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Environmental health aspects of lead

Die gesundheitlichen Aspekte der Umweltverschmutzung durch Blei

Les problèmes sanitaires posés par le plomb présent dans l'environnement

BIOLOGICAL EFFECTS OF LOW LEAD DOSES

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Abstract

With many conventional sources of lead exposure still remaining, we are now facing a situation where the total environment of man becomes more and more polluted with lead. A situation where the whole population is being exposed, creates a need for sensitive methods of assessing lead effects in various organ systems. The most sensitive indicator hitherto known is inactivation of erythrocyte ALA-D, measurable even at present levels of exposure in the urban environment. Subclinical nervous damage as well as psychological disturbances have also been demonstrated. These effects, although demonstrable in clinically symptomless subjects require higher levels of exposure than depression of ALA-D activity. The same is probably true for the chromosomal aberrations found in symptomless lead workers. A common feature for all these findings is that they may force us to reconsider the threshold concept. This question, however, is of primarily theoretical interest. For practical purposes it is much more important to reach agreement on what qualities and quantities of responses are unacceptable in terms of health. These considerations must also take into account the normal inter-individual variation, both with regard to accumulation and to response. Agreement on how broad safety margins should be applied is another important task.

Background: The problem

Lead poisoning is no new problem. It has been with us since ancient times, and epidemic outbreaks like the Devonshire colic in the 18th century and the industrial lead poisoning at the turn of the century are well known examples of its seriousness. What is new is that lead during the last few decades has become dispersed into the entire environment of man; thus the whole population is now being exposed through air, food and water. The main source of this global pollution is, as we all know, lead emitted through automobile exhaust gas. Lead smelters and other industry, although of lesser global importance, may create serious local problems.

A situation where the whole population, even its most vulnerable part, is being increasingly exposed creates a serious problem which has caused much concern in recent years. It is quite true that no severe illhealth, arising from the general pollution with lead, has been demonstrated yet. The acute problems are still of the conventional type: clinical poisoning in slum-district children from ingestion of flaking lead paint, industrial lead poisoning, endemic poisoning among consumers of illicit whiskey and users of leaded ceramics, etc. But since the trend of the general environmental pollution is going sharply upwards, as can be judged from the increasing consumption of lead in petrol,[1] exposure will increase in the future provided preventive measures are not undertaken. This means that an increasing fraction of the population may become exposed to potentially hazardous levels. It is quite obvious that such a situation must be prevented, since once dispersed in the entire environment, lead cannot easily be removed.

When prevention involves big economic and political decisions, hard facts are usually demanded to start action. In practice this may require demonstration of overt illness, the more severe, the more effective, in order to convince the authorities of the need for prevention. In the case of environmental lead pollution, since no severe effects have been demonstrated at present levels, the authorities, often supported by conventionally thinking toxicologists and clinicians, find it hard to believe that dangers will arise in the future.

Such conventional thinking in terms of clinical poisoning has retarded the necessary decisions. The philosophy applied in industry, where exposure is permitted to the level of recognizable biochemical alterations and even mild symptoms, cannot be allowed in the general population, especially since there are infants, pregnant women, as well as diseased and old people (its justification in industry can be questioned too).

1) The recent decisions, in a number of countries, to gradually reduce the lead content in petrol will probably turn the trend.

Much stricter criteria for safety are needed here. This creates a demand for sensitive methods to detect functional disturbances, and equally important, some sort of agreement on what quality and quantity of these disturbances should be considered significant in terms of health. The intention of this paper is to discuss a few questions related to these problems in the light of some recent observations.

Inhibition of ALA-D: The most sensitive indicator of biological effect 1)

Until some years ago, increased excretion of ALA and CP into the urine was considered the earliest effect of excessive absorption of lead into the organism. These effects become, on an average, measurable at a PbB of some 40 µg/dl (e.g., Selander and Cramér 1970). The fact that no functional disturbances could be detected below this level, gave rise to the concept that this was the threshold for lead effect.

However, recent studies have shown that erythrocyte ALA-D is partly inhibited at far lower concentrations of PbB and that no threshold for this effect can be demonstrated (de Bruin and Koolstra 1967, de Bruin 1968, Hernberg and Nikkanen 1970, Hernberg et al. 1970). Other research groups have later corroborated these findings (Millar et al. 1970, Meisenberg et al. 1971). Another interesting finding is that slight ALA-D inhibition is measurable even at PbB concentrations found in the general urban population and that this inhibition is proportional to PbB (Hernberg and Nikkanen 1970). In other words, it is now possible to demonstrate a biological effect of present environmental pollution, although its significance in terms of health cannot yet be explained. It is possible that the inhibition measured *in vitro* merely represents a reduction of "reserve enzyme capacity" that is not essential. Be this as it may, the ALA-D test provides a sensitive method for registering biological effects of low lead doses. We have already some practical experience with it. In Fig. 1, the effect of the distance of habitation from a lead smelter on the activity of ALA-D can be seen. There was a significant correlation between these parameters.

We have later demonstrated that ALA-D activity becomes inhibited even during the very first days of new lead exposure, and that it correlates closely with PbB not only in a steady state, but also in a positive and a negative lead balance (Hernberg et al. 1972). The sensitivity of the test, often blamed to be too

1) The following abbreviations are used: ALA-D = delta-aminolaevulinic acid dehydratase, ALA = delta-aminolaevulinic acid, CP = coproporhyrin, PbB = concentration of lead in the blood.

high, can furthermore be reduced by lowering the incubation pH (Nikkanen et al. 1972).

Since ALA-D is not only required for haemoglobin synthesis, but also for the formation of a number of haem containing respiratory enzymes, and since it is present in a large number of tissues, a correct evaluation of the biological significance of the inhibition requires studies on its behaviour in other tissues. Some investigations are already published. The finding by Millar et al. (1970) that ALA-D was inhibited in the brain of lead poisoned suckling rats is a pertinent one. The crucial question is to what extent the organism can compensate for partial inhibition of ALA-D activity, e.g., in the synthesis of haem containing enzymes in the developing brain.

Subclinical peripheral nervous damage

Some recent studies (Catton et al. 1970, Seppäläinen and Hernberg 1972) have revealed subclinical nervous damage in neurologically symptomless lead workers, using modern neurophysiological technique. The lesions found consist of EMG abnormalities (fibrillations and/or diminished number of motor units), reduction of the maximum conduction velocities in the popliteal, median and ulnar nerves, and prolonged distal latency in the median nerve (Table 1). In our study the pathological finding most often found was selective slowing of the conduction velocity in the slower fibres of the nerves, however. From this we can conclude that the latter parameter is the most sensitive indicator of subclinical nervous damage. All the findings are compatible with peripheral neuropathy, due to segmental demyelination with partial damage of the nerve trunks.

The significance of these findings lies in the fact that subclinical neuropathy now can be detected before neurological symptoms appear. But since most of the subjects studied were industrial workers exposed to fairly high concentrations of lead (the PbB's were above 80 µg/dl in 34 cases out of 39), we still do not know whether or not, or to what extent, lower exposures, like those occurring in extreme conditions of environmental pollution, are capable of causing neuropathy. In order to find the non-effect level for this response we have now started a study on industrial workers whose PbB's have never exceeded 50 µg/dl. According to our preliminary findings slight neuropathy occurs in some cases even in such low exposure.

These pertinent questions arising from these observations are: (1) At what intensity of exposure do the earliest neurological lesions occur, and (2) what is their significance in terms of health?

Subclinical effects on the central nervous system

There are several studies showing late behavioural effects in children who have ingested lead in early childhood (Wiener, 1972). At the Institute of Occupational Health, Helsinki, where psychological testing has been employed for many years, a variety of abnormalities, as compared to normal controls, has been shown in a group of lead workers (Hänninen, to be published) These include slowness of performance, psychomotor disturbances, and slight intelligence defects. Also personality changes were present, especially reduction of the mental energy. Considering also that Russian workers (Gusev 1960) have found behavioural impairment in animals exposed to low concentrations of lead (11 ug/m^3 of lead for 6 hours daily for 6 months), there are some suggestions of interaction with brain functions at exposures not generally recognized to cause encephalopathy. Even though more information is needed, the results referred to must be regarded as a warning signal.

Genetic effects

There are reports showing an increased proportion of mitoses with secondary chromosomal aberrations in lymphocytes of workers exposed to lead oxide (e.g. Schwanitz et al. 1970). Also nonspecific changes such as spiralizing defects, chromosomal atherion and pulverization have been found, as well as a slight increase of the proportion of tetraploid mitoses. In the study of Schwanitz et al., all subjects had clear evidence of increased lead absorption. The mitotic disturbances correlated with the urinary concentration of ALA. But also for these effects the lowest lead exposure causing damage is unknown, as is their biological significance.

Threshold or no-threshold?

According to conventional toxicological thinking there exists a threshold below which toxic agents have no effect on the organism. When this threshold is exceeded, different effects of increasing intensity begin to appear. This thinking has been the basis for establishing various safety norms, like the

(1971) may be quoted: "One of the most important principles upon which occupational health programs are based is that exposure to a toxic agent may be permitted up to some limit of tolerance above zero, within which man can cope successfully with the insult with no significant threat to his health. It is only on the demonstrated reality of this concept that the establishmentand continued operation of a great segment of modern industry can be justified, insofar as health maintenance is a determinant. The hazardous industries would have to shut down otherwise, since a zero level of contact with the toxic agent is probably not attainable in practical industrial situations. Any challenge to this operating principle must, therefore, be met with the utmost vigor by those responsible for industrial health maintenance; and, in this effort, they must be given full support by all others concerned with the survival and progress of industry".

Dinman (1972), although denying the no-threshold concept in a functional sense, admits that the concept is true in that, when one atom or molecule enters the reactive region of another, a chemical interaction will result. But he stresses that the word "effect" is neutral and does not necessarily imply a deleterious impact. This is so because there is a vast number of binding sites in the cell, many of them without functional significance, and because the organism has a potent capacity to maintain homeostasis. The conclusion of Dinman is that, since functional sense, there are thresholds. Such a differentiation between chemical and functional effects certainly is meaningful and places the disagreement on whether or not there are thresholds in its right perspective, namely that of an entirely [illegible] question. From a practical point of view these discussions of what qualities and quantities of effects are acceptable [illegible] no doubt the development of more sensitive methods will push thresholds downwards, even to the extent that they may fall below the detection limit for assessing the dose, as has been shown by the ALA-D test. In such cases the problem is not to look for thresholds but to define the limit for "unacceptable". On the other hand, there are other effects - and these still form the majority - where we are far from approaching the methodological sensitivity for registering effects at the "threshold level". In such cases, again, we have to agree upon what is unacceptable, but in contrast to the former situation this becomes a question of defining a broad enough safety margin.

Defining acceptable levels of effect

It should be clear that the purpose of defining what is acceptable and what is not, is to obtain a sound basis for setting upper limits for daily intake of lead under various conditions. The concept of a total daily intake then provides the basis for recommendations for the maximal permissible lead concentration in food, drinking water, and out-door and in-door air. The prerequisite for such recommendations is a comprehensive understanding of the toxicology of lead and of the dose-response relationships for the various effects. Since our knowledge of these matters is severely defective (this concerns primarily subclinical effects, long-term effects, and genetic effects), the following discussion will be kept mainly on the theoretical level.

For all lead effects two different normal biological variations must be considered. Firstly, a given quantity of exposure will result in varying accumulation of the metal in the organism because of inter-individual variations in absorption and excretion. For this reason, PbB will vary from one individual to another under the same conditions of exposure. Secondly, at identical levels of PbB (used here as a simplification to indicate the degree of absorption into the organism), there will be another variation, merely that of response, due to inter-individual differences in sensitivity. Present insufficient empirical data do not allow any calculations, but it may be assumed that the sum of these variations is bigger than any of the components alone. This implies that, when having agreed upon the non-acceptability of a given effect, a safety margin broad enough to protect the most vulnerable members of the population must be employed when defining the highest permissible dose (what per cent of them, if any, that will be left without protection must again be based on agreement).

This reasoning can be illustrated graphically. In Fig. 2, PbB (denoting the dose) is on the abscissa, and the distributions of four tentative positive responses in a population are depicted as a function of it. For reasons of simplification, the response has been classified as being dichotomous ("yes-or-no"). Thus, the points A_0, B_0, C_0 and D_0 denote the dose level where no matter of the population shows a response, and the points A_{100}, B_{100}, C_{100} and D_{100} the dose where all members respond. Response A can be thought to represent a very slight biochemical abnormality, like depression of ALA-D activity below a given level, and response D a very serious one, e.g. death. The first decision to be made is whether or not the response in question has any bearing at all in terms of health (response A may represent such a case). If not, there is no need to consider it at all when setting standards. If the answer is yes, it must

be decided what proportion of positive responses is acceptable in the population (illustrated by safety limits A_{20}, B_0 and B_5). There are, of course, also responses so severe that no question arises of whether or not they can be accepted (illustrated by responses C and D); the only problem is the magnitude of the safety margin.

This way of reasoning implies that there is agreement upon what is "positive" and what is "negative". Such agreement may be easy to obtain in the extreme ends of the multiple dose-response curve, starting from minute biochemical alterations (type A responses) and ending with death (type D response). The difficulties usually arise when dealing with "intermediate" effects. A model of such an effect (a continuous variable) is given in Fig. 3. ALA in urine may serve as an example. The problem is to define an artificial cutting point on the continuous dose-response curve above which the response is considered to be "positive", and , from this point, to decide the lead dose which corresponds to a given percentage of positive responses, or no positive responses at all, as discussed above.

From these considerations it should be evident that there is a need for agreement on the interpretation of the data available (of course there is also a need for new data). But most of them concern haematological effects of lead and there are other effects for which dose-response data are severely deficient or completely lacking. Such a situation calls for utmost caution, a thinking in terms of safety margins broad enough to minimize the risk. This view is quite in contrast to the trial and error thinking applied in occupational health in the Western countries, where the TLV's from time to time have to be revised downwards because of observed illhealth. The same way of thinking, for some reason, has infiltrated many environmental pollution problems too. I feel that the fundamental reason for the present disagreement on how to consider the lead problem is to be found from the conflict between these two ways of thinking.

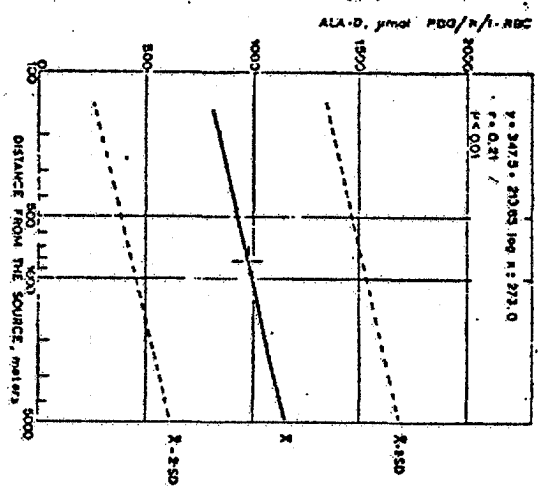

Fig. 1. Correlation between erythrocyte ALA-D and distance of habitation from a lead scrap smelter. The material studied consisted of 250 men and women without any occupational exposure to lead. There was also a negative correlation between PbB and the distance from the source (not shown in the Fig.)

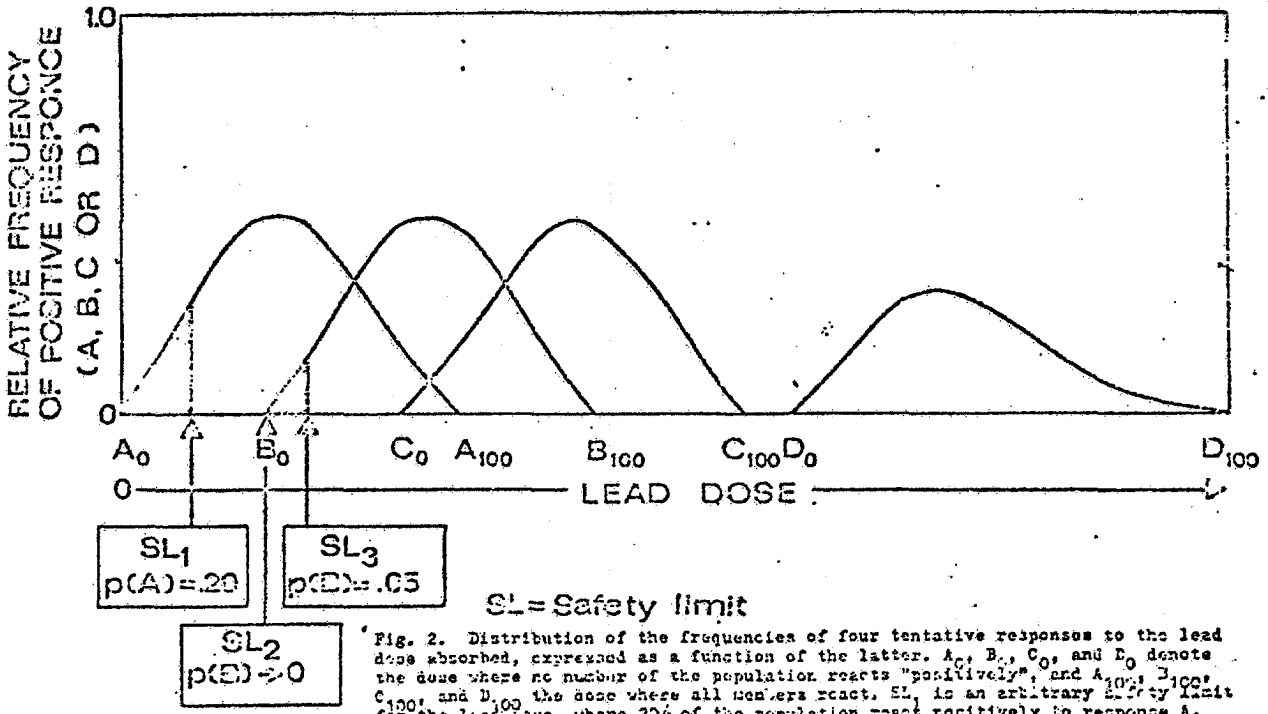

Fig. 2. Distribution of the frequencies of four tentative responses to the lead dose absorbed, expressed as a function of the latter. A_0, B_0, C_0, and D_0 denote the dose where no member of the population reacts "positively", and A_{100}, B_{100}, C_{100}, and D_{100} the dose where all members react. SL_1 is an arbitrary safety limit for the lead dose, where 20% of the population react positively to response A, SL_2 the limit where no "positive" response of type B is likely to occur, and SL_3 the limit for 5% "positive" B responses. There are safety margins for responses C and D.

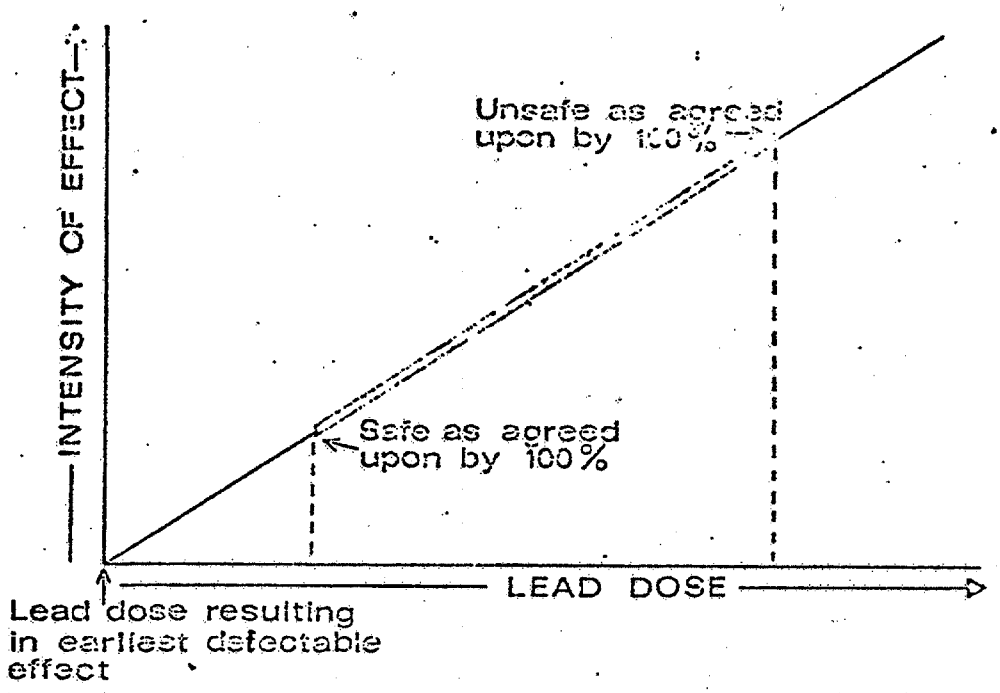

Fig. 3. The intensity of a given continuous effect as a function of the lead dose. The start point of the regression line may or may not be zero. In the first case there is no threshold, in the second the starting point denotes the threshold. The shadowed area around the regressi line represents the response levels where there may be different opinions of whether or not t response should be classified as "positive".

(S. Hernberg: Biological effects of low lead doses)

Table 1. Nerve conduction velocity findings in 39 lead workers and 39 age-matched controls (Seppäläinen and Hernberg, 1972).

Variable	Mean ± S.D.		T	P
	Exposed	Controls		
Age (years)	36.1 ± 11.7	35.5 ± 11.5		
MCV (m/sec) of the median nerve	55.3 ± 3.7	58.6 ± 3.7	4.00	<0.001
Distal latency (m/sec) of the median nerve	4.6 ± 0.6	4.0 ± 0.5	5.10	<0.001
MCV (m/sec) of the ulnar nerve	54.0 ± 5.2	56.7 ± 3.4	2.84	<0.01
CVSF (m/sec) of the ulnar nerve x)	39.0 ± 8.0	46.6 ± 3.7	4.90	<0.001
MCV (m/sec) of the lateral popliteal nerve	48.4 ± 5.1	50.7 ± 3.6	2.30	<0.025

x) Data from 32 exposed and 32 controls

MCV = Maximal Conduction Velocity

CVSF = Conduction Velocity of Slower Fibres

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