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Dose-Response Relationships for Inorganic Lead

I. Biochemical and Haematological Responses

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Summary. The author reviewed literature data on the relationship between lead in blood levels (PbB) and various biochemical and haematological responses. PbB levels may be regarded as representative for internal dose. The percentage of subjects with a specified intensity of a specified response in groups of subjects has been calculated in relation to PbB. This Dose-Response (D-R) relationship portrays the increase of biological effects with increasing internal dose, qualitatively and quantitatively, and can be used to evaluate the health significance of Pb exposure in occupational and public health. D-R-curves have been calculated for δ-aminolaevulinic acid dehydratase activity in erythrocytes (ALAD), δ-aminolaevulinic acid excretion in urine (ALAU), protoporphyrin in erythrocytes (PPE), Na^+-K^+-ATPase activity in erythrocytes and reduced glutathion content of erythrocytes. Various other biochemical and haematological responses are discussed in regard to their relationship with PbB. In a subsequent paper the prevalence of functional effects in relation to PbB will be discussed.

Key words: Lead - Biologic Response - Lead in Blood - ALAD in Erythrocytes - ALA in Urine - Protoporphyrin in Erythrocytes.

INTRODUCTION

The objective of part I and part II of this study is to evaluate the relationship between lead in blood (PbB) levels and subclinical *biochemical* and *haematological* (I) and subclinical functional (II) responses; if possible dose-response (D-R) relationships are calculated from literature data, published in recent years. The range of PbB = 0-70 µg/100 ml blood is covered. The resulting data on D-R-relationships and on no-response levels will be discussed in view of the significance for occupational and public health.

DOSE

Inorganic lead (Pb) exposure occurs through inhalation and ingestion. In occupational exposure respiratory uptake may largely exceed oral uptake; control of Pb concentration in air and of duration of exposure generally speaking achieves prevention of Pb poisoning. However, in exposure of the general public the relative contribution of oral uptake usually exceeds that of respiratory uptake.

The *effective total* exposure, i.e. *amounts* of Pb taken up by the body per unit of time over a stated period of time, is very difficult to measure quantitatively, particularly in the sphere of public health. This effective exposure yields an internal load; because Pb has a long biological half life ($t\frac{1}{2}$), a *body burden* is built up. The total body burden can be roughly divided into (Pietrovsky, 1970): 1. rapid exchange pool in blood and soft tissues; 2. intermediate exchange pool in skin, muscles; 3. exchange pool in bone: a) intermediate exchange in bone marrow, trabeculae, b) slow exchange in dense bone, teeth.

The total body burden therefore is composed out of various partial body burdens, in which the *rapid exchange pool* must probably reflects the *biologically effective body burden*, indicated by lead in blood, making up about 2% of total lead burden (Baloh, 1974). Approximately 90% of blood lead is bound to erythrocytes; plasma lead (0.2% of total burden) is made up of two fractions: plasma protein bound fraction and diffusable fraction, the latter being the metabolically active center of the body burden. In a more or less steady state there is a dynamic equilibrium between various compartments; the rate constants k (indicating the rapidity with which an equilibrium can be reached between two compartments) for different means of internal exchange between various compartments with the diffusable plasma lead probably decrease in the following order: k-plasmaprotein Pb, k-erythrocyte bound Pb, k-soft tissue Pb, k-hard tissue (Baloh, 1974).

The *diffusable plasma Pb* probably offers the best approximation of the biologically effective Pb burden; however, it is very difficult to measure in practice. The red blood cell/plasma partition of lead may be the important decisive factor for the development of toxic manifestations; the plasma fraction probably is not a constant fraction of total blood lead concentration, and as such cannot be predicted from it in an individual (Waldron, 1974); however for *groups* of subjects PbB will probably offer a reasonable indication of it.

Particularly in case of a steady state exposure there also exists a relationship between effective total external exposure and biologically effective Pb burden: the external dose

results in an aequivalent internal "dose". In evaluating D-R-relationships *lead in blood levels* (PbB) represent the internal dose and consequently also the effective *external dose.*

Lead in blood level undouptedly is the parameter used in most studies up till now available. Moreover sampling is not too inconvenient in practice. Not only because of the availability of literature data, but also because of theoretical reasons PbB as measure of dose is to be preferred above other possible parameters of internal exposure, such as Pb in urine, in hair, in teeth. EDTA-provocated Pb excretion in urine may provide a more direct measurement of the rapid exchange pool; however in public health practice, it has serious drawbacks: application of EDTA; preferably 24 hr specimen of urine; possibility of contaminations; this makes it difficult to use this method in epidemiological studies.

It should be stressed that measurement of PbB-levels encounters many pitfalls. Even in the most competent laboratories, on multiple runs of the same blood sample, there is a ± 15% error in the measured value (Baloh, 1974). Two recent intercomparison programmes on PbB analyses within the Europ. Econ. Comm. provided evidence of the often poor comparability of data (Berlin et al., 1974a).

In this paper particularly the internal *dose* as represented *by PbB up to 70 µg/100 ml total blood in its relationship with biologic responses* will be evaluated; the data are relevant for moderate occupational exposure, and cover the most relevant range of public exposure. According to modern notation in analytical chemistry, it is preferred to express PbB in ppb's (1 ppb = 1 µg/l = 0.1 µg/100 ml); however because up till now almost all literature data are expressed in µg/100 ml or µg/100 g, this notation is still used in order to avoid confusion.

DOSE-RESPONSE RELATIONSHIPS, INTRODUCTORY REMARKS

If in an *individual* subject the internal dose exceeds the no-effect level, biological responses occur: the intensity of a specified response may increase, and more types of responses may occur. In a *group* of subjects the number of persons with biological responses also increases with increasing dose.

One distinguishes:

dose-effect (D-E) relationship, i.e. the relationship between dose and intensity (quantity) of a specified parameter of response in an *individual* ("graded response");

dose-response (D-R) relationship, i.e. the relationship between dose and relative number (percentage) of individuals with a specified (quantity) intensity of a specified parameter of

response in a *group* of subjects ("quantal response").

Individual subjects differ in D-E-relationships both in regard to threshold level (no-effect level) and slope. For a group this interindividual variability manifests itself in the D-R-curve. As will be discussed more fully in part II, *exact* no-effect/response levels cannot be determined; one can only derive *practical* no-effect/response levels; the practical no-response level corresponds to that PbB level which does not induce a specified response in > 5% of subjects. It should be clearly understood that according to the concept given a "no-response level", does *not* indicate that *any* response does not exist, but that any *specified* (quantal) response does not exist.

δ-AMINOLAEVULINIC ACID DEHYDRATASE IN ERYTHROCYTES (ALAD)

It is wellknown that ALAD is extremely sensitive for Pb; inhibition of ALAD in erythrocytes parallels inhibition in other tissues, e.g. liver (Secchi et al., 1974). A review on the effects of Pb on ALAD has been published by Hernberg et al. (1972). There exists a negative relationship, particularly in the range PbB = 15-70 µg/100 ml. There is suggestive evidence that the no-effect level is about 10 µg Pb/100 ml (Schaller et al., 1971; Granick et al., 1973; Hernberg, 1974). Sakurai et al. (1974) plotted means of log ALAD in workers against each 5 µg/100 ml subdivision of PbB for PbB up to 65 µg/100 ml; the regression was not linear. In workers with PbB < 30 µg/100 ml no correlation existed between both parameters. The data suggested an inflection point somewhere around 25-30 µg Pb/100 ml. Moreover in the range of PbB = 0-30 µg/100 ml the ALAD in non-exposed controls was somewhat higher than in exposed workers. Tomokuni (1974) found a different behaviour of ALAD in non-exposed subjects and in exposed workers: the optimum pH for determination of ALAD shifted from 6.8 to 6.0; the reason for this is not yet clear. If one makes use of this different behaviour, the power of ALAD to discriminate exposed from non-exposed subjects at low PbB-levels increases.

The intraindividual variability in non-exposed males and females over 3 weeks is small: coefficient of variation 4.5-6.8% (Stuik, 1974). Recently the Europ. Econ. Comm. has standardized the ALAD determination; the interlaboratory comparibility proved to be much better than for PbB (Berlin et al., 1974b).

The significance of ALAD inhibition due to Pb in regard to health is still open for discussion. The present consensus

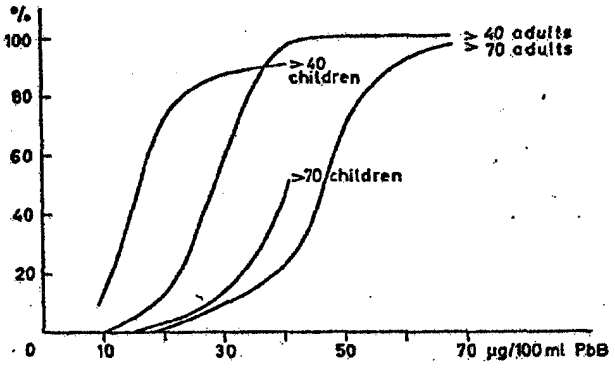

Fig.1
Percentage of subjects with more than 40% and 70% inhibition of ALAD with increasing PbB

appears aptly stated as follows by NAS (1972) in regard to ALAD for the range of PbB up to 40 µg/100 ml: "its biological significance is dubious, because it is unaccompanied by any detectable effects on the biological function of intact man". Maxfield et al. (1972) demonstrated that dogs fed with Pb acetate (100, 500 or 1000 ppm in diet) were similar to controls in their haematological functions, although blood ALAD levels were severely (to $\frac{1}{15}$ of preexposure level) depressed by the lead diet. Garber et al. (1973) administered Pb to 3 strains of mice with genetically different ALAD levels in the liver; there was no relationship with ALAD in acute and subacute toxicity studies as far as letality, body weight loss, liver and kidney weight changes or decrease in hematocrit are concerned. It appears that the toxicological properties of lead, at least as far as studied in above mentioned experiments, are not dependent upon the degree of ALAD inhibition.

The D-R-relationship has been calculated from 2 sources: a set of data on male workers, provided by Hernberg (Helsinki), n = 221; a set of data on children, provided by Schaller (Nürnberg), n= 80.

We calculated the percentage of subjects with ALAD < 700 µmol PBG/hr/l (i.e. lower limit in adults with PbB < 15 µg/100 ml) and with ALAD < 350 µmol PBG/hr/l; this corresponds to about 60 and 30% of average ALAD for PbB ⩽ 14 µg/100 ml, i.e. 40% and 70% inhibition. The recently agreed upon European standardised method had not yet been introduced; however the D-R-relationship will not be altered by using other units.

In adults the no-response level of PbB for 40% and 70% inhibition appears to be 15-20 µg Pb/100 ml and 25-30 µg/

100 ml respectively; the data suggest a lower no response level for children, particularly for inhibition > 40%: 5-10 µg/100 ml; for inhibition > 70% the level appears to be 20-25 µg/100 ml. The D-R curves are given in Fig.1.

δ-AMINOLAEVULINIC ACID EXCRETION IN URINE (ALAU)

Inhibition of ALAD hampers transformation of ALA to porphobilinogeen; increase of ALA in serum and in urine results; very few data on ALA in serum exist, many on ALAU. There is evidence that ALAU in children is a less valid parameter of response than in adults (Specter et al., 1971; Pawel et al., 1971) and that ALAU in females may be higher than in males (Roels et al., 1975). Because ALAU generally does not markedly increase at PbB < 40 µg/100 ml, it does not provide a good means of biological monitoring in the sphere of public health; particularly for PbB > 45 µg/100 ml there is a rapid increase in ALAU (Lauwerys et al., 1974; Zielhuis, 1973; Sakurai et al., 1974); however there are indications that in females increased ALAU already may occur at PbB < 40 µg/100 ml: Roels et al. (1975) found a positive correlation between PbB and ALAU in females and not in males for the range of PbB = 20-50 µg/100 ml.

ALAU as such probably has no direct relevance for health; increased ALA-excretion indicates that porphyrinsynthesis is impaired. McGillion et al. (1973) however observed increased activity in urine after i.p. injection of high doses of ALA. In occupational health ALAU > 10 mg/l is regarded as a warning signal and as indicator of potentially hazardous exposure (Zielhuis, 1969). There is a general consensus that in public health increase of ALAU should be regarded as unacceptable.

We calculated the percentage of male workers with ALAU > 5 mg/l (i.e. upper limit in non occupationally exposed subjects) and > 10 mg/l (acceptable limit in workers) from graphs published by Haeger-Aronsen (1971) and Selander et al. (1970); the method of Mauserall-Granick was applied for the majority of samples; a few were analysed according to Grabecki (Table 2).

COPROPORPHYRIN EXCRETION IN URINE (CPU)

It has often been shown that increase of PbB induces increased CPU; however CPU is less specific for Pb exposure than ALAU, and ALAU appears to be at least as sensitive as CPU. So, there is no advantage of monitoring CPU instead of ALAU: increase of CPU does not add new information in addition to increase of ALAU.

Table 1
Percentage of adults and children with more than 40% and 70% inhibition of averaged ALAD-activity in controls (PbB ≤ 14 µg/100 ml)

PbB	Adults			Children		
	n	>40%	>70%	n	>40%	>70%
≤ 14	-	-	-	9	11	0
15-24	30	13	3	37	73	8
25-34	26	62	12	24	88	13
35-44	32	97	22	10	90	50
45-54	53	100	68	-	-	-
55-64	37	100	92	-	-	-
65-74	43	100	95	-	-	-
	221			80		

Table 2
Percentage of male adults with ALAU > 5 mg/l and > 10 mg/l in relationship to PbB (µg/100 ml)

PbB µg/100 ml	n	>5	>10
11-20	17	0	0
21-30	27	0	0
31-40	36	14	3
41-50	55	33	11
51-60	38	74	37
61-70	34	88	50
	207		

In males the no-response level for ALAU > 5 µg/l is > 30 µg/100 ml, for > 10 mg/l > 40 µg/100 ml. The D-R-curve is given in Fig.2.

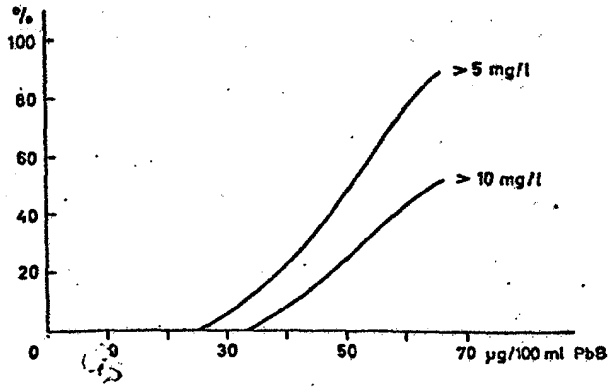

Fig.2
Percentage of subjects with ALAU > 5 mg/l and > 10 mg/l with increasing PbB

PROTOPORPHYRIN IX IN ERYTHROCYTES (PPE)

Increased lead burden interferes with utilisation of Fe^{++}; the haem synthesis is impaired. This process primarily takes place in the bone marrow. It causes increase of PPE in erythrocytes, excess Fe in blood, ultimately anaemia. There is a time lag up to 3 months before increase of PP may become apparent in peripheral erythrocytes (Sassa et al., 1973).

Increase of PPE appears to be sensitive and specific for lead exposure. According to Gajdos et al. (1973) a combination of increased ALAU, CPU and PPE without increased excretion of uroporphyrin is specific for lead effects; non-inhibited ALAD in combination with increased PPE indicates Fe-deficiency (Sassa et al., 1973); Fe deficiency may also contribute to increase of PPE in asymptomatic Pb absorption. There is one known rare disease, erythropoetic protoporphyria, that produces the markedly elevated PPE levels as seen in acute lead poisoning (Haeger-Aronsen et al., 1966). According to Baloh (1974) increase of erythrocyte porphyrins might even replace the blood lead test as the primary screening device for increased lead absorption.

In contrast to altered levels of ALAD or ALAU an elevated PPE may persist for months, even after PbB has already decreased considerably. The increase of PPE with PbB is curvilinear. The increase of PPE in lead exposure has not received much attention until recent years. Various methods are in use, some of them measuring protoporphyrin in erythrocytes (PPE) itself, others measuring free erythrocyte porphyrins (FEP), 90% of which is PP (Baloh, 1974).

In a human volunteer study with oral ingestion of Pb acetate Stuik (1974) observed a difference between adult males and females in their response of PPE: the increase in females occurred at lower PbB (25-35 µg/100 ml against 35-45 µg/100 ml in males), and the slope was steeper. This has recently been confirmed for FEP in an epidemiological study in occupationally exposed males and females (Roels et al., 1975).

Sassa et al. (1973) studied FEP levels in children; they came to the following conclusions:

in a large group of children (n = 138) with PbB = 20-80 µg/100 ml the coefficient of correlation between log FEP and PbB = + 0.72;

in a group of these children (n = 26) known to have had constant Pb levels for at least 3 months r = + 0.91.

Because methods for measuring PPE and FEP are not standardised, the levels as such reported in literature cannot be grouped together. The author therefore took as *cut off level* the PPE/FEP level not exceeded by about 95% of subjects with PbB < 20 µg/100 ml.

Table 3
Percentage of adult male subjects exceeding FEP levels as found in subjects with PbB < 20 µg/100 ml (data Roels, 1974)

PbB	n	% > "normal" level
11-20	26	0
21-30	43	7
31-40	32	19
41-50	4	100
51-60	2	
61-70	2	
	109	

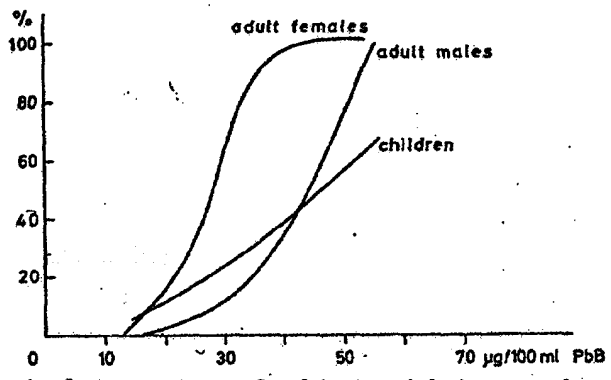

Fig.3. Percentage of subjects with increased FEP with increasing PbB

In order to calculate the D-R-curve for *adult male subjects* the author used the following data:
FEP levels in 109 subjects (non-exposed and exposed) studied by Roels (University of Louvain, personal communication 1974); 95% of subjects with PbB < 20 µg/100 ml did not exceed 80 µg FEP/100 ml ery. The D-R-relationship is given in Table 3 and Fig.3.

The D-R-relationship for *adult females* (non exposed and exposed), also based upon the study by Roels et al. (1975), is given in Table 4 and Fig.3.

The D-R-relationship for *children* has been calculated by combining data on FEP given by Schaller (Nürnberg) and Piomelli (Balloh, 1974) (Table 5 and Fig.3). Sassa et al.'s (1973) data were not used for the calculation, because they did not examine children in the PbB-range < 14 µg/100 ml, and because they reported their FEP levels only at PbB 20, 30, 40 etc. µg/100 ml.

Table 4
Percentage of adult female subjects exceeding FEP levels as found in subjects with PbB < 20 µg/100 ml

PbB	n		% > "normal" level	
11-20	28		4	
21-30	9		33	
31-40	8		90	
41-50				
51-60	4		100	
61-70				
	49			

Table 5
Percentage of children exceeding FEP levels in subjects with PbB < 20 µg/100 ml

PbB	n		% > normal level	
<20	87		5	
21-30	72		21	
31-40	24		29	
41-50	14			
51-60	12	36	64	
61-70	10			
	219			

Comparison of the 3 D-R-curves highly suggests an *increased response* of PPE (FEP) in *adult females* in comparison to adult males; however, the number of data on females is still very limited. The data are also suggestive for increased response in children; earlier response in children is also suggested by recent data from Roels et al. (1975).

Increase of PP in erythrocytes should be regarded as an early biologic response, indicating interference of Pb with haemsynthesis. The response appears to be more sensitive than increase of ALAU, also in adult male subjects. Presence of Fe-deficiency (in women due to menstrual blood loss, in children due to low socio-economic status and malnutrition?) may be a wide spread intervening factor, asking for extra caution. It should be granted, this is still a hypothesis, not adequately studied yet.

The no-response level for increase of PPE (FEP) will be about PbB 20-25 µg/100 ml in adult females and children, and 25-30 µg/100 ml in adult males.

OTHER BIOCHEMICAL PARAMETERS OF RESPONSE

In a review paper De Bruin (1971) surveyed many possible biological responses as reported in literature, the majority of them observed in animal studies; in case of human exposure PbB levels often were not reported; moreover most human studies have been performed in long term exposed workers, particularly in those with clinical intoxication; they probably not always are relevant for the dose range of PbB as discussed in this paper.

Increased urinary excretion of *hydroxy-indolacetic acid* (HIAA) has been studied in 11 yr old children living in a highly polluted area (Pb in air 31 $\mu g/m^3$); HIAA was reported to be more sensitive than ALAU (Ghelberg et al., 1966, 1974). In workers Urbanowicz et al. (1969) found that increase of ALAU was always accompanied by HIAA; HIAA reached its maximum earlier than ALAU or CPU in relatively highly exposed workers. Stankovic et al. (1974) observed increased excretion of both ALA and HIAA in non-occupationally exposed subjects, living near a lead plant. In above mentioned studies PbB was not measured; PbB > 40 µg/100 ml will probably have been present in many cases. Szadkowski et al. (1973) however reported a decreased HIAA excretion (and not an increase) in policemen with a slightly increased PbB (20.4 ± 5.0 µg/100 ml), without increase of ALAU; these authors emphasized that analysis of HIAA is very timeconsuming, and up to now not suitable for epidemiological studies. At this moment it is not possible to arrive at a consensus on the relationship between PbB and HIAA-excretion. Moreover, the meaningfulness in regard to health is not clear; neither is the mechanism of action.

In 1973 Cooper et al. reported on blood chemistry in over 300 workers; average duration of exposure 16.3 yrs; in 37% of workers PbB was > 70 µg/100 ml; median PbB = 63 µg/100 ml. The following conclusions were drawn: no relationship with PbB existed for Ca, P, glucose, cholesterol, total proteins, serum albumin, alk. phosphatase, lactic acid dehydrogenase, urea nitrogen; uric acid had a low positive correlation (r = 0.164); there was an indication of increased bilirubin for PbB > 70 µg/100 ml; transaminase (SGOT) had a low positive correlation (r = 0.175). The slight changes in a few biochemical parameters in this group (with PbB > 70 µg/100 ml in over a third of subjects) do not indicate health impairment in subjects with PbB < 70 µg/100 ml; the no-effect levels for these types of changes will probably be above 40 µg/100 ml.

Moncrief et al. (1964) reported an increased *pyruvate level* after glucose dosage in about 50% of children with PbB =

40-60 µg/100 ml; this presents evidence of abnormal citric acid cycle. Not enough data are available to suggest a D-R-relation; a no-effect-level cannot be given.

HAEMATOLOGICAL RESPONSES

Lead affects blood cells in various ways, sometimes more or less independent from effects on porphyrinogenesis. Hernberg (1970) presented a review of work by the Finnish group on subtle effects on erythrocytes function.

Lead affects the *erythrocyte membrane*. In exposed workers, some of them with clinical intoxication, Hernberg (1970) described decreased *Na^+-K^+-ATPase activity*; no correlation existed with conventional haematological parameters (e.g. PbB); this lack of correlation was thought to be due to effect of Pb on developing cells in bone marrow and not in peripheral blood. There did not exist conclusive evidence of increased K^+ turnover from the erythrocytes; active transport was unaffected even though activity of Na^+-K^+-ATPase apparently was partly inhibited. There existed a wide range of variation in this enzyme activity. Secchi et al. (1973) studied this enzyme in critical population groups, not occupationally exposed to Pb: in males with PbB = 38 ± 10 µg/100 ml (n = 10) or with PbB = 36 ± 9.3 µg/100 ml (n = 22) they found a decreased Na^+-K^+-ATPase activity if compared with a group with PbB = 32 ± 8.2 (n = 26). From the individual data of this study (received by personal communication) the author calculated the percentage of subjects with < 40 µmol P/hr/mg tyrosine as indicator of decreased Na^+-K^+-ATPase activity (Table 6). The D-R-relationship is given in Fig.4.

In this study by Secchi et al. in critical population groups living in Miland (Italy) PbB levels are high if compared to levels as reported from other Western-European and American cities. If PbB determination had provided too high values because of faulty techniques, the D-R-curve would even shift to lower PbB levels. The coefficient of correlation between PbB and Na^+-K^+-ATPase activity was rather small (r = -0.37); sensitivity and specificity apparently is poor. Up till now this study presents the only indication that at rather low levels of PbB (< 30 µg/100 ml) about 50% of subjects already had a moderate inhibition; the slope of the curve is small; subjects with PbB < 20 µg/100 ml already had an inhibition in 15-20% of cases. One has to await for confirmation in more studies, before the health significance can be evaluated.

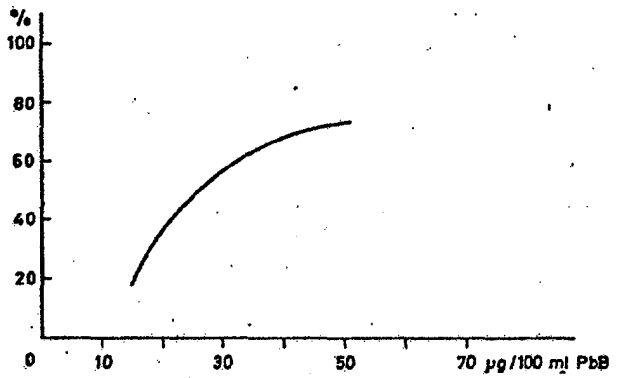

Fig.4
Percentage of subjects with inhibited Na^+-K^+-ATPase with increasing PbB

Table 6
Percentage of subjects with inhibited Na^+-K^+-ATPase activity (<40 µmol P/hr/mg tyrosine) in relationship to PbB (µg/100 ml)

PbB	n	Na^+-K^+-ATPase < 40 (%)
10-19	11	17
20-29	21	48
30-39	33	64
≥40	18	72
	83	

The Finnish group also studied *oxydative degradation*: increase of glucose consumption; the average *life span of erythrocytes* decreased from 120 to 101 days in heavily exposed workers with PbB = 59-162 µg/100 ml; the degree of shortening correlated best with that of reticulocytosis, but also with anaemia, CPU, PbB (Hernberg et al., 1967). The no-response level for these parameters probably is > 50 µg/100 ml (Hernberg, 1974, personal communication).

Roels et al. (1974) established a negative correlation between PbB and reduced glutathion (GSH) ($r = 0.42$; $n = 110$). From the individual data of this study (received by personal communication) we calculated the D-R-relationship for GSH < 58 and < 70 mg/100 ml rbc. (Table 7). The D-R-curve is given in Fig.5. This study presents evidence that at rather low PbB levels (< 30 µg/100 ml) slight reduction of GSH already starts to occur; however sensitivity and specificity in regard to PbB apparently appears to be rather poor; the slope of the curve is slight. The health significance of this not yet confirmed finding is still under discussion. The no

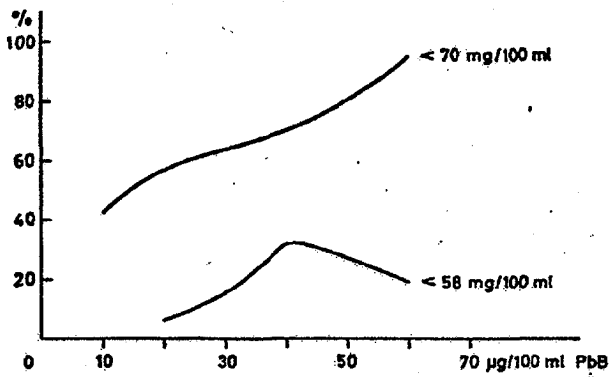

Fig.5. Percentage of subjects with decreased GSH with increasing PbB

Table 7
Percentage of subjects with GSH < 58 and < 70 mg/100 ml rbc in relationship to PbB (µg/100 ml)

PbB	n	GSH < 70	GSH < 58
<14	17	41	0
15-24	32	63	6
25-34	23	57	13
35-44	15	67	33
45-54	23	95	18
55-64			
65-74			
	110		

response level of PbB for decrease of GSH < 58 µg/100 ml rbc probably is about 25 µg/100 ml.

Lead may induce increased *osmotic resistance* of erythrocytes. According to Quazi (1971) this phenomenon might be used as a simple screening test in children with positive results in 85% of subjects with PbB > 60 µg/100 ml; it was not positive at levels below 40 µg/100 ml. Not enough data are available to suggest a D-R-relationship.

Ghelberg et al. (1966) and Barnea et al. (1968) observed increased prevalence of erythrocytes with *Heinzbodies* in children (PbB was not measured); the data as given by the authors suggest that exposure may have been rather high, with PbB levels exceeding 35-40 µg/100 ml. No D-R-relationship can be given.

It is wellknown that *anaemia*, i.e. decrease of *haemoglobin* (Hb) and of *number of erythrocytes* may occur in exposed subjects before clinical phenomena become manifest. Anaemia probably does not occur at PbB < 40-50 µg/100 ml. Sakurai et al.

(1974) did not observe any decrease of Hb and number of erythrocytes in a large group of workers with PbB up to 50 µg/100 ml. Betts et al. (1973) found a significant negative correlation between Hb and PbB; a decrease already occurred in 36% of children with PbB = 37-60 µg/100 ml, against 14% in case of PbB < 37 µg/100 ml. Peuschel et al. (1972) examining 58 children of 1-6 yrs with an increased lead burden (PbB > 40 µg/100 ml) observed a curvilinear decrease in Hb between PbB = 40 and 130 µg/100 ml; however the socio-economic condition of this group was very poor.

Cooper et al. (1973) studied several haematological parameters in a group of workers, one third of them with a PbB > 70 µg/100 ml; median PbB = 63 µg/100 ml. The following conclusions could be drawn: average Hb did not decrease up to PbB = 100 µg/100 ml; red blood cell counts and haematocrites did not correlate with PbB; 14% of workers with PbB > 70 µg/100 ml had a low mean corpuscular volume, against 2% in those with PbB < 70 µg/100 ml; microcytosis occurred in 25.9% of subjects in the high PbB group, against 8.6% in the low Pb group; macrocytosis in 6% and 2.7% respectively. Also Kochen et al. (1973) could not find any relation between Ht and PbB. Ghelberg et al. (1974) observed a tendency to *macrocytosis* in an adult population with increasing exposure; PbB was not measured.

From this short review on haematological responses the following conclusions may be drawn:

little evidence exists that erythrocyte functions are impaired in subjects with PbB < 35-45 µg/100 ml;

haematological parameters do appear to be neither sensitive nor specific in regard to increase of PbB;

the suggested decrease of GSH and of Na^+-K^+-ATPase activity at low PbB should be confirmed by other studies, before the health significance can be evaluated.

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