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TO:

H. E. Hesselberg
R. Butler ✓
J. C. Calandra
E. J. Gay
R. Sugimoto

*Excellent Summary of
proposed Pb guideline.*

FROM:

D. R. Lynam, Ph.D.

Gentlemen:

Enclosed are two items which may be of interest.

1. Paper entitled, "Biological Quality Guide for Inorganic Lead", by Prof. R. L. Zielhuis.

This paper was received from Dr. Zielhuis who indicated that it had been sent to the Division of Health Protection, Economic Community of Europe. It was further indicated that the report has been submitted for publication to a Scientific Journal and at this time is not officially released.

2. Letter from Dr. R. A. Willoughby, University of Guelph.

At the ILZRO Idea Meetings in May it was proposed that we ask Dr. Willoughby for his comments regarding the research work of Dr. Buck in Iowa.

If you have any questions or comments about these items, please let us know.

Sincerely,



Donald R. Lynam, Ph.D.
Assistant Manager
Environmental Health

jm

encs.

cc: J. F. Cole
E. B. McCabe

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BIOLOGICAL QUALITY GUIDE FOR INORGANIC LEAD
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Prof. Dr R.L. Zielhuis, Amsterdam⁺

Environmental quality standards and guides
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Environmental quality standards are tools for governments to achieve and maintain environmental quality; they are the outcome of political decision making, taking into account scientific data, economic possibilities, socio-cultural factors, etc. Environmental quality guides are recommendations by scientific advisory bodies, mainly based upon dose-response curves (criteria), only taking into account effects on human beings (public health), plants, animals and material (Zielhuis 1973). Standards and guides may be issued for air, water, food, etc.

If a noxious substance is predominantly present in air, an air quality standard may serve the objective of protecting health. However, if the target (we will limit ourselves to human beings) is exposed to this agent by various routes of entry (e.g. respiratory, oral, dermal pathways) neither an air quality standard nor a food (water) quality standard will achieve adequate protection. The total environmental load has to be taken into account.

In the case of inorganic lead it is a well established fact that in the sphere of public health oral uptake may give a greater contribution to the body burden than respiratory uptake. In industry respiratory exposure is predominant, and in that case an air quality standard (Maximum allowable concentration, Threshold limit value) may serve the objective of protecting health of workers, whereas in public health emphasis upon one single route of exposure does not assure adequate protection.

Ambient air quality standards therefore only serve the objective of protecting public health if exposure takes place solely or predominantly by way of inhaling ambient air. In the case of e.g. lead, cadmium, mercury, ambient air quality standards as such apparently do not achieve this objective. An other approach has to be taken.

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In this paper this alternative approach will be discussed. A proposal will be worked out for inorganic lead exposure; a similar approach appears to be feasible for many other environmental pollutants.

Exposure - response
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In regard to exposure one should distinguish:

1. external exposure: concentration in air + duration of exposure; presence in food, water, etc., on skin
2. external load: the real amount of agent offered to the body per unit of time, taking into account respiratory volume, particle size, oral uptake, skin penetration, etc.
3. internal load: the amount present in the body as consequence of 1 and 2 and of elimination; in the case of inorganic lead to be distinguished into (Pietrowsky 1970):
 - rapid exchange pool (blood, soft tissues)
 - intermediate exchange pool (muscles, skin)
 - slow exchange pool (bone).

A relationship exists between various parameters of exposure: lead in blood (PbB) indirectly reflects external exposure and external load, and it also indicates the internal biologically available lead, the "real" dose; lead in urin (with or without provocation) may serve the same purposes.

If the no-effect level in the dose-response relationship is exceeded, effects will occur; effects of biological systems serve as parameters of response; in case of lead: disturbed porphyrin synthesis, obstipation, lead colic, encephalopathia, disturbed mental development, etc. Because there exists a relationship between internal load (particularly rapid exchange pool) and effect (qualitative and quantitative), effects may indirectly be used as predictors of internal load, and of external exposure.

Sequence of operation

Because the ultimate objective is to prevent adverse effects on public health, parameters of response should first be taken into account; one should determine the dose-response relationship. Dependent on the acceptability of effects from the viewpoint of public health, the acceptable internal or external dose should be determined. Such a sequence of operation is implied in establishing air quality guides for e.g. SO_2 , particulates, NO_2 , O_3 . The fact that Pb enters the body through various routes, complicates the setting of guides, and consequently of standards.

In the case of inorganic lead as a public health problem, the sequence of operation should be:

1. determine relationship between internal load and response (effects)
2. determine acceptability of response (For extensive discussion of the sequence of decisions to be taken see Zielhuis 1973)
3. determine levels of lead in blood (hair, teeth, urine, possibly after provocation test) which correspond with no-effect-levels or no-adverse effect levels. These levels represent the acceptable quality of biological systems, e.g. expressed as Pb in blood or Pb in urine, and serve as biological quality guides
4. determine relationship between biological quality guides and total uptake (pro unit of time, and duration of exposure): acceptable total external load
5. determine contribution through various routes and sources to this acceptable total external load
6. determine various quality guides for main sources of uptake: food, water, air
7. determine various emission guides based upon the contribution of sources of emission to sources of uptake
8. various guides become standards, if imposed by governmental authorities.

Contribution from oral uptake

In the USA the Env. Protection Agency (EPA)(1972) suggested that further reductions of air lead concentrations below $2 \mu\text{g}/\text{m}^3$ appeared to be indicated; they based this suggestion upon:

1. an assumed average daily intake through food and water
2. an assumed relative contribution of traffic exhaust to sources of uptake.

USSR issued ambient air quality standards for lead ($0.7 \mu\text{g}/\text{m}^3$) dis-regarding uptake through food and water.

However, there are strong indications that oral uptake of lead may differ considerably

- between individuals in one region
- between various regional groups.

The average uptake does not enough take into account the tails of the distribution curves. In UK average uptake is about $200 \mu\text{g}/\text{Pb}/\text{day}$, with extremes up to $400 \mu\text{g}/\text{Pb}/\text{day}$ (Martin 1973); Thompson (1971) found a range of $70-750 \mu\text{g}/\text{Pb}/\text{day}$ in 5 individuals in UK; Lehnert et al (1969) calculated for Germany (FRG) an average uptake of $518 \mu\text{g}/\text{Pb}/\text{day}$; Vigliani et al (196) suggested for miland $400-500 \mu\text{g}/\text{Pb}/\text{day}$. Zielhuis (1972a) calculated that within Western Europe average uptake probably differed by a factor 2 (and individual uptakes therefore by a factor much larger than 2) between various regions.

Considerable differences probably exist between (and also within) Western Europe and USA in e.g.

1. relative contribution of Pb in paint
2. relative presence of pica
3. relative contribution of Pb in wine, beverages, foodstuffs
4. choice of foodstuffs.

In Europe one can only use American data on the relationship between total uptake - internal load - response, and not data on e.g. relationship between Pb in air and Pb in blood; this may even be true in comparing various European regions.

The group of experts on lead, convened by the Div. Sanitary Protection Eur. Econ. Comm. (1972, 1973), agreed that not enough knowledge is available in regard to oral uptake (average and range) in Western Europe; it proposed investigations to gather relevant data. The conclusion of this must be that in such a situation adequate air quality guides and standards also cannot be recommended.

TEH 0470256

The use of biological quality guides

Parameters of internal load and of response in human subjects may be used for indirect monitoring of total environmental exposure, because there exists a clear relationship between external load and internal load (or response).

Biological quality guides (or standards) refer to acceptable levels of parameters in biological specimen in selected groups of human subjects; they indirectly measure the acceptability of the macro-environment.

Groups of subjects live in a certain environment (region, area, city) and are exposed to the agent under discussion through e.g. respiratory and oral uptake. In addition some individuals may have a specific micro-environment, due to peculiar food habits, environmental situations in their house or living (working) conditions; they may therefore exceed the given guide levels, not because the macro-environment for the whole group exceeds acceptable levels, but because the specific situation for these single individuals is "abnormal".

If within a group one or a few individual subjects exceed the guide levels, authorities should take action in regard to the micro-environment of these individuals. If however the group as such exceeds the guide level, there exists an unacceptable macro-environment specific for the group under discussion; this indicates a signal for action in regard to the total environment of the group.

As a matter of choice, one may take two as the percentage of exceptionally exposed subjects within a group; 98% of the group should not exceed acceptable level.

Target groups

Groups serving to monitor the ambient environment should be carefully composed:

1. at least 50 subjects, preferably about 100
2. the group should represent high risk groups, either in regard to exposure, or in regard to susceptibility; if these high risk groups do not exceed guide levels, one may conclude that the environment of other population groups will also be acceptable (the reverse is not necessarily true)

TEH 0470257

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3. similar social-cultural class
4. narrow age range, e.g. children 1-4 yr, pregnant women 20-30 yr, traffic policemen 30-40 yr
5. same sex
6. the subjects should live for the greater part of the day in the environment under discussion.

Percentile distribution

Even within target groups, as discussed before, biological levels of exposure or response will not be similar, due to difference in food uptake (quantitative, qualitative), habits of playing (indoor-outdoor), susceptibility, rate of absorption, etcetera. The environment and the susceptibility may differ for individual subjects, even within a carefully composed target group. The macro-environment should protect individuals living in it, even with their "normal variability" in way of living and in susceptibility, only disregarding about 2% of individuals with clearly exceptional exposure.

It is therefore not allowed to propose only one acceptable level, not to be exceeded in any member of the target group, as done by EPA (1972). The distribution of levels should be taken into account. If one chooses only one acceptable level, the exposure for all group members with lower levels could be increased. Such an approach is not feasible, because it does not take into account the "normal variability" between human beings. Therefore, a biological quality guide should give an acceptable distribution of levels; it serves as a guide for a group-environment, and not for a single individual micro-environment.

The distribution of levels can be given as such, but it is more appropriate to give the cumulative percentile distribution up to e.g. 50% (median value), 90% and 98% of members of the target group.

If one has to propose biological guides for xenobiotic agents, one should also take into account that - due to insufficiently developed or absent homeostatic mechanisms - levels in blood and tissues show a skewed distribution, e.g. blood levels for Pb, Cd, Hg in contrast to levels for Ca, Zn, Mg. This is another reason to use percentile distributions, because with skewed distribution average (arithmetic)

levels and standard deviations do not give an adequate insight in the range of levels occurring. Many literature sources only present e.g. arithmetic average, standard deviation (not allowed in skewed distributions) and range; such data do not present enough information on the group as such. Moreover, in setting guides and standards the tails of the distribution (increased exposure or susceptibility) very often have to determine the acceptability of exposure to the group as a whole (Zielhuis 1972b).

Maximum individual acceptable level of lead in blood
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In the Amsterdam Symposium on Environmental Health Aspects of Lead (1972) the author discussed the question whether "an internal chemical load as indicated by PbB levels up to 40 μ g Pb/100 ml presents any risk to public health" (Zielhuis 1972). The following conclusions were drawn:

1. the no-effect level of PbB in regard to increased excretion of δ -aminolaevulinic acid (ALA) in urine is about 40 μ g Pb/100 ml (see also NAS 1972);
 2. there are indications that the no-effect level of PbB in regard to decreased activity of δ -ALA-dehydratase (ALAD) in erythrocytes is 5-15 μ g Pb/100 ml;
 3. the no-effect level of PbB in regard to increase of protoporphyrin in erythrocytes (PPE) is at least 40 μ g Pb/100 ml;
 4. various effects on erythrocytes (e.g. lifespan, Na^+ - K^+ -ATPase activity in membranes, K^+ efflux), various other biochemical effects (e.g. immunobiological activity, alk. phosphatase, aminoaciduria, serumprotein pattern), various clinical effects on kidney function, vascular tension, cerebrovascular incidents probably do not appear in subjects who never exceeded PbB = 40 μ g Pb/100 ml.
- Some of these conclusions merit further discussion.

Decrease of ALAD activity is apparent already with PbB < 40 μ g Pb/100 ml, with a high positive correlation. Data of Schaller et al (1971) suggest a no-effect-level at PbB 5-15 μ g Pb/100 ml, but adequate proof is not available. An important question is whether decreased ALAD has any relevance to health, even in life time exposure. Some scientists even doubt whether the decrease in ALAD determined

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in vitro necessarily reflects an inhibition in vivo: the analytical method requires haemolysis of erythrocytes, Pb bound to membranes is liberated and may inhibit ALAD, which becomes extracellular; ALAD in vivo hardly comes into contact with Pb; this could explain the negative correlation between PbB and ALAD. If this hypothesis should hold true, then decrease of ALAD in vitro can not be regarded as a parameter of response, but merely as an indirect parameter of internal load. However, even if decrease of ALAD should be regarded as an effect, one should determine whether this effect is relevant for health (in broad sense: fitness, functional capacity, "quality of life"). NAS (1972) concludes in regard to decrease of ALAD at PbB 40 µg Pb/100 ml that "its biologic significance is dubious, because it is unaccompanied by any detectable effects on the biologic function of intact man". Only when PbB exceeds 40 µg Pb/100 ml decrease of ALAD may be significant in vivo, e.g. affecting ALA synthesis and excretion. Some studies on ALAD activity in other tissues (brain, liver) have been performed; in rats Millar et al (1970) found a more or less parallel decrease with ALAD in blood; however, at PbB 30 µg Pb/100 ml ALAD in the brain was not significantly reduced. The physiological significance of decreased activity of ALAD at a range of PbB 40 µg Pb/100 ml should be a topic for further research; at this moment, there are no reasons to regard decrease of ALAD activity as such as an adverse effect on health.

Effects on central nervous system, manifesting themselves in behavioral changes are discussed by NAS (1972): "existing studies, if not definitive, nevertheless afford some presumptive evidence of central nervous system dysfunction". However, this conclusion was mainly based upon data in children with a history of clearly unacceptable PbB (>>40 µg Pb/100 ml), although manifest encephalopathy could be absent. EPA (1972) also summarized some studies in children with manifest lead poisoning or with asymptomatic increased absorption (PbB 50 µg Pb/100 ml); the data could not discard the possibility of subtle brain damage. EPA pays much attention to the recent study of David et al (1972), suggesting lead as one of the causes of hyperactivity in children. The authors themselves stress the lack of proof of a causal relation. Bulpitt (1972) seriously criticized the suggestion of such a causal relation, because the statistical treatment had been biased. We may regard this study as a relevant indicator for future research, but at this moment the causal relationship

is still speculative. The same may be said for the recent study of de la Burde et al (1972): 70 children who had had exposure to lead (PbB 40-100 μ g Pb/100 ml or over 30 μ g Pb/100 ml in combination with lead lines in long bones), but who did not experience symptoms related to it, were evaluated at 4 yr of age using a series of psychological tests; 70 children with similar socio-economic background but presumably without unusual exposure to lead served as controls. The authors found an increased number of deficits in the lead-group (I.Q., motor development, concept formation, behavior). The control group was not matched for psychological factors as maternal care, intra family relationships, although both groups came from the same basic population. The authors themselves admitted that "the differences found may be due to environmental factors other than lead"; the results should be regarded preliminary; they have to be confirmed in a rigidly controlled study. Moreover, the children probably had PbB levels >40 μ g/100 ml either at the moment of investigation, or in the past.

Seppäläinen et al (1972) observed peripheral nerve damage by means of a highly sensitive technique (conduction velocity) in lead workers with no clinical symptoms; however most of the workers had experienced excessive Pb absorption, many even clinical poisoning. Not yet published data (Hernberg 1973) on workers never having a PbB >70 μ g/100 ml suggested the possibility of similar findings. However, Hernberg himself agreed that at this moment the validity of these data, and the relevance in regard to health are not adequately studied; they can not yet be taken into account in setting guides and standards.

The same group of workers (PbB >40 μ g Pb/100 ml) was also examined by Hänninen (Hernberg 1972) with psychological methods; she found slowness of performance, psychomotor disturbance, slight intelligence defects, personality changes. In both studies no good relationship existed with PbB, ALA in urine and Hb. This might suggest an other dose-response relationship as the one valid for commonly used criteria (Editorial, 1973). However, so far, evidence has not been brought forward that such possible neurophysiologic effects are induced at lead levels below 40-50 μ g Pb/100 ml. This clearly is still an area for research.

Recently Stuyk et al (1973) found a sex difference in a human volunteer study (20 µg Pb/kg body weight for 3 wk): female adults showed an increase (factor about 2) in protoporphyrin levels in erythrocytes in contrast to male adults; the levels hardly exceeded the acceptable level proposed by Albahary (1971). In addition, the authors suggested that the relatively rapid increase in PbB might be of significance. Further studies in women with PbB 25-35 µg Pb/100 ml have to be undertaken to establish the relevance of this finding for public health.

Another area for concern is the possible effect on chromosomes. Although some authors reported chromosomal changes in lymphocytes in workers (Schwanitz et al 1970, Forni et al 1971), others could not confirm this, neither in human beings, nor in animal experiments. This topic was extensively discussed at a Berlin-conference "Blei und Umwelt" (Lead and Environment, 1971) and at the Amsterdam Symposium on Lead in the Environment (1972). No agreement has yet been reached; there certainly is not enough evidence to suggest effects on chromosomes in subjects never exceeding PbB up to 40 to 50 µg Pb/100 ml.

Chromosomes

This discussion on possible effects of lead had to be very limited. Extensive reviews of literature are available (De Bruin 1971, NAS 1972, and many others). This short review of certainties, probabilities and speculations only served to strengthen the previously reached (Zielhuis 1972a) conclusion that:

- according to present knowledge no reasonably proven or probable evidence exists that health in a broad sense is affected if individual blood levels never exceed 40 µg Pb/100 ml;
- the level of PbB = 40 µg Pb/100 ml can be used as the upper acceptable level in the sphere of public health.

Pb in blood levels generally are given as Pb in µg/100 ml total blood. However, over 90% of Pb is present in erythrocytes; the haematocrite (Ht), indicating the volume of erythrocytes per volume of total blood, is about 10% lower in females than in males. Therefore Pb in erythrocytes-levels more adequately portray the real internal load (Pb in µg/100 ml ery); future studies should use this parameter. PbB levels as reported in literature for females should be corrected to make them more comparable to PbB levels in males: $PbB_{corr} = PbB_{obs} \times 1.10$. If PbB = 40 µg/100 ml is taken as the upper acceptable level in males, than PbB = 36 µg/100 ml should be taken as the corresponding level in females.

Infancy and pregnancy

The conclusions arrived at above, need some further evaluation in regard to possibly increased susceptibility of young children and pregnant women. There exists a wide spread belief that both sub-groups of the population deserve special attention in regard to possible health effects of inorganic lead. The main question is whether the developing infant (intra- and extra-uterine) is more susceptible to lead, particularly in regard to nervous system and behavior, than the normal adult. Pregnant women as such probably may not run a higher risk at the relevant dose levels, but they determine the load to the developing fetus and newborn.

The exposure of children tends to evoke emotional involvement, and such an attitude may affect rational judgement too easily. The fact that large epidemics of serious lead poisoning, with possibly disturbed mental development, and epidemics of apparently notably increased absorption occur in metropolitans of the US (and also around lead smelters elsewhere), quite rightly has created much concern. There apparently exists increased exposure (pica, dilapidated houses, lead emission from smelters, street dust, etc.) in some groups of young children, particularly in toddlers. However, as such this does not prove increased susceptibility.

EPA (1972) summed up some arguments in favour of increased susceptibility of children:

- the "speculation that children may be suffering subtle but unrecognized neurological impairments"
- "blood lead levels considered safe for adults may not always be safe for children; clinical symptoms often occur at lower blood lead levels in children than in adults"
- the possibility of increased rate of absorption may exist;
- "in view of the possibility that young children may be more susceptible to lead than older children, the newborn and fetus would be expected especially vulnerable. The conservative view favors a reasonable safety factor between what is considered an acceptable lead exposure among the fetus and newborn compared to older children and adults".

Based upon these considerations EPA (1972) came to the following upper acceptable levels of lead in blood:

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adults	40	g Pb/100 ml
expectant mothers	30	"
children	40	"
fetus and newborn	30	"

EPA itself states that this recommendation must be regarded as a judgement which has not yet been adequately validated by scientific studies".

NAS (1972) also discussed the possible differences between adults and children. We quote:

- "poisoning (in children) is more likely to be recognized first at a late stage on the basis of nervous-system involvement; adult poisoning is associated with occupational exposure, which is usually less severe than the types of exposure associated with childhood lead poisoning. When the factor of dose is taken into account, the clinical response - particularly at high doses - appears to be comparable in children and adults. Nevertheless, a rapidly growing child's response to moderately increased lead may well differ from that of an adult, despite the current inability to perceive the response".
- "Whether asymptomatic increased lead absorption can cause subtle but permanent impairment of nervous system function in young children is not known".

An other argument favouring higher vulnerability in children is that the relative proportion of the body burden present in the slow exchange pool may be smaller (Barltrop 1969).

The Am. Acad. of Pediatrics (1971) stated that 40 g Pb/100 ml appeared to be a safe limit, i.e. the same as in adults. However, the biological safety margin might be smaller in children.

There are some arguments not favouring increased susceptibility in the young child, although each of them as such not presents conclusive evidence:

- There is a rule of thumb that medical drug dosage for children is about $\frac{n}{n+12}$ of the daily dosage for adults (n = age in years); this apparently implies a higher dosage/kg body weight in children.
- Effects of drugs as thalidomide have only an effect on the intra-uterine development when present during a certain circumscribed stage of pregnancy; such a typical effect has not been elucidated for lead.

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- The ad hoc Comm. Env. Management (Dept. Hlth Welfare USA) considers 300 μ g Pb/day as the maximum permissible daily intake from all sources for children; this leaves about 150 μ g Pb/day from non-food sources. Barltrop (1972) suggests a permissible intake of 133 μ g Pb/day from food for a 2 yr old child. These levels are much higher than the accepted levels for adults, if taken per kg body weight or per m^2 body surface.
- Haas et al (1972) determined PbB in umbilical cord and in the pregnant mother; levels were about the same, with a significant correlation ($r=0.533$, $n=294$). The umbilical blood contained considerably more lead than blood in 8 days - 8 yr old children. These authors did not take into account the very large difference in composition of the blood between mother and child. According to Stave (1970) and Cooke (1965) the following differences generally exist in blood volume, plasma- and erythrocytvol/kg, b.w.:

	plasma ml/kg	red cell ml/kg	blood ml/kg	red cell/ blood	red cell/ plasma
non pregnant women	50	27	77	0.36	0.54
pregnant, 40 wk	72	27	99	0.27	0.38
newborn, age 0-1 hr	40	50	85-100	0.55	1.25
newborn, age 72 hr	44-51	41-49	82-99	0.50	1.00

Apparently there is an about 3 fold difference in quotient red cell/plasma and 2 fold difference in quotient red cell/blood vol between mother and newborn at the time of delivery.

A PbB of e.g. 20 μ g Pb/100 ml in the mother may have quite another biological significance than in the neonate. This can be shown in the following example

- assume PbB = 20 μ g/ml in mother and neonate
- assume $\frac{\text{conc. Pb in ery (Ce)}}{\text{conc. Pb in plasma (Cp)}} = 10$; $Ce = 10 Cp$
- haematocryt (Ht) in mother 0.27, in neonate 0.55

amount Pb in ery + amount Pb in plasma = PbB

$$Ht \times Ce + (1-Ht) \times Cp = PbB$$

$$Ht \times 10 Cp + (1-Ht) \times Cp = PbB$$

$$Cp (10 Ht + 1 - Ht) = PbB (9Ht + 1) = PbB.$$

$$C_p = \frac{PbB}{9Ht+1}$$

$$C_e = \frac{10PbB}{9Ht+1}$$

If PbB = 20 g Pb/100 ml

mother Ce = 60 g/100 ml neonate: Ce = 34 g/100 ml

Cp = 6 g/100 ml Cp = 3.4 g/100 ml.

The same lead in whole blood indicates a lower Pb content of diffusible plasma Pb in the neonate if compared with the mother. This phenomenon indicates an extra margin of safety for the neonate.

The conclusion of this short review is that:

- at levels > 40 g Pb/100 ml an increased susceptibility might exist in children
- at levels < 40 g Pb/100 ml no conclusive or suggestive evidence for an increased susceptibility has been presented
- pregnant women as such (in the relevant dosage range) do not appear to constitute a special group to be considered in establishing guides.

However, it should be fully recognized that the range of uncertainty is larger in regard to young children and the developing embryo than in regard to adults. This uncertainty as such should increase the safety factor, and - for the time being - decrease the upper acceptable level.

Biological quality guides - taken as an acceptable percentile distribution of PbB levels - indirectly measure the environmental exposure. It is not feasible to propose different levels for pregnant women and for non pregnant (potentially pregnant) women and male adults. So, because of this the upper acceptable level in 98% of the population should be 35 g Pb/100 ml.

Available data on percentile distribution of PbB

In literature most data on PbB levels are given as average ($\bar{x}$) and standard deviation (σ) or range; individual data usually are not presented. Such a procedure may - strictly spoken - only be applied if the parameters follow a Gaussian distribution. Such an unwarranted assumption does not need to be made for percentile distributions.

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One should express guides and standards in such a way that they are consistent with the distribution of data as occurring in practice. So, one should evaluate the available evidence on distribution of PbB levels as occurring in target groups of the population as presented in literature.

Taking into account the distribution of levels as occurring in practice, does not imply that the levels as such are regarded as acceptable: not the occurring levels (e.g. 40 µg/100 ml, 50 µg/100 ml), but the cumulative distribution curve - an expression of occurring variability - is taken as granted.

In table 1 percentile distribution of Pb-levels for total blood are given as calculated from available European data (groups n 50). Two categories are distinguished:

- I. children and male or female adults, non occupational exposure, no exceptional environmental condition (vicinity of lead emitting sources)
- II. adults, possibly with specific living conditions.

In table 2 the data of the recent 7-City Study in the USA (Tepper et al 1972) are given: mainly women volunteers, 20-79 yr, living in urban and suburban conditions.

Proposed biological quality guide

From both sets of data (group I Western Europe and 7-City Study) one may conclude that 98% of adult males and non-pregnant females, without any specific non-occupational living conditions (such as garbage collecting, wine drinking (?)) have Pb in total blood levels below about 30-35 µg Pb/100 ml, 90% below 25-30 µg Pb/100 ml, 50% below 20 µg Pb/100 ml. This percentile distribution can therefore be taken as a biological quality guide, because it does not exceed 35 µg Pb/100 ml in 98% of the female population, and it also presents the "normal" variability of internal load, and indirectly of the "normal" total external load.

Based upon the proposed maximal acceptable PbB-level of 35 µg/100 ml in 98% of the target population, and upon the distribution of PbB levels in various target groups, the following biological quality guide for lead in total blood is proposed, to be used in public health:

Table 1. Percentile distribution of PbB (μ g Pb/100 ml) levels in population groups (n $\geq$ 50) -- Western Europe; 98% levels (or first higher % level) underlined.

<u>Group I</u>		curve	n	sex	<70	<60	<50	<40	<35	<30	<25	<20	remarks
source	yr	number in fig.1											
<u>adults</u>													
Haeger-Aronsen	1971	1	50	m	100	100	100	100	100	100	<u>100</u>	94	Sweden
Lehnert	1968	2	400	m.f.	100	100	100	100	100	<u>100</u>	95	84	FRG
	1968	3	101	m	100	100	100	100	100	100	<u>99</u>	93	FRG
	1968	4	104	f	100	100	100	100	100	100	100	<u>97</u>	FRG
Haas et al	1972	5	294	f	100	100	100	99	<u>98</u>	95	82	62	FRG, pregnant
<u>children</u>													
Moncrieff et al	1964	6	80	m.f.	100	100	100	<u>99</u>	95	69	52	25	UK, hospital children?
Millar et al	1970	7	51	m.f.	100	100	100	<u>98</u>	96	92	90	76	"
<u>Group II</u>													
<u>adults</u>													
Lehnert et al	1970	8	138	m	100	100	<u>98</u>	86	69	60	48	32	FRG, garbage collectors
Vigliani et al	1968	9	87	m.f.	100	-	90	80	-	53	-	5	Italy, Miland
Secchi et al	1971	10	122	m.f.	100	100	<u>99</u>	74	60	38	19	11	Italy, Miland

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Table 2. Percentile distribution of PbB ($\mu\text{g Pb}/100\text{ g}$) levels mainly in women volunteers, 7 City Study USA (Tepper et al 1972); 98% levels (or first higher % level) underlined.

City	n	curve number in fig.2	<50	<40	<35	<30	<25	<20
Okeana	162	1	100	100	100	<u>98</u>	93	79
Ardmore	150	2	100	100	<u>100</u>	95	87	57
Rittenhouse	136	3	100	<u>98</u>	96	89	80	41
Pasadena	193	4	100	100	<u>99</u>	96	92	65
Los Alamos (male)	80	5	100	100	99	<u>99</u>	94	73
Los Alamos (fem.)	191	6	100	100	100	<u>99</u>	99	88
Washington D.C.	219	7	100	100	<u>100</u>	95	89	52
Port Washington	198	8	100	100	100	<u>100</u>	96	84
Greenwich Village	140	9	100	100	99	<u>99</u>	96	74
Lombard	208	10	100	100	100	100	<u>98</u>	94
Bridgeport	147	11	100	100	<u>99</u>	97	95	68
Houston	191	12	100	100	100	100	<u>100</u>	94

- individual maximum:	40 µg Pb/100 ml
- 98 percentile	: 35 µg Pb/100 ml
- 90 percentile	: 30 µg Pb/100 ml
- 50 percentile	: 20 µg Pb/100 ml

This leaves even space for correction of PbB levels based upon the difference in Ht between males and females.

These acceptable percentiles together should be regarded as one combined level. In this way it is possible to put data of target-groups in a diagram, and see whether the percentiles exceed the accepted guide. If the distribution of PbB levels remains below the guide line, then the environmental exposure is acceptable for the group as such. If individuals (2%) exceed 35-40 µg Pb/100 ml, then this constitute a signal for action as to the individual micro-environment. If the group as such exceeds the guideline, then this constitutes a signal for action for the macroenvironment of the group.

Of course, adequate expertise should determine whether action should be taken, and if so, what action; the proposed guide should not be regarded as a sharp line dividing areas of yes- and of no-risk.

In diagram 1 and 2 the data of table 1 and table 2 are presented, together with the proposed guideline. It is clear that group II exceeds the guideline at various points.

In diagram 3 the proposed guideline and two hypothetical lines A and B are given. Distribution A shows a steep incline, and particularly exceeds the guideline at the high PbB levels: this indicates clearly increased Pb uptake in a certain number of subjects in the target group; there probably is a point source within the area in which the target group is living. Distribution B shows a generally increased level of uptake, i.e. throughout the whole area as such there exists excessive lead uptake.

Reevaluation

The proposed biological quality guide should be considered as temporary, and should be reevaluated if new data come available.

However, at this moment the proposed guide could be recommended to governments, being the outcome of present available evidence. In this case, the government should reevaluate the guide after a period of 5 years.

Shortterm - long term goal

2
Previously a necessary sequence of operation has been suggested. If in a region the PbB level distribution does not exceed the proposed guideline, steps 4 to 8 do not need to be taken. The government can devote man power and money to other environmental problems.

Inorganic lead probably is a non-essential element, although recently Schwarz (1973) has suggested otherwise. However, because Pb is present everywhere the suggested essential uptake is easily guaranteed even in non polluted environments. As a long term goal one should try to decrease the lead body burden up to the minimal "natural" levels; the "costs" of such an approach will exponentially increase with decreasing PbB-levels. At this moment, the proposed biological quality guide can serve as a short term goal. Whether one wants to go further, is a matter of determining priorities within the total effort to achieve and maintain environmental quality.

Lead in urine and hair

It is a wellknown fact that the concentration of Pb in urine (PbU) reflects Pb in blood. One could also try to devise a quality guide based upon PbU-levels. However, there are some drawbacks:

- influence of diuresis: necessity of correction of concentration levels
- contamination of samples
- relatively few data on PbU levels in the general population are available

A provocation test of PbU with EDTA (Teisinger et al 1966) may give a more adequate estimation of the biologically available internal lead; however, not enough data are available to use this parameter for the purpose discussed.

Pb in hair (PbH) also reflects body burden to a certain extent (Klevay 1973). However - apart from the possibility of external contamination - PbH probably does not reflect the rapid exchange

pool adequately enough. Moreover, not enough data on normal PbH-levels in various population groups are available in relation to Pb. Even if PbU- and PbH-levels could theoretically be used as a biological guide, available data do not allow to make such a proposal at this moment.

Reliability of lead levels

It is a wellknown fact that the analytical comparability of PbB levels sometimes is poor (Berlin et al 1972). The proposed biological guide is based upon literature data; the levels as such are accepted as reliable, i.e. as presenting the "true" Pb in blood levels. The guide is predominantly based upon lead in blood measurements performed in the Erlangen-Group (Lehnert, Haas et al), in Lund (Sweden) and in the Kettering Laboratory (7 City Study). These laboratories have a large experience, and may be regarded as reliable sources of lead in blood levels.

If governments want to adopt the proposed guide, then they should make sure that the validity of the lead in blood analysis is adequate. Otherwise, unjustified conclusions might be drawn from investigation of target groups.

Use of parameters of response

At this moment determination of lead in blood levels provides a method to estimate the internal biologically available load as indirect measurement of total environmental exposure to lead. However, reliance on PbB levels has some drawbacks:

1. one has to use at least about 5 ml of blood; so venous puncture is necessary. Microanalytical techniques (finger prick) are not yet sufficiently developed to provide good comparability with the standard method;
2. the analytical procedure is rather difficult, and preferably requires expensive laboratory equipment (atomic absorption spectrophotometer).

So, it might be feasible to use methods which allow measurement in drops of blood, with rather simple techniques, not using expensive equipment.

ALAD-levels as parameter

According to Hernberg et al (1970, 1972) measurement of aminolaevulinic acid dehydratase (ALAD) in erythrocytes provides a very reliable indirect indicator of PbB-levels ($r=-0.90$). They called it a "poor man's method". However in other studies r was much lower, particularly in the range PbB 0-50 $\mu\text{g Pb}/100\text{ ml}$. So, one could examine the possibility to propose a biological quality guide based upon ALAD-levels. ALAD activity particularly decreases in the PbB range relevant for public health (0-40 $\mu\text{g Pb}/100\text{ ml}$), whereas the concentration of ALA in urine appears to be more suitable for monitoring in occupational health: diagram 4 (Zielhuis 1972).

ALAD-levels can be measured in 0.2-0.3 ml blood. If in children venous puncture might have to be avoided, the method still needs a rather large amount of blood by finger prick: 4-6 drops.

As stated before, increase of ALAD activity with increasing PbB levels either may be an artifact or a highly sensitive and rather specific parameter of response. Whatever it may be, if we accept PbB = 35 $\mu\text{g Pb}/100\text{ ml}$ as the upper acceptable level, the wellknown decrease of ALAD levels already in the range of PbB 10-40 $\mu\text{g Pb}/100\text{ ml}$ cannot be taken as a parameter of meaningful response. If it might prove to be feasible to propose a biological quality guide based upon ALAD-levels, this guide should only be used as a predictor of PbB, and so of total environmental exposure.

Notwithstanding vast experience in the last decade, many more or less different techniques have been used to measure ALAD-activity (Schaller et al 1971), resulting in quite different absolute amounts (units of measurement) although with very similar procentual average decrease with increasing PbB-levels (Zielhuis 1972). However, the biological quality guide does not depend on average levels, but on individual levels. It is not possible in cross-sectional studies to determine the procentual individual

TEH 0470273

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decrease in ALAD. It will therefore be necessary to adopt a standard-method. In this paper the author will try to develop a guide for two widely used methods; if one or both methods will provide a reliable guide, it will be a matter for discussion between authorities and research workers to choose one standard method. Within the Common Market discussion on this point have already started.

The author received two sets of data:

1. Dr B.Haeger-Aronsen, Lund Sweden, provided 138 sets of levels of PbB, ALAD and ALA in urine, each set determined in the same person at the same time, in the range of PbB 18-70 μ g Pb/100 ml (venous puncture). The correlation coefficient between PbB and log ALAD = $r = -0.68$; this coefficient has been calculated on the independent data: only the lowest individual PbB, $n=30$. These data came from 30 male workers, observed during exposure and during recovery after the end of exposure (factory closed). The different sets of levels therefore are not fully independent from each other (diagram 5).
2. Dr Sv. Hernberg, Helsinki Finland, provided 206 sets of levels of PbB, ALAD and ALA in urine, each set determined at the same time, in the range of 9-70 μ g Pb/100 ml, the correlation coefficient between PbB and log ALAD $r = -0.74$. These data came from a number of occupationally exposed male workers. The different sets of levels therefore are independent from each other (diagram 6).

Both investigators used different methods, and gave different units of measurement: Bonsignore Units (method described in Haeger-Aronsen 1971) and μ mol PBG/h/l erythr. (Hernberg; method described by Nekkanen et al 1972).

Validity of ALAD-levels

ALAD levels highly correlate with PbB-levels; however, a high coefficient of correlation not necessarily implies a high predictive validity. One should calculate (Zielhuis et al 1973) the sensitivity (sc), i.e. the extent to which subjects who truly manifest a characteristic are so classified, and the specificity (sp), i.e. the extent to which subjects who do not mani-

test a characteristic are correctly classified; $se + sp$ yields the predictive validity, i.e. the extent to which a situation as observed reflects the "true" situation. If $se + sp > 1.80$, predictive validity is good (max. 2); 1.50 - 1.80 is to be regarded as moderate; < 1.50 as rather poor. If one wants to predict e.g. $PbB > 35 \mu g Pb/100 ml$, one can calculate sensitivity and specificity (and therefore validity) of a certain ALAD-cutoff level, e.g. $ALAD < aU$ (or $a mol PBG/h/l ery$). A low sensitivity implies many false negative data: $ALAD < a$ corresponds to $PbB > 35 \mu g Pb/100 ml$; individuals with high PbB levels are overlooked. A low specificity implies many false positive data: $ALAD < a$ corresponds to $PbB < 35 \mu g Pb/100 ml$; individuals with low PbB levels are regarded to have high PbB levels. In examining a target population, one does not want to overlook individuals with high PbB levels: a high sensitivity is necessary; specificity should not be too low either, because one might become too conservative (too many low PbB levels regarded as high); conclusions and actions taken will become unjustified.

In order to examine the feasibility of a biological quality guide based upon ALAD-levels, we calculated the validity of two cutoff levels for ALAD, based upon a sensitivity = 1.00 and 0.90 (10% false negatives). The results are given in table 3. The validity was only calculated for prediction of $PbB > 35$ and $> 30 \mu g Pb/100 ml$; there were too few levels $PbB < 20$ to make a calculation feasible. If we take sensitivity = 1.00 (i.e. no false negatives), validity was rather poor; if we allow 10% false negative data (i.e. overlooking too high PbB levels in 10% of individuals), validity is still moderate, and never exceeds 1.80.

From this we may conclude that it is not possible to base a biological quality guide on individual ALAD-levels. Similar results would have been gained from other cutoff levels of ALAD, because - notwithstanding a correlation between PbB - and ALAD-levels - the range of ALAD for each PbB -level is very large, the extremes often differing with a factor 2. Average levels of ALAD highly discriminate between groups with different average PbB -levels (and with different exposure); however this does not apply to individuals.

Table 3. Validity of ALAD-cutoff levels as predictors of PbB-levels;
se = 1.00 and 0.90

PbB > 35 µg Pb/100 ml				PbB > 30 µg Pb/100 ml			
data Haeger-Aronsen		data Hernberg		data Haeger-Aronsen		data Hernberg	
(in Bons. U)		(in mol PBG/h/l ery)		(in Bons. U)		(in mol PBG/h/l ery)	
ALAD	< 70 < 45	< 750 < 450		< 112 < 62		< 850 < 560	
sensitivity	1.00 0.91	1.00 0.90		1.00 0.90		1.00 0.90	
specificity	0.44 0.76	0.55 0.80		0.17 0.61		0.48 0.82	
validity	1.44 1.67	1.55 1.70		1.17 1.51		1.48 1.7 ²	

Other response parameters

The data of Haeger-Aronsen and of Hernberg also included levels of δ -aminolaevulinic acid in urine (ALAU): in both sets of data increase of ALAU starts at PbB $> 40-50 \mu\text{g Pb}/100 \text{ ml}$, and they confirm the schematic presentation of diagram 4. ALAU-levels cannot be used as a biological quality guide in the sphere of public health.

Up to now very few data exist regarding other biochemical parameters; the scanty data available on Protoporphyrin in erythrocytes do not suggest a high validity in predicting PbB levels in the range of $0-40 \mu\text{g Pb}/100 \text{ ml}$; the procedure of determination is laborious, individual differences appear to be large (Stuik et al 1973).

Indirect effects on health and wellbeing

The proposed biological quality guide only protects human beings to direct adverse effects of lead exposure. In proposing environmental quality standards other effects of lead pollution may have to be taken into account: ecological effects, etc. with a potential indirect effect on health and wellbeing. Such indirect effects are not prevented by adherence to the proposed guide.

Conclusions and Summary

1. If environmental exposure of the general public to a considerable extent takes place through various routes of entry, quality standards for one source of exposure (e.g. air, food, water) will not protect public health adequately. This is the case for inorganic lead.
2. Biologically available lead (lead in blood levels) and parameters of subclinical response may be expected to be feasible for indirect estimation of total environmental exposure; the feasibility has been studied.
3. Lead in blood levels (PbB) in target groups of the general population portray the total environmental exposure to Pb for this

- group. Such groups should include at least 50 subjects, of same sex, similar socio-cultural class, with narrow age range, and preferably at high risk (exposure or susceptibility).
4. Neither average levels nor one maximum level, but the distribution of levels in 98% of the target group should be taken as parameter of external exposure.
 5. The maximum acceptable individual level for adults is $PbB = 40 \mu g Pb/100 ml$; because of increased uncertainty in regard to pregnancy and developing neonate this level should be lowered to $PbB = 35 \mu g Pb/100 ml$.
 6. Taking into account the maximum acceptable level of $35 \mu g Pb/100 ml$ in 98% of subjects, and the normal variability of PbB levels as occurring in practice, the following distribution of PbB levels is proposed as biological quality guide:
 - 98% $\leq 35 \mu g Pb/100 ml$
 - 90% $\leq 30 \mu g Pb/100 ml$
 - 50% $\leq 20 \mu g Pb/100 ml$

PbB levels in women should be corrected to male level on the basis of hematocrite.
 7. If the general distribution of PbB levels in a target group exceeds the proposed guide, total exposure in the environment studied is too high; action should be undertaken directed at the total environment. If the distribution only exceeds the guide at high PbB levels, a point source of external lead exposure is probable; action should be directed at this source.
 8. If in the environment total exposure to lead is too high, subsequent studies should determine contribution through various routes and sources: quality standards for air, food, water may have to be imposed; the same applies to emission standards.
 9. Due attention to errors of measurement of Pb in blood is necessary.
 10. It is not yet possible to propose a biological quality guide based upon Pb in urine or hair.
 11. It is not possible to propose a biological quality guide based upon ALAD-activity in erythrocytes, neither on ALA-excretion in urine.
 12. The proposed biological quality guide for lead in blood could enter governmental regulations, and so become a biological quality standard, if prevention of direct adverse effect on human

TEH 0470278

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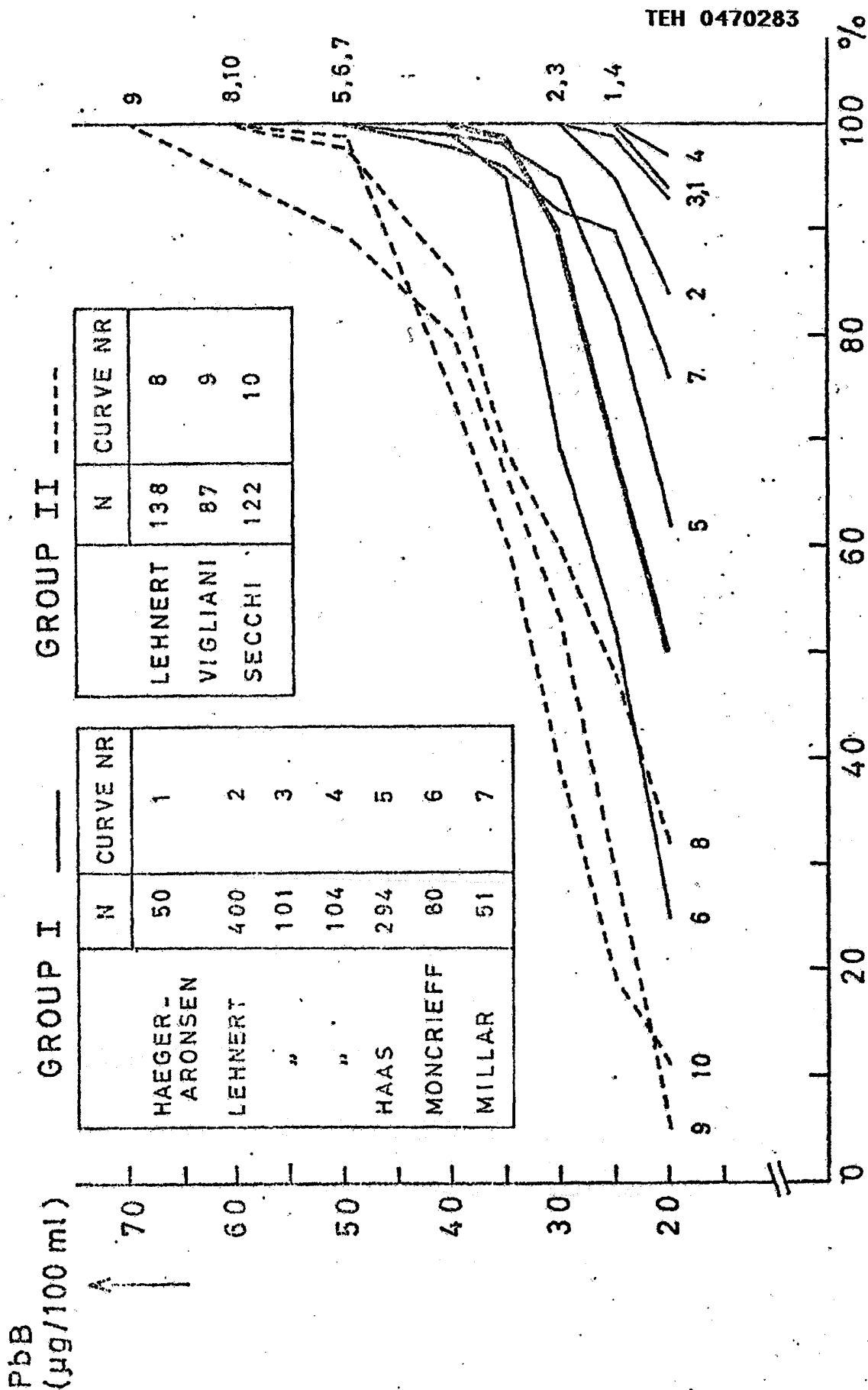
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DIAGRAM 1: PERCENTILE DISTRIBUTION OF PbB ($\mu\text{g}/100\text{ml}$).

- TABLE I -

THE PROPOSED GUIDE IS GIVEN AS A HEAVY LINE.



TEH 0470283

DIAGRAM 2: PERCENTILE DISTRIBUTION OF PbB (

- TABLE 2 -

THE PROPOSED GUIDE IS GIVEN AS A

PbB
($\mu\text{g}/100\text{ g}$)



70

60

50

40

30

20

	N	CURVE NR.
OKEANA	162	1
ARDMORE	150	2
RITTENHOUSE	136	3
PASADENA	193	4
LOS ALAMOS (m)	80	5
(f)	191	6
WASHINGTON D.C.	219	7
PORT WASHINGTON	198	8
GREENWICH VILLAGE	140	9
LOMBARD	208	10
BRIDGEPORT	147	11
HOUSTON	191	12

3

7

2

4

11

5,9

1

8

0

20

40

60

80

DIAGRAM 3: PROPOSED GUIDE FOR PbB ($\mu\text{g}/100\text{ ml}$), AND
TWO HYPOTHETICAL DISTRIBUTIONS A and B.

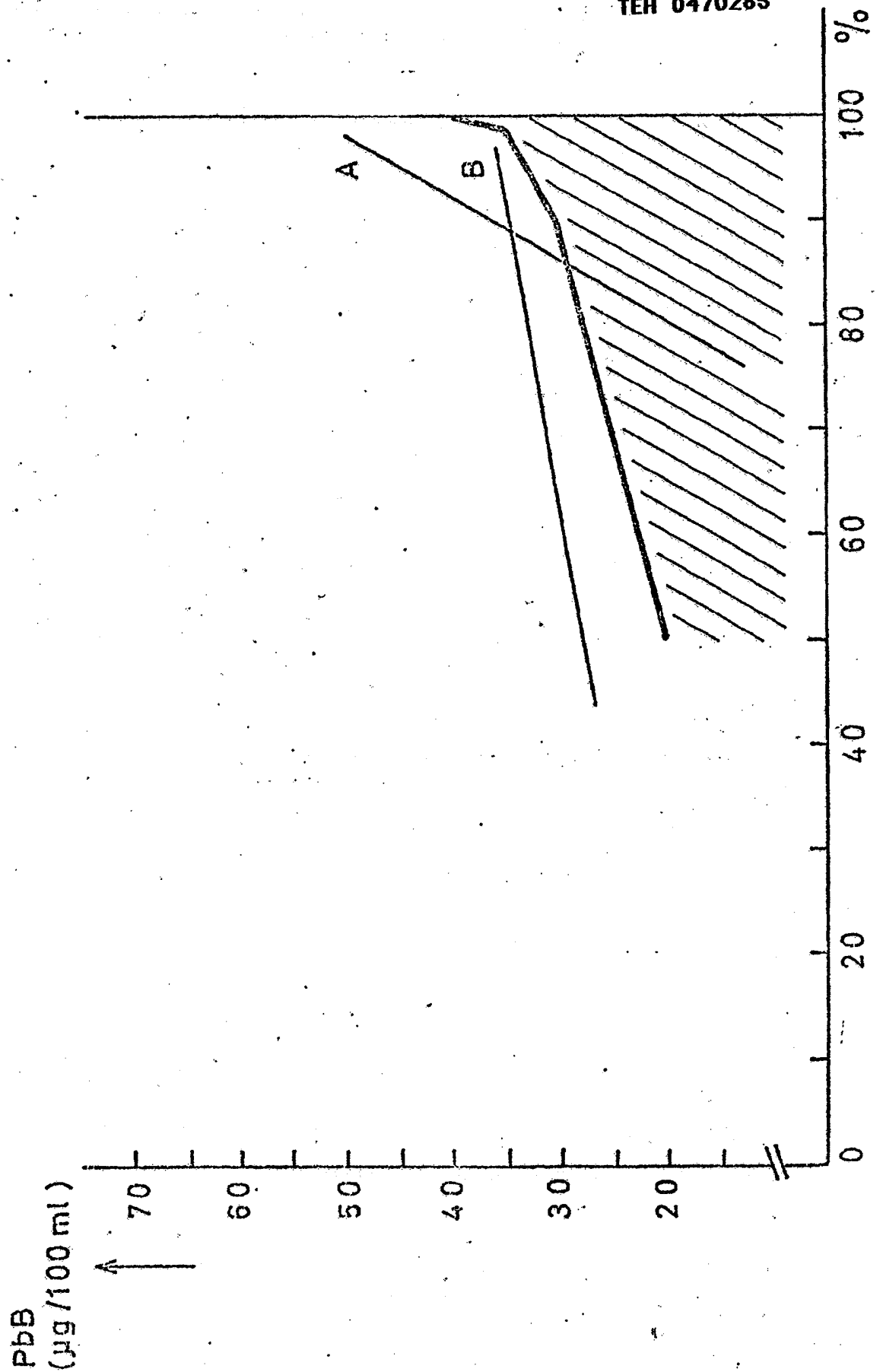
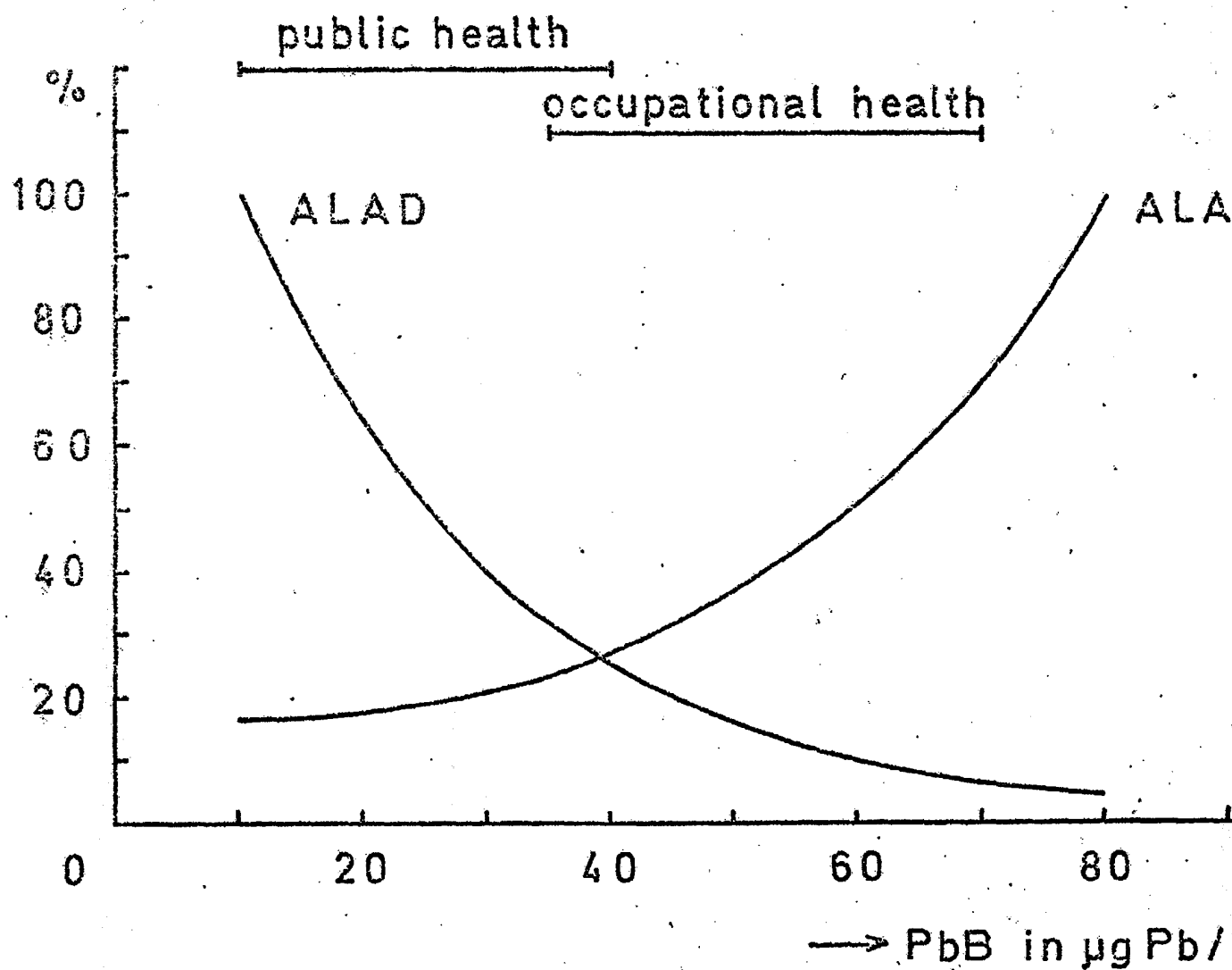


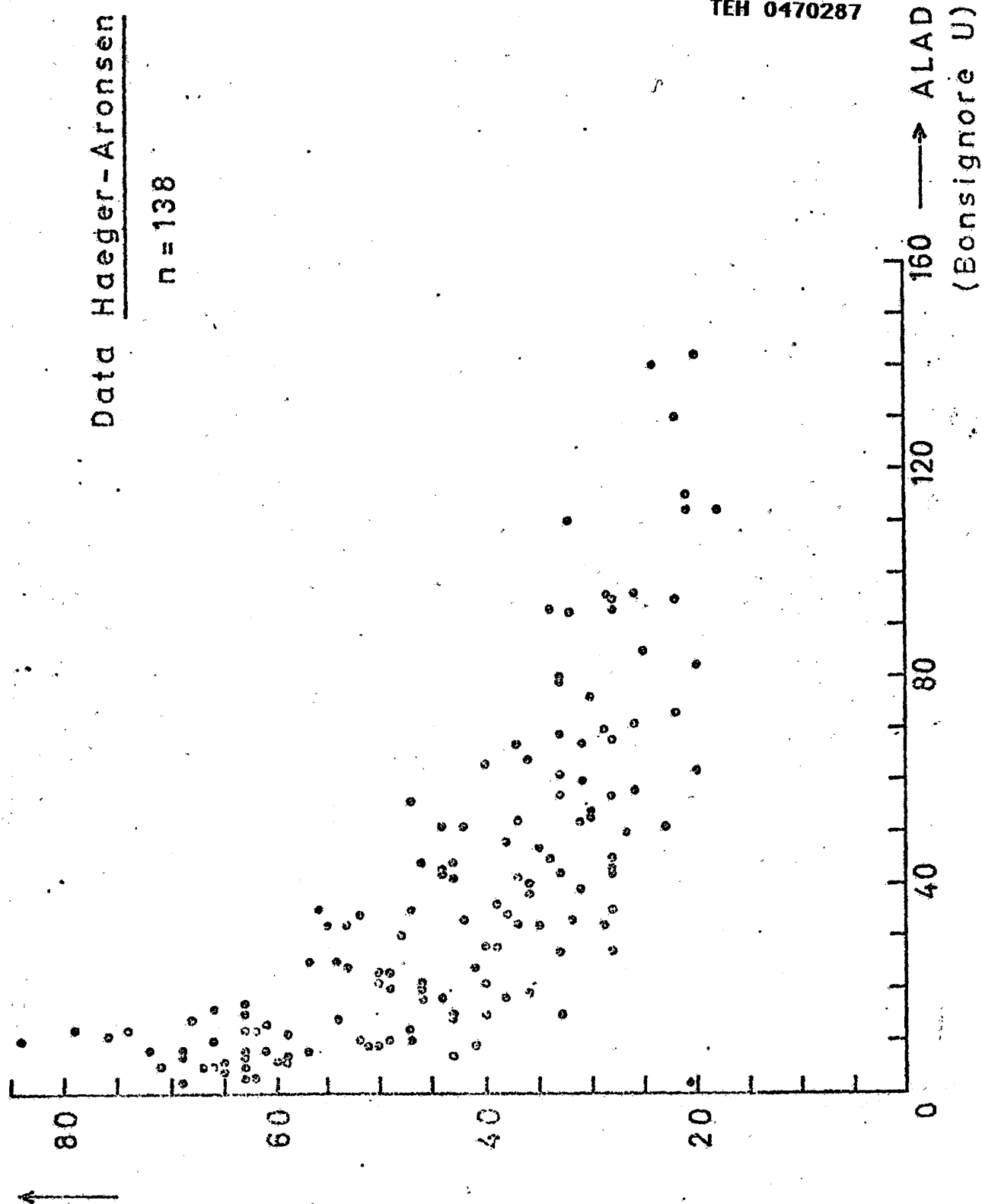
Diagram 4. Percentual change in ALAD en ALAU
in relationship to PbB



PbB

($\mu\text{g}/100\text{ ml}$)

Diagram 5. PbB and ALAD levels, 138 data in 30 workers.



TEH 0470287

Diagram 6. PbB and ALAD levels in 206 workers.

