Int.Arch.Occup.Hlth 35,19-35 (1975)

Dose-Response Relationships for Inorganic Lead

II. Subjective and Functional Responses – Chronic Sequelae – No-Response Levels

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Received January 20, 1975 / Accepted February 5, 1975

Summary. Following a proposal of dose-response (D-R) relationships for various biochemical and haematological parameters in part I, this paper discusses D-R-relationships for subjective and functional responses and for chronic sequelae. Lead in blood levels (PbB) are regarded as "internal dose". It appears not to be possible to suggest adequate D-R-relationships; however various no-response levels could be suggested. The concept of no-response level and of D-R-relationship is reevaluated. Various interfering factors are mentioned, which allow only approximative answers in regard to no-response levels and place and/or shape of D-R-curves. An overall view of the D-R-relationships presented endorses the previously proposed Biological Quality Guide for the distribution of PbB levels within a population group: adherence to this guide very probably will prevent any health impairment in children and adults.

Key words: Lead - Biological Response - Lead in Blood - Central Nervous System.

INTRODUCTION

In part I of this paper (Zielhuis, 1975) the concept of dose-response (D-R) relationships has been discussed. Lead in blood levels may be used as indicators of "internal dose". D-R-relationships for various biochemical and haematological responses have been proposed for the dose-range of PbB = 0-70 µg/100 ml. In this paper the same approach will be followed for subjective and functional responses, mainly from the nervous system, and for chronic sequelae. However, much less quantitative data are available; moreover the *specificity* of these responses is poor. It will not be possible to propose quantal dose-response data, although proposals for no-

response levels will be presented. This review will conclude with a reappraisal of the concept of D-R-relationships as given in part I.

SUBJECTIVE SYMPTOMS

Subjective symptoms due to increased lead exposure are highly *non-specific*. One therefore has to rely on carefully conducted epidemiological studies using standardised questionnaires.

Sakurai et al. (1974) studied 142 shiftworkers exposed for 1/2 - 21 yrs; average age 30.5 yrs; PbB = 9-63 µg/100 ml. This group was compared with a control group (not matched: no shiftworkers); n = 76, mean age 27.4 yrs, PbB = 3-25 µg/100 ml. The exposed group gave significantly more positive answers on a modified Cornell Medical Index Questionnaire (245 questions); and also more positive answers on a Pb-symptoms questionnaire (26 questions). However the authors quite rightly did not pay great attention to these differences because the groups were not matched (e.g. shiftwork versus non-shiftwork). More indicative was their finding that *within* the exposed group no relation existed between number of symptoms and PbB levels. The authors therefore concluded that the symptoms are *not* likely to be *induced by lead when PbB < 50 µg/100 ml*.

Guinee et al. (1974) asked parents of children (1-4 yrs of age), screened by the lead poisoning control program of New York City, about several lead associated symptoms; all children had a PbB > 60 µg/100 ml. The percentage of children with these symptoms in dependance of PbB was calculated from the data presented by the authors (Table 1).

Because no data are presented on children with PbB < 60 µg/100 ml, no reference data are available for non-exposed children; a no-response level cannot be given. About 40 % of children with PbB = 60-69 µg/100 ml had symptoms, but 60 - 70% of those with blood levels > 90 µg/100 ml; although the symptoms are highly non-specific (e.g. poor appetite, vomiting, pallor, diarrhee, headache, abdominal pain), decreased fitness with rising PbB is evident.

One may conclude that at the present state of knowledge it is not possible to derive a no-response level for subjective symptoms in children, let alone an adequate D-R curve. More carefully designed studies should be undertaken: standardised questionnaires, matched controls, both in children and adults, paying due attention to interfering variables as socio-economic status, nutrition, interhuman relationships.

Table 1
Percentage of children with subjective symptoms in dependance of PbB (Guinee et al., 1974)

PbB µg/100 ml	years of age 1	2	3	4
60-69	43.0	41.4	40.5	40.1
70-79	45.9	50.3	44.7	50.9
80-89	54.5	51.6	53.7	50.0
90-99	70.0	64.5	68.4	60.0
>100	61.7	68.8	66.7	72.7
No.of children	835	710	413	296

CENTRAL NERVOUS SYSTEM, BEHAVIOR

In children and adults *acute encephalopathy* undoubtedly is one of the most serious consequences of (highly) increased lead burden. Such events may occur in adults with excessively high PbB-levels (> 80 µg/100 ml). According to NAS (1972) acute or chronic encephalopathy may occur at PbB > 80 µg/100 ml in adults and > 60 µg/100 ml in children. Betts et al. (1973) described 8 cases of encephalopathy in children; in all cases PbB was > 99 µg/100 ml. Within the large number of children examined by Guinee et al. (1974) there was a 1.0-1.5% incidence of convulsions in case of PbB 60-79 µg/100 ml, 5% at PbB 90-99 µg/100 ml and 10.6% at PbB > 100 µg/100 ml. The no-effect level for clinically manifest encephalopathy appears to be lower in children than in adults; according to Chisolm (1971) it does not occur at PbB < 50 µg/100 ml; the range of PbB = 50-80 µg/100 ml remains an area for concern.

At this moment the hazard of effects on the central nervous system, manifesting themselves in *behavioral changes* or in *"minimal brain dysfunction"*, constitute one of the main topics of research. In 1972 NAS concluded: "existing studies, if not definitive, nevertheless afford some presumptive evidence of central nervous system dysfunction". Drawbacks in the study designs very often are: interference of socio-economic condition, presence of high PbB (>> 50 µg/100 ml) - even of acute poisoning - in the past. The question is not any longer whether lead can induce such effects, but whether slightly to moderately increased PbB levels, e.g. up to 50-70 µg/100 ml are to be regarded as causative. In 1970 Wiener reviewed the literature up to 1968. He concluded "that none of the studies provided a definitive answer to the question: Is mental deficiency associated with lead ingestion which is asymptomatic

or which produces symptoms less severe than encephalitis? Those reports which claimed positive findings had either used too few cases from which to generalize or had not provided controls for relevant variables as social class, pica or premorbid status". Klein et al. (1974) also stated that uncontrolled follow-up studies "strongly suggested, but failed to prove that the large number of asymptomatic children with lead levels between 40 µg/100 ml and 80 µg/100 ml were at risk for central nervous system damage".

In the USA David et al. (1972) suggested lead as one of the causes of *hyperactivity* in children; the authors themselves stressed the lack of proof of a causal relation; Bulpitt (1972) critisized their statistical treatment of data. In London Lansdown et al. (1974) examined a population of school children (< 17 yrs of age); there was no relationship between PbB and intelligence (Wechsler test, reading test) and behavior (e.g. overactivity as rated by the teachers); the authors suggested that social factors were more important than exposure to lead in determining mental development. This study has been critisized by Bryce-Smith et al., Landrigan et al., David et al. (1974); the authors however, discussing various comments, did not see any reason to reconsider their conclusion. In the opinion of the author, neither David's positive, nor Lansdown et al's negative study are adequately conclusive.

De la Burde et al. (1972) and Peuschel et al. (1972) observed evidence of increased incidence of dysfunction of the central nervous system (irritability, clumsiness, fine motor dysfunction, impaired concept formation, etc.) in groups of children; however PbB was always evidently increased, in most cases > 60 µg/100 ml. Kotok (1972) established that development deficiencies (the Denver Development Screening test, according to the author a somewhat insensitive measure of development, was used) in a group of asymptomatic children with elevated lead levels were identical to those of a control group similar in age, sex, race, environment, neonatal condition, presence of pica; moreover the deficiencies could be correlated with inadequacies in the childrens' environment. Klein et al. (1974) pointed out that in many studies pica is not used as a controlled variable; it is possible that pica rather than lead is the variable that resulted in differences between groups, because pica is often seen in children with mental retardation not secondary to plumbism and has been related to emotional factors arising from a disturbed mother-child relationship.

Recently McNeil et al. (1974) published an initial evaluation of longterm effects of elevated PbB levels in asymptomatic children, living in El Paso, USA. In 138 of 206 chil-

dren, who volunteered (possibility of selection?) to participate, 21 mths-18 yrs of age (median 9 yrs), the authors could not find any evidence of non-specific complaints, hyperactivity, psychometric testing values, if compared with a matched control group. There existed a significant difference in one personality test; however this was explained by geographic isolation etc., and not by Pb exposure. The average PbB levels were respectively 50 µg/100 ml (14-93) and 16 µg/100 ml (10-28). The authors concluded that initial evaluation of this group of children suggests that prolonged exposure to subclinical lead levels in the 40-80 µg/100 ml range had not resulted in apparent deleterious effects.

In a group of adults Hänninen (Hernberg, 1973) observed slowness of performance, psychomotor disturbance, slight intelligence defects, changes in personality; however, these subjects either had experienced a clinical intoxication or an evidently increased Pb body burden (PbB > 60 µg/100 ml). Morgan et al. (1974) recently reported preliminary results of an extensive study of behavioral functions in lead exposed workers (n=190) (PbB= 60.48 ± 16.96 µg/100 ml, in 68% of subjects PbB < 80 µg/100 ml; majority of subjects < 5 yrs or > 20 yrs exposed). The research group examined 36 non-independent measures of general performance; in addition 44 measures of sensory, psychomotor and psychological functions were obtained. Preliminary analysis suggested the following: PbB correlated with several response-time measures, ALAD with measures from strength-endurance-recovery tasks; both correlated with eye-hand coördination. This study therefore suggested that in the range of PbB < 80 µg/100 ml some behavioral changes did occur in adult workers; in addition variability of performance increased with PbB; only during periods of high-demand performance a worker's capacity probably may increasingly be degraded by increase of body burden of lead. The authors themselves stressed that this *preliminary* analysis still has to be confirmed by further analysis and research.

In their book "Subclinical lead poisoning" Waldron et al. (1974) quoted available literature on children; the authors concluded that "the evidence is sufficient to indicate that organic and inorganic lead can produce disturbances in brain metabolism. It is certain that it can produce mental impairment and so it would seem desirable that every effort be made to reduce the body burden of children to as low a level as possible". The statement appears to be correct in its general sense; however, most of the data quoted refer to children who had, either at present or in the past, evidence of markedly increased lead body burdens. Their survey does not present any evidence that mental impairment is probable

to occur in children who never exceeded 40-50 µg Pb/100 ml.

However, a few recent *experiments in animals* sound a note of caution. Goldberg et al. (1974) exposed suckling mice from birth, first through their mother's milk and afterwards through drinking water (2 mg Pb/l); the exposed mice became more than three times as active as controls; a number of drugs used in treatment and diagnosis of minimal brain dysfunction in children acted in the same manner in the exposed animals as in hyperactive children; although no classical signs of lead toxicity were observed, neither cerebral oedema nor histopathology, growth of the offspring was decreased 10%; this suggests a more intensive attack on biological systems than will be the case in children with moderately increased lead burden. Carson et al. (1974) gave lead (ingestion) to two groups of ewes in sufficient quantity to maintain PbB = 34 µg/100 ml (4.5 mg Pb/kg/day) and 18 µg/100 ml (2.3 mg Pb/kg/day); lambs from both groups had PbB = 24 and 17 µg Pb/100 ml respectively (in controls 6 µg/100 ml). Between 10 and 15 months of age the lambs of the first group required significantly more days to learn visual discrimination function than lambs of the second group and controls. The authors considered the data consistent with clinical reports on effects of lead poisoning in children (however, usually with higher PbB's). In extrapolating from ewes and lambs to mothers and children, one should take into account the apparently very different pharmacokinesis of lead: the authors needed the hugh dosages of 2.3 - 4.5 mg/Pb/kg/day for 5 weeks to induce PbB = 18 and 34 µg/100 ml; in case of human beings one should have expected much higher PbB levels; the experimental data are suggestive for a striking difference in uptake and/or distribution of Pb through the body.

Animal studies have also suggested increased incidence of *gliomas* due to chronic feeding of Pb to young rats. However, Zaworski (1973), comparing Pb levels in brains of subjects with no known occupational history of Pb exposure, with Pb levels in cases of brain tumors, could not find any significant differences. The data also demonstrated an increase of Pb in brain tissue with age: a maximum level is reached after the 2nd or 3rd decade of life; the highest concentrations are from 4 to 10 times that at birth or in childhood. According to Waldron et al. (1974) the concentration of lead in the adult brain is less than in the infant; however this is not confirmed by the data they quote themselves in their own tables 29 and 30.

One may draw the following *conclusions* from this review of literature:

1. Lead exposure can induce *acute* and *chronic encephalopathy* in adults and in children; there exists some suggestive evidence that *no effect levels* will be somewhat lower in children (probably > 50-60 µg/100 ml) than in adults (> 80 µg/100ml).

2. *Minimal brain dysfunction* and consequently *deviant behavior* may be caused by increased lead intake; there does not exist clear evidence that this will occur in case of PbB levels never exceeding 40-50 µg/100 ml, neither in children nor in adults.

3. At this moment the potential effects of Pb on brain function constitute one of the main topics for concern, more so in children than in adults. More carefully planned *prospective* studies are badly needed. Because mental and behavior development are determined by a *multitude of factors*, the study design should take these factors (e.g. nutrition, socio-economic status, parental care) into account as much as possible.

NEUROLOGICAL DISORDERS

It is not well possible to distinguish various neurological disorders very clearly from the potential effects on the central nervous system as discussed above. However, because emphasis will be placed upon the *peripheral* nervous system, a separate review may bring out the variety of effects on the nervous system, proved or suggested to be caused by increased Pb exposure.

The occurrence of paralysis of peripheral nerves (mainly n.radialis) in highly exposed workers is a well established signal for effects of Pb on the peripheral nervous system. Warren (1974) reviewed literature on various neurological diseases, some of them occurring in animals. He produced preliminary evidence to support the hypothesis that there is some relationship between lead insult and demyelination, and so with the geographical distribution of multiple sclerosis in humans, swayback in sweep, scrapie in sheep, kuru in humans, lead lameness in lambs, amyotrophic lateral sclerosis in humans. There apparently exist some indications which warrant further investigation, but the positive evidence is still very scanty. A relationship with multiple sclerosis could not be established by Westerman et al. (1974).

More relevant for the topic under discussion however are the data of Seppäläinen et al. (1972) and Seppäläinen (1974): with a sensitive electrophysiological technique she established impaired *motor conduction velocity* of ulnar and median nerves and particularly impaired conduction velocity of

slower motor fibers of n.ulnaris, not only in subjects who had experienced a clinical intoxication, but also in 28 workers, whose PbB did not exceed 70 µg/100 ml in the last 3-4 yrs and in whom no clinical signs of lead poisoning had been noticed during the period of employment (up to 23 yrs). The deviation of function in the last group placed itself between average conduction velocity in the highly exposed group and in the controls; a dose response relationship was evident. Abnormal findings already occurred in the range of PbB = 50-60 µg/100 ml. There was no correlation between neurological signs and biochemical tests of exposure or response; so one can not be sure of preventing neurological impairment by prevention of impaired haematopoesis. The Finnish studies suggest that the generally agreed upon PbB = 70 µg/100 ml as acceptable level for occupationally exposed workers, should be reevaluated. It is not possible to derive a no-effect level; Hernberg (personal communication, 1974) suggests 50 µg/100 ml, however with a question mark.

CLINICAL SEQUELAE

Lead exposure might possibly induce increased incidence of various chronic diseases, each of them not specific for lead induced responses. Epidemiological studies have usually been performed in adult workers with long term exposure to lead; because of change of jobs, retirement, drop outs for various reasons, it is very difficult to conduct adequate field studies. Moreover, for the discussion in this paper it is not relevant to know whether late clinical sequelae occur in subjects who experienced one or more lead intoxications, neither in those whose lead burden was unacceptably high (PbB > 70-80 µg/100 ml). The same applies to studies in children.

According to Malcolm (1970, 1971), Cramer et al. (1966) and Goyer (1971) there is no evidence of increased incidence of hypertension, cerebrovascular incidents, heart disease, cancer, (probably) chest disease, impaired kidney function in workers with long term exposure (PbB < 70-80 µg/100 ml). Stopps (1966) examined the health status of male workers exposed to organic lead (TEL); Pb in urine was twice that in a control group; there was no increased prevalence of hypertension, coronary heart disease, peptic ulcer, leucocytes count, electrocardiographic abnormalities, even although Hb might be slightly lowered. In the large scale mortality study of Cooper et al. (1974), already referred to in part I, the standardized mortality ratio (SMR) for all causes was 107 for

smelter workers and 99 for battery plant workers. Death from neoplasms were in slight excess in smelters, but not increased in battery plants; there was no excess of kidney tumors (although induced in animal experiments). The SMR for cardiovascular-renal disease was 96, respectively 101, i.e. roughly the same as for the general populations, but not as good as would be expected in an employed population; there was definitely no excess from either stroke or hypertensive heart disease; however, deaths classified as "*other hypertensive disease*" or "*chronic or unspecified nephritis*" were higher than expected. The life expectancy was approximately the same as that of all US males. The authors concluded: "considering the high levels of exposure and the relatively small deviations from expected mortality, one can be optimistic in predicting no detectable impact on mortality for male adults occupationally exposed to lead controlled in conformity to current standards" (this corresponds to PbB < 70-80 µg/100 ml).

Some authors, particularly from Eastern Europe (e.g. Alexieva et al., 1972; Panova, 1972) mentioned non-specific diseases or subclinical functional disturbances in lead workers: liver function, gastric secretion, food digestion, dermal vascular reactivity, ovarial function; in most cases exposure probably has been rather high; moreover data from adequately controlled studies are hardly available.

Hickey et al. (1967) studied specific mortality in general population groups in various parts of the USA; they could not find any relationship between Pb in ambient air and mortality from various diseases. Szadkowsky et al. (1969) studied PbB in 176 patients suffering from various internal diseases; they found no evidence that Pb could be held responsible as a causative factor.

An area for concern is the potential effect on *chromosomes*; this has extensively been discussed at a Berlin conference "Blei und Umwelt" (1971) and at the Amsterdam ECE-EPA symposium on Lead in the Environment (1972, published in 1973); conflicting data are reported; no consensus has yet been reached. Recently Forni (personal communication, 1974) reported on studies in Italy: a follow up of several subjects from preemployment to several months of exposure suggested an increased rate of chromatic and unstable chromosome changes as a very early occurrence in workers exposed to lead. These findings should still be regarded as preliminary and not as definitive.

Of great importance is the question whether chronic lead exposure may induce impaired *renal function* or *kidney disease*. In an extensive review Goyer (1971) concluded that there is no

evidence that current levels of lead in the present day (American) environment will result in impaired renal function, neither in children, nor in adults. Cramer et al. (1974) examined humans with prolonged high exposure; their study suggests that there may be 2 or 3 stages in the response of the kidney: early phase, lasting less than 1 year, with nuclear inclusion bodies in proximal renal tubular cells, no impaired renal function, relatively high urinary output, reversible; second phase, after 4 or more years of exposure, no ability to form inclusion bodies, excretion of Pb decreased, moderate degree of interstitial fibrosis, no gross impairment of renal function; possibly a third phase with frank renal failure after severe prolonged exposure. This study on sequelae of high exposure is consistent with the views expressed by Goyer on present day ambient exposure, and by Cooper et al. (1974) on longterm occupational exposure.

From this short review we may draw the following *conclusions:* there does not exist evidence of any increased incidence of various non specific disease states - as discussed above - in adults or children, whose internal dose *never* exceeds *40-60 µg Pb/100 ml;* the no-response level may even be considerably higher. It is not possible to derive adequate D-R-relationships.

NO-RESPONSE LEVELS

In analogy with the distinction made previously (part I) between dose-effect (D-E) and dose-response (D-R) relationships, we might distinguish between:

no-effect level, i.e. the maximal dose which does *not* induce a *specified effect* in *an individual*; this definition is more strict than in official documents of WHO/FAO, etc.;

no-response level, i.e. the maximal dose which does not induce a *specified effect* with a *specified intensity* in any individual belonging to a *group* of subjects exposed.

These definitions may be regarded as describing *ideal* no-effect/response levels. However, in an *individual* presence of an effect can not be easily determined in an early stage. In the ideal case one should follow up the individual from pre-exposure into exposure, and frequently measure the parameter to be studied; whether a statistically significant change is going to be observed, depends inter alia upon the number of observations and the analytical variability. A second possibility is to compare the level of the parameter with that in a non-exposed control group; if the level exceeds $\bar{x} \pm 2\sigma$,

one may conclude to a significant deviation of the parameter; however, before such a deviation is reached, an early deviation may already have been presented. So, in many instances a no-effect level in an individual can only be estimated as a *practical no-effect level*.

In a *group* of exposed subjects the ideal no-response level indicates that none of the group members shows any specified intensity of a specified parameter of response. However, this level can not exactly be determined. One has to extrapolate from the D-R curve; because the curve approaches the horizontal (D)-axis asymptotically, it is not possible to determine an exact point. If the number of subjects examined changes, particularly the lower and upper parts of the curve also change. Estimation of a level corresponding to a certain percentage of affected workers provides a better way of prediction; because literature data do not yet cover large groups of exposed subjects, one should not approach the zero-% too much, e.g. 0.1, 1.0%; one should take about 5% as the cut-off percentage. So, one can estimate a *practical no-response level*, i.e. not inducing a specified intensity of a specified parameter of response in *5% of subjects*.

The word "effect/response" is *neutral*, it does *not* imply a deleterious impact on health; it does not correspond to "unacceptability" as such.

In both papers (I and II) internal dose is represented by PbB. Whether in an *individual* an *effect* is observed at a specified PbB level depends upon some decisions made and upon some intervening factors:

an effect is only observed, if one chooses to look for it (method of examination);

validity (sensitivity, specificity) of method (Zielhuis et al., 1974);

number of observations (longitudinal study);

biological and analytical variability of PbB and of effect;

detection limit of method.

Whether a *response* is observed in a specified *group* of subjects, *also* depends upon

number of subjects examined.

Whether a response is observed in a *population, also* depends upon

right choice of at risk groups.

It may be merely a theoretical question whether a threshold dose below which no effect occurs really exists; when some molecules or atoms enter the reactive region of other molecules or atoms, a chemical reaction may result; in this sense there may not exist a true no-effect level. However, in a

practical sense there do exist thresholds; intermolecular reactions not necessarily induce measurable and/or health-relevant effects (Hernberg, 1973). In regard to lead there do exist *practical no-effect levels* and *no-response levels*.

An effect should always be defined

qualitatively, e.g. change in ALAD, ALAU, nerve conduction velocity, subjective feelings;

quantitatively, e.g. a 40% inhibition of ALAD, an increase of ALAU > 5 mg/l or 10 mg/l, a threefold increase in spontaneous activity.

In practice it is impossible to determine exactly no-effect/response levels because of the factors mentioned above; therefore, levels suggested indicate the *approximate* level of PbB at which no effect is observed in individuals.

In part I and II D-R-relationships between PbB and various potential effects of lead have been discussed. Groups of subjects with PbB < 15-20 µg/100 ml have been regarded as controls, except in case of ALAD. From this review the following *conclusions* can be drawn:

ALAD: no-response level (no inhibition) about 10 µg/100 ml; no-response level for > 40% inhibition in adults 15-20 µg/100 ml, in children 5-10 µg/100 ml; for > 70% inhibition in adults 25-30 µg/100 ml, in children 20-25 µg/100 ml.

ALAU: no-response level for ALAU > 5 mg/l 30-40 µg/100 ml; no-response level for ALAU > 10 mg/l 40-50 µg/100 ml. The levels for *CPU* will be about the same; there are indications that in women these levels may be lower.

PPE/FEP: no-response level in adult males 25-30 µg/100 ml; in adult females and children 20-25 µg/100 ml.

Various other biochemical parameters: in most cases the no-response level will be at least 50-60 µg/100 ml.

Haematological effects: preliminary evidence is brought forward that at low PbB levels reduction of GSH and Na^+-K^+-ATPase activity already may occur; however the slope of the D-R curve is slight; if Na^+-K^+-ATPase activity < 40 µmol P/hr/mg tyrosine is taken as specified response, the percentage of responses increases already at PbB =20-29 µg/100 ml; for GSH < 58 µg/100 ml rbc at PbB = 25-30 µg/100 ml. Anaemia (decreased *Hb*) does not occur in otherwise healthy adults below PbB = 70-80 µg/100 ml; in socio-economically poor children not below PbB = 40-50 µg/100 ml.

Subjective symptoms: no-response level > 50 µg/100 ml in adults.

Encephalopathy: in adults no-response level >> 80 µg/100 ml; in children > 50-60 µg Pb/100 ml.

Minimal brain dysfunction, behavioral changes: no-response level > 50 µg Pb/100 ml.

Peripheral neuropathy: no-response level > 40 µg Pb/100 ml.
Late clinical sequelae: no-response level > 50-60 µg Pb/100 ml.

DOSE-RESPONSE RELATIONSHIPS REEVALUATED

In part I of this paper various D-R-relationships have been presented: with increasing PbB the percentage of subjects with specified intensities of specified effects also increases. However, one should not regard the given response frequencies as fixed figures because of various reasons:

If within a group of subjects a certain number of responding subjects is observed, then a repeated investigation of a similar group with the same methods not necessarily gives the same frequencies. Each calculated percentage has its statistical variability. The confidence range may be considerable when either the total number of subjects within a certain class of PbB's is small, or when the total number of responding subjects within even a large group of subjects is small. In case of relatively large groups for each class of PbB's, the confidence range will become relatively smaller with increasing percentage of subjects responding. The calculations as given previously often are based upon too small numbers of subjects with a stated PbB level.

Some D-R-relationships presented are based upon data from different laboratories, with maybe slight differences in techniques, e.g. for ALAD-adults and ALAD-children.

In addition to the statistically determined variability of response frequencies as mentioned above, the variability of the methods used and of effects/responses observed also increases the confidence range.

Groups of subjects with low PbB levels used as controls may not always belong to the same population group (socio-economic status, nutrition, age etc.) as groups with higher PbB-levels.

Because of this, the D-R-relationships and the no-response levels as presented should be regarded with caution as *suggestive indicators* of the *true* D-R-relationships, which certainly have to be confirmed in future epidemiological studies, paying due attention to size of groups examined and comparability of methods used.

In Fig.1 various D-R-relationships as presented in part I have been brought together. Even when taking into account the uncertainties in regard to the "exact" place of the no-response levels and the percentages of subjects with various responses as discussed before, this combination of D-R curves

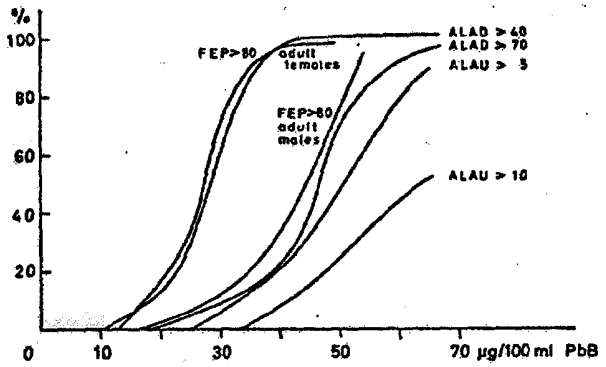

Fig.1. Dose-response relationships combined

highly suggests a specific *sequence of increasing responses and* a sequence of qualitatively *different responses* with increasing PbB-levels: as might be expected moderate (> 40%) inhibition of ALAD in adults proves to be much more sensitive than even slight increase of ALAU (> 5 mg/l); however slight increase of FEP (> 80 µg/100 ml rbc) in females is about as sensitive as ALAD-inhibition > 40% in adults, but not so in adult males. A marked inhibition of ALAD (> 70%) follows about the same pattern as increase of ALAU > 5 mg/l and FEP > 80 µg/100 ml rbc in adult males.

This sequence suggests the following conclusion for *biological monitoring* of population groups: if one wants to study the percentage of subjects with beginning evidence of response to lead, i.e. deviating from subjects with PbB < 14-20 µg/100 ml, measurement of ALAD-inhibition and increase of PPE (FEP) may serve as very good parameters, particularly in females (and children?), much more so than in males. In males PPE (FEP) has not much to offer above ALAU. For all subjects ALAD-inhibition remains the most sensitive parameter.

The D-R-relations as presented also indicate that for a population group with a distribution of PbB's according to the *Biological Quality Guide (BQG)*, as suggested before (Zielhuis, 1974), only a limited number of individuals, particularly females (and children?) might already show a slight increase of PPE (FEP), because in such a population 98% of subjects are below PbB = 35 µg/100 ml, but 10% > PbB = 30 µg/100 ml and 50% > PbB = 20 µg/100 ml; increase of ALAU will hardly occur. Further study will have to evaluate whether such a slight increase of PPE (FEP) in females and children with PbB = 20-35 µg/100 ml has to be regarded as acceptable or not. If not, than the BQG has to be decreased, because this guide should be geared to the most sensitive population group. On

the other hand, the BQG very much minimizes the possibility of subclinical effects on the central and peripheral nervous system and of any chronic sequelae.

Still, in this paper various uncertainties have been stressed; a few maybe very early biochemical changes are recently reported in literature (e.g. GSH, Na^+-K^+-ATPase), chromosomal aberrations are observed by some, and the question of minimal brain dysfunction and hyperactivity has not been adequately solved. There certainly is reason to reevaluate the guide for occupationally exposed workers as adhered to in western countries (PbB = 70 µg/100 ml); the recently discovered difference between adult females and males has to be studied, also in its pathophysiological mechanisms; emancipation movements tend to discard all restriction on female work opportunities. Moreover, in regard to public health, as stated before the potential effects on the behavioral development of children will still have to be studied more adequately.

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