)

X_2 = haemoglobin content (g/100 ml)

X_3 = coproporphyrin in urine (μg/l.), transformed into scores on a scale varying from 0–5;

* Read before the XIth International Congress on Occupational Health, Naples, 1954.

† Presented at XIth International Congress on Occupational Health, Naples, 1954.

Coproporphyrin (μg/l.)	*Scores*
Under 50	0
50–75	1
75–100	2
100–250	3
250–500	4
Over 500	5

(Mid-points were adopted in case of ambiguous classifications)

X_4 = lead in blood (μg/100 g)

X_5 = lead in urine (μg/day)

A critical value of $Z = 1200$ has been accepted for diagnosis by means of the discriminant function. For greater convenience, a nomograph has been devised to avoid the calculation involved in obtaining the value of Z.