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Biological Quality Guide for Inorganic Lead*

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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 μg Pb/100 ml; because of increased uncertainty in regard to pregnancy and developing neonate this level should be lowered to PbB = 35 μg Pb/100 ml.

6. Taking into account the maximum acceptable level of 35 μg 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% ≦ 35 μg Pb/100 ml, 90% ≦ 30 μg Pb/100 ml, 50% ≦ 20 μg 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.

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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 health is aimed at.

Key words: Inorganic lead — Public health — Biological monitoring — Biological guide.

Environmental Quality Standards and Guides

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.

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

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 µg/m³ 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 µg/m³) disregarding 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 µg/Pb/day, with extremes up to 400 µg Pb/day (Martin, 1973); Thompson (1971) found a range of 70—750 µg Pb/day in 5 individuals in UK; Lehnert *et al.* (1969) calculated for Germany (FRG) an average uptake of 518 µg Pb/day; Vigliani and Zurlo (1968) suggested for Miland 400—500 µg Pb/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.

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 macroenvironment.*

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);
3. similar social-cultural class;
4. narrow age range, e.g. children 1—4 years, pregnant women 20—30 years, traffic policemen 30—40 years;
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), suscepti-

bility, 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 homoiostatic 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

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 μg Pb/100 ml presents any risk to public health" (Zielhuis, 1972a). 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 μg 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 μg Pb/100 ml;
3. the no-effect level of PbB in regard to increase of protoporphyrin in erythrocytes (PPE) is at least 40 μg 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, serum-protein pattern), various clinical effects on kidney function, vascular tension, cerebrovascular incidents probably do not appear in subjects who never exceeded PbB = 40 μg Pb/100 ml.

Some of these conclusions merit further discussion.

Decrease of ALAD activity is apparent already with PbB < 40 μg Pb/100 ml, with a high positive correlationship. Data of Schaller *et al.* (1971) suggest a no-effect-level at PbB 5—15 μg 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 *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 μg Pb/100 ml or over 30 μg Pb/100 ml in combination with lead lines in long bones), but who did not experience symptoms related to it, were evaluated at 4 years 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 μg/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 μg per 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 μg 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 μg Pb/100 ml. This clearly is still an area for research.

Recently Stuik *et al.* (1973) found a sex difference in a human volunteer study (20 μg Pb/kg body weight for 3 weeks): 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—50 μg Pb/100 ml.

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 subgroups 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 subtile 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:

adults	40 µg Pb/100 ml,
expectant mothers	30 µg Pb/100 ml,
children	40 µg Pb/100 ml,
fetus and newborn	30 µg Pb/100 ml.

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 American Academy of Pediatrics (1971) stated that 40 µg Pb per 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 intrauterine development when present during a certain circumscript stage of pregnancy; such a typical effect has not been elucidated for lead.

The ad hoc Comm. Env. Management (Dept. Hlth, Welfare, USA) considers 300 µg Pb/day as the maximum permissible daily intake from all sources for children; this leaves about 150 µg Pb/day from nonfood sources. Barltrop (1972) suggests a permissible intake of 133 µg Pb/day from food for a 2-year-old child. These levels are much higher than the accepted levels for adults, if taken per kilogram body weight or per square metre 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 ($r = 0.538$, $n = 294$). The umbilical blood contained considerably more lead than blood in 8-day—8-year-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 weeks	72	27	99	0.27	0.38
Newborn, age 0—1 hr	40	50	85—100	0.55	1.25
Newborn, age 72 hrs	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 µg 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 µg/ml in mother and neonate

assume $\frac{\text{conc. Pb in ery (Ce)}}{\text{conc. Pb in plasma (Cp)}} = 10$; Ce = 10 Cp

haemotocrit (Ht) in mother 0.27, in neonate 0.55, amount Pb in ery + amount Pb in Plasma = PbB

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

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

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

$$Cp = \frac{PbB}{9\,Ht + 1}$$

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

If PbB = 20 µg Pb/100 ml

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

Cp = 6 µg/100 ml Cp = 3.4 µg/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 µg Pb/100 ml an increased susceptibility might exist in children,

at levels <40 µg 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 µg 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.

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 years, 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

Table 1. Percentile distribution of PbB (μg Pb/100 ml) levels in population groups ($n \geq 50$) — Western Europe; 98% levels (or first higher percent level) bold face

Source	Year	Curve number in Fig. 1	n	Sex	<70	<60	<50	<40	<35	<30	<25	<20	Remarks
Group I			*Adults*										
Hagger-Aronsen	1971	1	50	m	100	100	100	100	100	100	100	94	Sweden
Lehnert	1968	2	400	m, f	100	100	100	100	100	100	95	84	FRG
	1968	3	101	m	100	100	100	100	100	100	99	93	FRG
	1968	4	104	f	100	100	100	100	100	100	100	97	FRG
Haas *et al.*	1972	5	294	f	100	100	100	99	98	95	82	62	FRG, pregnant
							Children						
Monorieff *et al.*	1964	6	80	m, f	100	100	100	99	95	69	52	25	UK, hospital children ?
Miller *et al.*	1970	7	51	m, f	100	100	100	98	96	92	90	76	UK, hospital children ?
Group II			*Adults*										
Lehnert *et al.*	1970	8	138	m	100	100	98	86	69	60	48	32	FRG, garbage collectors
Viglani *et al.*	1968	9	87	m, f	100	—	90	80	—	53	—	5	Italy, Milano
Secchi *et al.*	1971	10	122	m, f	100	100	99	74	60	38	19	11	Italy, Milano

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 per 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:*

individual maximum: 40 μg Pb/100 ml, 90 percentile: 30 μg Pb/100 ml,
98 percentile: 35 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 guide* 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 macro-environment 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.

Table 2. Percentile distribution of PbB (μg Pb/100 g) levels mainly in women volunteers, 7-City Study USA (Topper *et al.*, 1972); 98% levels (or first higher percent level) bold face

City	n	Curve number in Fig. 2	<50	<40	<35	<30	<25	<20
Oceana	102	1	100	100	100	98	93	79
Ardmore	150	2	100	100	100	95	87	57
Rittenhouse	136	3	100	98	96	89	80	41
Pasadena	103	4	100	100	99	96	92	65
Los Alamos (male)	80	5	100	99	99	99	94	73
Los Alamos (fem.)	191	6	100	100	100	99	99	88
Washington D.C.	219	7	100	100	100	95	89	62
Port Washington	198	8	100	100	100	100	90	84
Greenwich Village	140	9	100	100	99	99	96	74
Lombard	208	10	100	100	100	100	98	94
Bridgeport	147	11	100	100	99	97	95	68
Houston	191	12	100	100	100	100	100	94

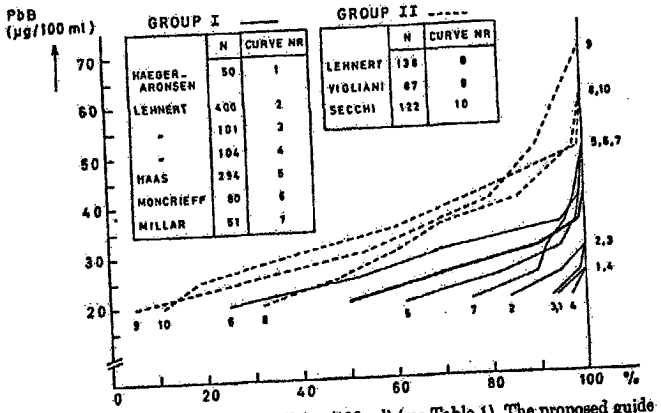

Fig. 1. Percentile distribution of PbB (µg/100 ml) (see Table 1). The proposed guide is given as a heavy line

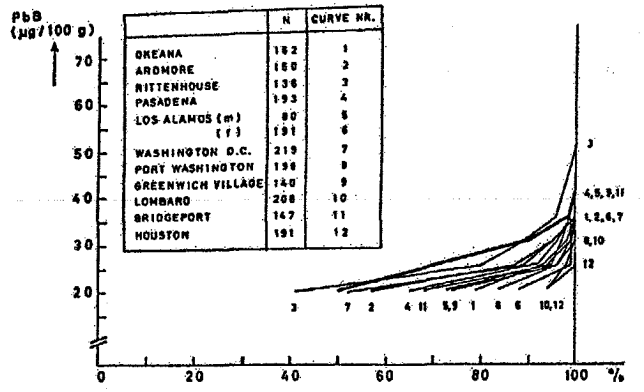

Fig. 2. Percentile distribution of PbB (µg/100 g) (see Table 2). The proposed guide is given as a heavy line

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

In Fig. 3 the proposed guideline and two hypothetical lines A and B are given. Distribution A shows a steep incline, and particularly exceeds

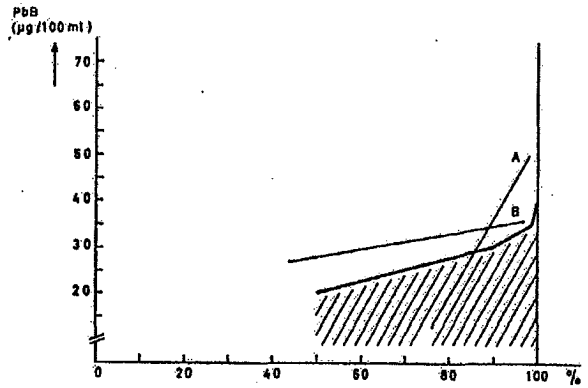

Fig. 3. Proposed guide for PbB (µg/100 ml), and two hypothetical distributions *A* and *B*

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 — Longterm Goal

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, 1968; Haas *et al.*, 1972), 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 µg Pb/100 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 µg Pb/100 ml), whereas the concentration of ALA in urine appears to be more suitable for monitoring in occupational health (Fig. 4) (Zielhuis, 1972a).

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, decrease 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 µg

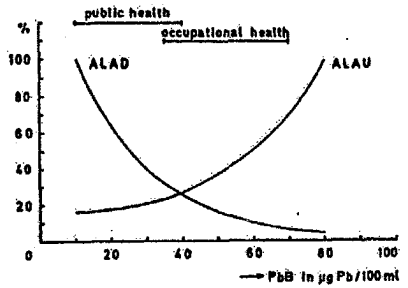

Fig. 4. Percentual change in ALAD en ALAU in relationship to PbB

Pb/100 ml as the upper acceptable level, the wellknown decrease of ALAD levels already in the range of PbB 10—40 μg Pb/100 ml cannot be taken as a parameter of meaningfull 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, 1972a). 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 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 discussions 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 μg 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 und during recovery after the end of exposure (factory closed). The different sets of levels therefore are not fully independent from each other (Fig. 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 μg 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 (Fig. 6).

Both investigators used different methods, and gave different units of measurement: Bonsignore Units (method described in Haeger-Aronsen, 1971) and μmol PBG/hr/l erythr. (Hernberg, 1973; method described by Nikkanen *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.

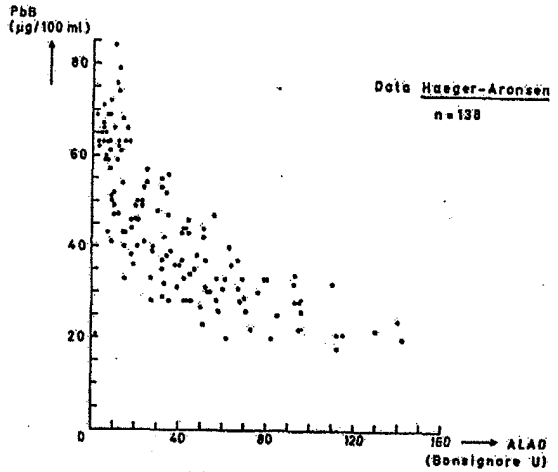

Fig. 5. PbB and ALAD levels, 138 data in 30 workers

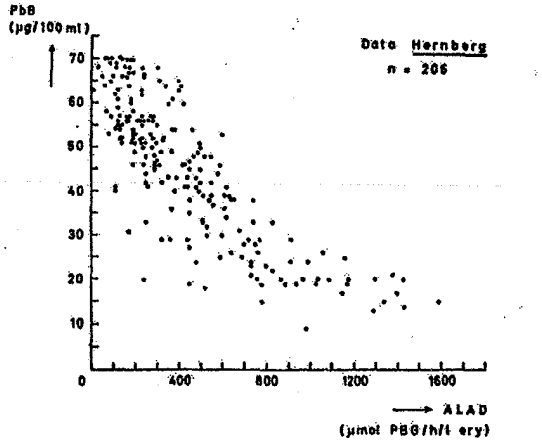

Fig. 6. PbB and ALAD levels in 206 workers

One should calculate (Zielhuis *et al.*, 1973) the *sensitivity* (se), 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

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 (in Bons. U)		data Hornberg (in mol PBG/hr/l ery)		data Haeger-Aronsen (in Bons. U)		data Hernberg (in mol PBG/hr/l ery)	
	ALAD							
	< 70	< 45	< 750	< 450	< 112	< 62	< 850	< 500
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	1.72

do not manifest 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 μg Pb/100 ml, one can calculate sensitivity and specificity (and therefore validity) of a certain ALAD-*cutoff level*, e.g. ALAD < a U (or μmol PBG/hr/l ery). A low sensitivity implies many false negative data: ALAD ≧ a corresponds to PbB > 35 μg Pb/100 ml; individuals with high PbB levels are overlooked. A low specificity implies many false positive data: ALAD < a corresponds to PbB ≦ 35 μg 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 μg 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*.

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 μg Pb/100 ml, and they confirm the schematic presentation of Fig. 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 μg Pb/100 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.

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