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ENVIRONMENTAL HEALTH ASPECTS OF LEAD

LES PROBLEMES SANITAIRES POSES PAR LE PLOMB PRESENT DANS L'ENVIRONNEMENT

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LEAD ABSORPTION AND PUBLIC HEALTH: AN APPRAISAL OF HAZARDS

: ZIELHUIS, R. L.

Coronel Laboratory, Faculty of Medicine, University of Amsterdam, Amsterdam, Netherlands

ZUSAMMENFASSUNG

Der Bleigehalt im Blut (PbB) *ist ein indirektes Maß für die biologisch wirksame Körperlast. In den meisten Fällen ist der* PbB-Wert $\leqslant$ 40 µg Pb/100 ml. *Bis zu dieser Grenze sind weder eine nennenswerte Erhöhung der* ALA-*Exkretion im Harn noch akute oder chronische Wirkungen des Bleis festzustellen. Es gibt hier einen hohen Sicherheitsfaktor, verglichen mit der zumutbaren Berufsbelastung. Die* ALA-*Dehydratase* (ALAD) *in den Erythrozyten nimmt bis auf* $\geqslant$ 1/3 *ab; zusammen mit dem* PbB *stellt sie einen empfindlichen und spezifischen indirekten Indikator für die biologisch wirksame Körperlast dar. Die Normen sollten sich auf die Gesamttagesbelastung und nicht auf die Atembelastung allein beziehen. Die zulässige Gesamttagesbelastung entspricht den annehmbaren biologischen Parametern für* PbB, ALAU *und* ALAD; *für Personengruppen und Einzelpersonen werden Richtwerte vorgeschlagen. Würde dem in Benzin enthaltenen Blei zu viel Aufmerksamkeit geschenkt, so könnten Geldmittel und Arbeitskräfte anderen, weit wichtigeren Aufgaben entzogen werden, die mit der Beeinträchtigung der Volksgesundheit durch den Verkehr zusammenhängen. Viel mehr Gewicht sollte auf die ökologischen Wirkungen des Bleis gelegt werden.*

SUMMARY

Pb *in blood* (PbB) *indirectly measures biologically active body burden. Usually* PbB $\leqslant$ 40 µg Pb/100 ml. *This level prevents evident increase of* ALA *in urine and acute or chronic effects of lead. There is a large safety factor if compared to acceptable occupational load.* ALA-*dehydratase in erythrocytes decreases to* $\geqslant$ 1/3; *together with* PbB *it provides a sensitive and specific indirect indicator of biologically active body burden. Standards should apply to total daily load, and not to respiratory load. Acceptable total daily load corresponds to acceptable biological parameters for* PbB, ALAU *and* ALAD; *guidelines are suggested for groups and individuals. Undue attention to* Pb *in petrol misdirects allocation of funds and manpower from other much more important effects from traffic on public health. More attention should be paid to ecological effects of* Pb.

RÉSUMÉ

La détermination du plomb sanguin (PbB) *permet indirectement de mesurer la charge du corps biologiquement active. En général, le* PbB *est inférieur ou égal à* 40 µg Pb/100 ml. *Jusqu'à ce niveau, on ne constate pas d'augmentation de l'*ALA *urinaire et le plomb n'exerce aucun effet aigu ou chronique. On dispose encore d'un facteur de sécurité important par rapport à la charge professionnelle admissible. La déshydratase* ALA *érythrocytaire décroît jusqu'à* ⩾ 1/3; *avec le* PbB, *elle constitue un indice indirect sensible et spécifique de la charge du corps biologiquement active. Il conviendrait de définir des normes applicables non pas aux doses inhalables, mais bien aux doses journalières totales. La dose journalière totale admissible correspond à certains paramètres biologiques admissibles pour le* PbB, *l'*ALAU *et l'*ALAD; *on donne des principes directeurs pour certains groupes ou individus. En mettant indûment l'accent sur le* Pb *contenu dans l'essence, on détourne les moyens financiers et les forces de travail dont on dispose d'autres effets plus importants qu'exerce la circulation routière sur la santé publique. Il y aurait lieu d'accorder plus d'attention aux effets écologiques du* Pb.

1 — INTRODUCTION

The question to be discussed is: Does exposure to lead by non-occupationally exposed human subjects under normal living conditions produce any biological responses, and if so, do these responses present any risk to health and wellbeing? Specific conditions of slum areas, of living near Pb emitting plants, or of pica do not present "normal living conditions", and are not relevant for the main topic of discussion.

Due to limitations in space, this paper may sometimes appear to be apodictical; many literature sources could not be discussed as such.

2 — PARAMETERS OF ABSORPTION

One should like to measure the internal chemical load to those receptor sites which react with a specific and sensitive response, at the same time being relevant for health. A direct parameter is not available in epidemiology. In practice one has to rely on an indirect approach: determination of lead in blood (PbB), although valid objections exist against this parameter:

1. It is an indirect parameter of Pb burden in receptor sites;
2. Various internal and external factors may influence Pb distribution through the body;
3. The body burden may be divided into: rapid exchange pool (blood, internal organs), intermediate exchange pool (muscles, skin), slow exchange pool (bone) (Pitrowsky 1970) [42]; PbB therefore does not indicate the total body burden. EDTA-induced Pb excretion (Teisinger *et al.* 1966) [57] might yield a more valid parameter for the rapid exchange pool than PbB.

Conclusion: in individuals PbB has its limitations; in *groups* variability will average out; up to the present distribution of PbB levels ($\bar{x} \pm \sigma$) offers the best practical tool to estimate the biologically active lead burden in groups of population.

Table 1 and Figure 1 present a survey of PbB levels in various population groups from geographically widely distributed areas, published after 1960. We may draw the following conclusions from this table and from literature:

1. The normal range of PbB is 10-40 µg Pb/100 ml, with mean levels <30 µg Pb/100 ml;
2. In the majority of cases the upper limit does not exceed 40 µg Pb/100 ml, if high risk groups (a.o. slum areas) are excluded;
3. In last decades PbB has not evidently increased (Stopps 1966) [54];
4. Urban PbB may be slightly higher than rural PbB.

TABLE 1

PbB *levels* (µg Pb/100 ml) *in population groups; published after* 1960

Country	Authors year of publication	Number of subjects	$\bar{x}\pm\sigma$	Range	Remarks
Adults					
Germany (DBR)	Szadkowsky *et al.* 1969a [55]	176	$\bar{x}$: 10.3-19.2 σ: 3.0- 9.6	—	various internal diseases
Germany (DBR)	Szadkowsky *et al.* 1969b [56]	53	16.7±6.8	—	—
Germany (DBR)	Lehnert 1968 [35]	400	14.9±4.8	—	—
Germany (DBR)	Reichel *et al.* 1970 [44]	44	15.1±3.6	—	—
		10	12.2±5.9	—	policeman
USA	Stopps 1966 [53]	3637	about 22	—	some values outside USA; a few values up to 50-60
USA	Weissberg *et al.* 1971 [61]	26	—	15-40	—
Finland	Hernberg *et al.* 1970 [23]	16	—	5-16	—
Sweden	Haeger-Aronsen 1971a [19]	100	8.5±2,6 (♀)	—	—
			12.3±4.3 (♂)	—	—
		35	—	<40	traffic workers
Switzerland	Lob *et al.* 1971 [37]	78	—	19-71	prisoners, alcoholics
Italy	Vigliani *et al.* 1969 [60]	118	21.1 (♀)	0-70	up to 70
			30.0 (♂)	0-70	
Japan	Horiuchi 1970a [26]	63	25	0-69	—
Un. Kingdom	Wilson 1966 [63]	8	8.7	0-20.4	pregnant women
S. America, Australia, Africa,	Stopps 1969 [54]	204	—	12-23	primitive conditions
Various countries	Goldwater *et al.* 1967 [18]	801	17±11	—	98% <50, in most countries <40
Children					
Germany (DBR)	Schaller *et al.* 1971 [45]	196	11.5±4.9	—	6-9 year
Unit. Kingdom	Moncrieff *et al.* 1964 [41]	80	—	14-42	4 month - 14½ year
Unit. Kingdom	Millar *et al.* 1970 [40]	30	12.3±2.7	—	IQ>70
		27	14.7±3.8	—	IQ<70
Sweden	Haeger-Aronsen 1971a [19]	15	10.9±2.9	—	2 month-12 year
USA	Blanksma *et al.* 1969 [8]	746	23.5±7.8	—	10-14 year

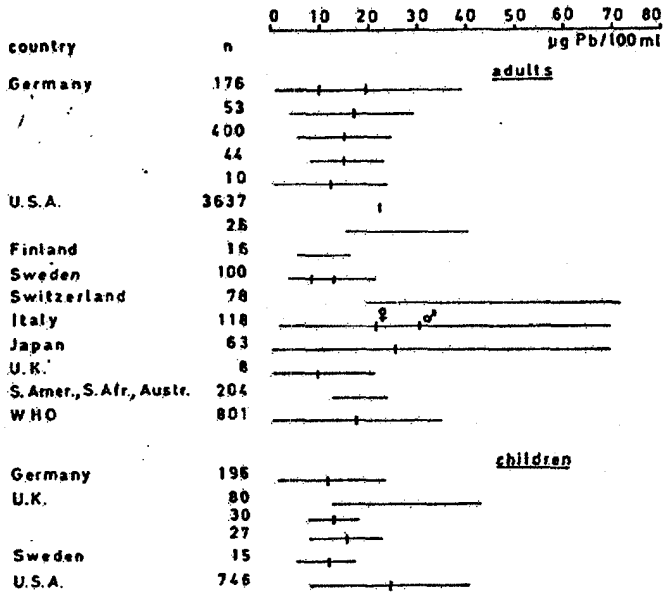

Fig. 1 — PbB levels: $\bar{x} \pm 2\sigma$ (—|—) or range (——) in various countries, published after 1960.

The question to be discussed may now be rephrased as follows: Does an internal chemical load as indicated by PbB levels up to 40 µg Pb/100 ml present any risk to public health?

3 — PARAMETERS OF RESPONSE

The internal chemical load induces biological responses (effects). A no-effect level of PbB only indicates absence of specified effects to be determined with specified methods (analytical, statistical), and does not indicate absence of any effects.

3.1 — Effects on porphyrin synthesis

If effects on porphyrin synthesis do not exceed specified limits, acute intoxication or chronic sequelae will not occur. Hb does not decrease below PbB < 50 µg Pb/100 ml. The workshop on inorganic lead Perm. Cee Int. Ass. Occ. Health agreed upon following limits for adult occupationally exposed workers: PbB 70 µg Pb/100 ml, PbU 130 µg/l, ALAU 10 mg/l, CPU 300 µg/l (Zielhuis 1969) [64]. ALAU (amino-

laevulinic acid excretion in urin) is more specific and more sensitive than CPU (coproporphyrin in urin), so for public health ALAU is more relevant.

Table 2 and Figure 2 present the relationship between PbB and ALAU. The following conclusions may be drawn:

1. The no-effect level of PbB is abaut 40 µg Pb/100 ml; increase in Figure 2 below 40 µg Pb/100 ml derives from mathematical calculation and is hardly evident in practice;
2. ALAU does not present a sensitive parameter for biologic monitoring in public health.

According to some authors (a.o. Chisolm 1971) [12] ALAU does not appear to be sensitive in children.

More sensitive and more specific is the decrease in activity of δ-ALA-dehydratase

TABLE 2

Relationship between PbB (x) *and* ALA-U (y)

Author(s)	Year of publication	Number of subjects	Relationship	Remarks
Haeger-Aronsen	1971a [19]	110	$\log y = 0.01294x - 0.8605$	PbB 10-120 µg/100 ml y in mg/100 ml $r = 0.61$
Lehnert *et al.*	1970 [66]	158	no increase of y	PbB<55 µg/100 ml
Lehnert *et al.*	1969 [67]	127	$y = 0.9x + 6.1$	PbB 47.3±24.8 µg/100 ml $r = 0.36$
		138	no increase	PbB 26.0±12.4 µg/100 ml
Hernberg *et al.*	1970 [23]	141	$x<50$ µg/100 ml no increase of y; $x>50$ µg/100 ml increase of y	PbB 10-130 µg/100 ml
Haeger-Aronsen *et al.*	1971b [20]	260	$x<50$ µg/100 ml no increase of y; $x>50$ µg/100 ml increase of y	PbB 10-90 µg/100 ml
Selander *et al.*	1970 [50]	150	$\log y = 0.0157x - 1.0985$	y in mg/100 ml

in erythrocytes (ALAD); it appears to be too sensitive for use in monitoring of workers. Table 3 and Figure 3 present the relationship with PbB. From these and other literature data the following conclusions may be drawn:

1. ALAD is highly specific for early responses to lead;
2. In patients with neurological and haematological disorders no decrease of ALAD has been noted;

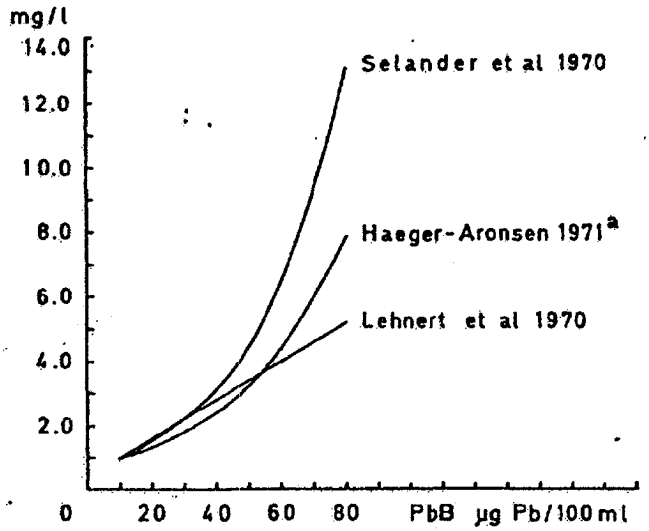

Fig. 2 — Increase of ALAU in relationship to PbB.

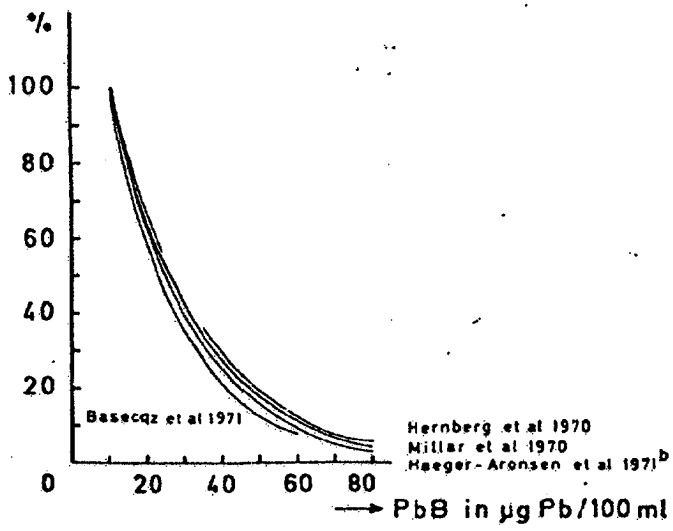

Fig. 3 — Percentual decrease in ALAD in relationship to PbB.

TABLE 3

Relationship between ALAD-*activity* (y) in *erythrocytes and* PbB (x)

Author(s)	Year of publication	Number of subjects	Relationship	Remarks
Weissberg *et al.*	1971 [61]	234	linear	in total blood; children and adults; PbB<80 µg/100 ml
Schaller *et al.*	1971 [45]	196	no relationship	PbB 11,5±4.9 µg/100 ml
		30	significant, $r = -0.41$	PbB 16-30 µg/100 ml
		15	significant, $r = -0.63$	PbB 20-30 µg/100 ml
		70	significant, $r = -0.25$	adults, average PbB 14.9 µg/100 ml
Hernberg *et al.*	1970 [23]	158	$\log y = 2.274 - 0.018x$ $r = -0.90$	PbB 5-95 µg/100 ml
Haeger-Aronsen *et al.*	1971b [20]	260	$\log y = 2.291 - 0.020x$ $r = -0.83$	PbB 10-90 µg/100 ml children and adults
Millar *et al.*	1970 [40]	57	$\log y = 6.7685 - 0.0436x$ $r = -0.80$	children. PbB 10-20 µg/100 ml
Secchi *et al.*	1971 [49]	102	$r = -0.41$	PbB probably <50 µg/100 ml not occupationally exposed
Basecqz *et al.*	1971 [7]	47	curvilinear $r = -0.82$	PbB 20-75 µg/100 ml (expressed as µg/100 ml ery)

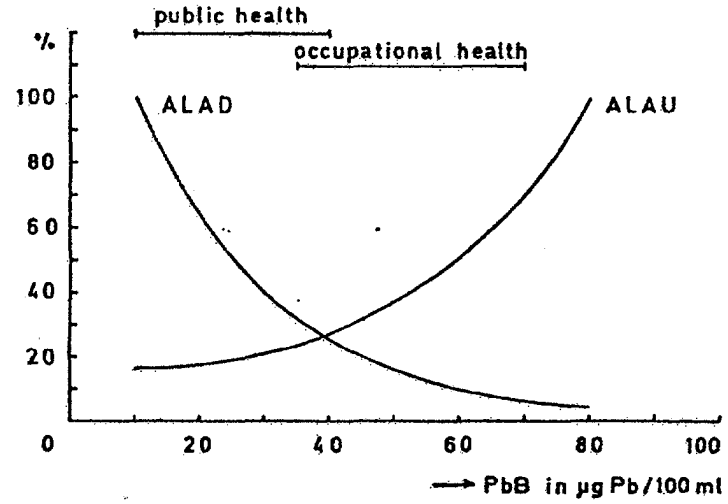

Fig. 4 — Percentual change in ALAD en ALAU in relationship to PbB.

3. Haemsynthesis is probably not affected if ALAD > 1/3 normal level;
4. In rats there exists a linear relationship between ALAD in blood and in brain;
5. Relationship PbB × ALAD is the same in adults and in children;
6. There do exist indications that the no-effect level of PbB is about 5-15 µg Pb/100 ml (Schaller *et al.* 1971) [45].

The difference in sensitivity in regard to PbB between ALAU and ALAD is presented schematically in Figure 4: ALAD has little significance for occupational health, ALAU has little significance for public health.

As far as known decrease of ALAD as such has no or little significance for health, if the activity remains > 1/3 normal level; the body appears to possess a high reserve capacity. ALAD is a highly sensitive and specific parameter for early response, and indirectly for biologically active internal load, but as such is not relevant for health.

Protoporphyrin in erythrocytes (PP) increases from about PbB = 40 µg Pb/100 ml (Haeger-Aronsen 1971a) [19]; it is less sensitive than ALAU (Albahary 1968) [2]; and therefore not relevant for public health.

3.2 — Effects on erythrocytes

Lead affects erythrocytes: decreased: Na^+-K^+-ATPase activity in membranes, life span, increased: K^+ efflux, glucose consumption, osmotic resistance, pyruvate levels after glucose dosage, prevalence of Heinz bodies. These responses however are less specific and less sensitive than ALAU; they probably do not appear below PbB = 40 µg Pb/100 ml (Hernberg 1970 [22], Qazi 1971 [43], Moncrieff *et al.* 1964 [41], Ghelberg 1966a [16]).

3.3 — Other biochemical effects

Numerous effects have been reviewed by De Bruin (1971) [10]: decreased: immunobiological reactivity, alkaline phosphatase, cholinesterase, carbon anhydrase, amino acid levels, increased: serum aldolase and catalase, modifications in serum protein pattern, etcetera. Most or all of these effects have only been observed in workers with symptoms of poisoning or with relatively high exposure. They do not appear to be relevant for PbB < 40 µg Pb/100 ml: One animal experiment (Bingham 1969) [65] may appear to be relevant: decrease in alveolar macrophags in young male rats, if exposed to Pb in air (PbA) = 10 µg Pb/m^3; this reversible effect still has to be studied in human subjects in order to evaluate its relevance for health.

Ghelberg *et al.* (1966b) [17] found increased urinary excretion of 5-hydroxyindolacetic acid in 11 year old children living in the vicinity of a lead emitting industry (PbA about 31 µg Pb/m^3); this parameter is less sensitive than ALAU (Urbanowicz *et al.* 1969) [59].

3.4 — Effects on clinical health and life span

Possible effects on kidney function, tension, cerebrovascular incidents are only seen in subjects with longterm high exposure (PbA >150 µg Pb/m^3) or with acute intoxications in their medical history (Malcolm 1970 [38], 1971 [39]; Cramer *et al.* 1966 [13], Stopps 1966 [53]). Hickey *et al.* (1967) [25] studied specific mortality rates in the general population in relationship to air pollution with metals (PbA: $\bar{x} = 1.1396$ µg Pb/m^3); there was no relationship with disease classification, in contrast to possible relationship with Cd and V. Szadkowsky *et al.* (1969) [55, 56] did not observe any pathogenetic relationship between PbB and various internal diseases. In a soft water area with relative high Pb intake the increased cardiovascular mortality did not appear to be related to Pb intake (Crawford *et al.* 1969) [14]. Effects on chromosomes have been reported, however only in subjects with high PbB (Schwanitz *et al.* 1970) [48]; in drosophila there was no effect of inorganic lead (Ahlberg *et al.* 1972) [1].

The animal experiments of Schroeder *et al.* (a.o. 1968) [47] have drawn much attention: in mice and rats long term oral intake of 5 ppm Pb in drinking water gave rise to Pb levels in soft tissues in the same order of magnitude as in American adults; moreover there was a decreased life span. However, these data cannot be extrapolated to human beings, because apparently the kinetics of lead in rats and mice differ considerably from those in man; the daily oral intake of these animals was 400-500 µg/kg body weight, about 80-100 times that in human beings; moreover the rats received a Cr-deficient diet. Schroeder *et al.* (1968) [47] found increased Pb content of ribs in American adults up to the 5th decade; the lack of increase in older age groups might—according to Schroeder *et al.*—be caused by shortened life span due to increasing Pb body burden. These data have been severily critisised by Kehoe (1969) [29] and could not be confirmed by Barry *et al.* 1970) [6].

Conclusion: A lead body burden, represented by PbB <40 µg Pb/100 ml probably is consistent with absence of effects on ALAU, PP, many other biochemical parameters, clinical health and life span. Conclusive evidence of such effects have not been established, and data with suggestive evidence hardly exist.

4 — RELATIONSHIP DAILY Pb UPTAKE AND PbB

There does not exist adequate information on the relationship between longterm daily exposure and PbB. The Nat. Research Council—NAS (EPA 1972) [15] suggested a curvilinear relationship between total daily uptake (PbA in µg) and PbB: PbB $= -69.2052 + 54.7605 \log$ PbA. This aequation apparently is very approximate, more or less a "guestimate". The following assumptions have been made:

1. 24 hr continuous exposure → overestimation of daily exposure;

2. Daily respiratory volume 23 m^3 → overestimated; 15-20 m^3 appear to be more reasonable;
3. 30% retention and 100% resorption; one may assume maximal 100% resorption after maximal 50% retention (Schlipköter 1972) [46];
4. Daily oral intake 300 µg Pb, which appears to be questionable.

The aequation probably gives maximal PbB in regard to current PbA levels and overestimates the realistic relationship.

Some data from other sources (Kehoe 1961, 1966 [28]; Williams 1968) [62] (respiratory and/or oral intake) have been recalculated, and added to the NAS-aequation (Table 4): multiplication of PbA with 5 corresponds to multiplication of PbB with about 2.

The maximal allowable PbB for adult workers is 70 µg Pb/100 ml according to Working group on inorganic lead Perm. Cee Int. Ass. Occ. Hlth (Zielhuis 1969) [64]; this corresponds to a safety factor of 10-20 for continuous 24 hr exposure to Pb for the adult general population. This safety factor is large if compared to safety factors as applied in food additives (from animal → man: 10; from man → man: 10).

TABLE 4

Relationship between lead in air (PbA in µg Pb/m^3) *and lead in blood* (PbB in µg Pb/100 ml)

PbA NAS	PbA Kehoe	PbA Williams	PbB NAS	PbB Kehoe	PbB Williams
2.0	—	—	21.3	—	—
4.0	—	—	27.3	—	—
5.0	5.0	—	30.3	30	—
10.0	—	10.0	40.0	—	35
—	15.0	—	—	55	—
20.0	—	—	53.8	—	—
—	25.0	—	—	70	—
—	—	40	—	—	65
50.0	—	50	71.6	—	75
100.0	—	—	87.2	—	—
—	150	—	—	145	—

The relationship between PbA and PbB is based upon calculations used in occupational health for uptake of particles with aerodynamic properties, and about 1 µ in diameter. Recently Lawther *et al.* (1972) [33] seriously critisized this procedure, because in sampling air near a heavy traffic road in London Pb proved to be present in aggregates and particles of much smaller diameter, e.g. 0.01 µ; according to Lawther one may presume a maximal retention × absorption of 10-12%, much lower

TABLE 5

Oral lead uptake in µg/day *in various groups of adolescents within the Common Market*, 1965-1967

Foodstuff	Milk	Cereals	Cheese	Vegetables	Potatoes	Meat	Total/day
Lead content	16.95 µg Pb/100 ml	16.20 1 g Pb/100 g	61.00 µg Pb/100 g	83.86 µg Pb/100 g	9.15 µg Pb/100 g	36.04 µg Pb/100 g	
Munster	85.43	83.59	18.30	209.65	33.12	62.71	492.80 µg Pb
Münich	33.56	103.19	13.42	245.71	33.67	63.79	493.34 µg Pb
Friberg	33.73	59.45	9.76	96.44	19.22	47.57	266.17 µg Pb
Zeist	112.38	61.07	13.42	93.92	16.01	37.49	334.28 µg Pb
Brussels	71.19	46.82	11.59	182.81	96.81	93.70	502.92 µg Pb
Rome	36.10	120.37	40.26	188.69	25.16	43.61	454.19 µg Pb
Catania	55.09	150.34	31.72	127.47	8.42	33.88	406.92 µg Pb
Milan	42.38	128.14	20.74	192.81	10.34	54.78	439.19 µg Pb
Sceaux	37.46	110.16	23.18	281.77	23.15	73.88	549.60 µg Pb

The calculated daily uptake is based upon:

1. Table 27: The principal diet constituents consumption and their variation coefficient, in Eur 3945, Comparison of the radioactive contamination of the total diet of adolescents in the community. Data for 1965-1967 (Smeets *et al.* 1970) [51].
2. G. Lehnert *et al.*, Usuelle Bleibelastung durch Nahrungsmittel und Getränke. *Arch. f. Hyg. und Bakteriologie*, 5 (1969) 403 [36].

than assumed retention × absorption of 30-50%. This appeared particularly true for Pb emitted by motorcars. Therefore the safety factor in regard to respiratory Pb uptake from traffic exhaust may increase with a factor 2-4, and become 20-40.

In Table 4 a daily oral uptake of 300 μg Pb has been assumed (review by Karhausen 1972) [27]. This intake may differ considerably: 100-500 μg Pb/day. In Europe Lehnert *et al.* (1969) [36] calculated a daily intake of 518 μg Pb for Germany (DBR), in U.K. Thompson (1971) [58] measured average 274 μg Pb (70-750), Kloke *et al.* (1968) [30] estimated for Germany (DBR) an intake up to 1400 μg Pb/day, Vigliani *et al.* (1969)[60] estimated 400-500 μg Pb/day for Milan, Italy; Horiuchi (1970) [26] measured 230-320 μg Pb/day for Japan. The Comm. Europ. Communities undertook a comparison of total diets, excluding alcoholics, of adolescents in various countries within the Common Market (Smeets *et al.* 1970) [51]. If we apply the data of Lehnert *et al.* (1969) [36] to the average diet, we arrive at a *relative* difference in oral daily Pb intake with a factor 2 (Table 5). If between groups the long term oral Pb uptake differs 200 μg Pb/day, then daily gastrointestinal absorption will differ about 20 μg Pb. This corresponds to a difference in 12 hr respiratory exposure of about 5 μg Pb/m^3. Such a large difference in daily respiratory exposure appears to be more unrealistic than a corresponding difference in oral exposure, at least for Europe.

These considerations emphasize an important point: the total Pb uptake mainly stems from oral uptake; it is therefore unrealistic to propose MIC values, one should determine an acceptable total daily load. However, it is very difficult to measure this. This may emphasize the feasibility of biological sampling, either through parameters of absorption (PbB) or parameters of response (ALAD), both indirectly measuring the biologically active body burden, and at least in groups of the population with a reasonable degree of reliability. In adults the biologically active body burden appears to a large extent to be independent from age (Barry *et al.* 1970) [6], in contrast to the slow or hardly exchangeable body burden in teeth and bones.

Children, especially in younger age groups, should be regarded as a special group, distinct from adults. They probably differ in:

1. Increased hazard of oral uptake, particularly in toddlers;
2. Increased gastrointestinal resorption: in young rats up to 80% if milk with a low Ca/P ratio is being administered (Kostial *et al.* 1971a [31], 1971b) [32];
3. The daily oral uptake if taken per kg body weight far exceeds that in adults (Chisolm *et al.* 1956 [11], Baltrop *et al.* 1967 [3]: average 120-130 μg Pb, 95% <183 μg);
4. The relative proportion of the body burden present in the slow exchange pool is smaller (Barry *et al.* 1970) [6].

5 — ASSESSMENT OF RISKS FOR ADULTS IN THE GENERAL POPULATION

The data regarding adult population groups so far discussed may be summarized as follows:

1. PbB normally does not exceed 40 μg Pb/100 ml;
2. The no effect level in regard to increased ALAU is about 40 μg Pb/100 ml and very probably higher for most signs and symptoms relevant for health;
3. ALAD in erythrocytes decreases from PbB = about 10 μg Pb/100 ml to 1/3 of its activity at PbB = 40 μg Pb/100 ml; up to now there is no evidence that this decrease as such has any significance in regard to health or wellbeing, either at short or at long term;
4. There exists a safety factor of at least 10-20 in respiratory 24 hr uptake for the adult general population if referred to acceptable respiratory uptake of workers, based upon the relationship between PbA and PbB;
5. Between population groups oral uptake probably differs to a larger extent than respiratory uptake; total daily uptake mainly stems from oral uptake; one should determine total acceptable daily Pb uptake;
6. Biological monitoring (PbB or ALAD) provides an easier, more realistic and more valid indirect yardstick of total daily uptake in population groups than a multitude of individual direct measurements of Pb in food, beverages and air.

There are gaps in knowledge; even when research is going on, gaps in knowledge will always remain. Nevertheless, at this moment there are sufficient data available in order to come to a justified policy for establishing acceptable total daily loads for adult population groups. However, we should bear in mind the gaps in knowledge as mentioned by for instance Hardy (1969) [21] and Smith (1969) [52]:

1. Not enough data exist regarding the extent of variability in total daily exposure;
2. High risk groups (PbB 30-50 μg Pb/100 ml) especially should be studied more fully;
3. There exists the possibility of increased susceptibility due to genetic defects, e.g. sickle cell trait, or due to pregnancy.

6 — ASSESSMENT OF RISKS FOR CHILDREN

For children we must add some extra points for discussion, summarizing the data mentioned so far:

1. The total daily load per kg body weight is appreciably higher;
2. The possibilities for oral uptake, particularly in toddlers, are higher, whereas intestinal resorption may appreciably go beyond the 10% as assumed for adults;

3. The oxygen consumption in the brain is relatively high; there are indications that a body burden corresponding to PbB > 40 µg Pb/100 ml may aggravate an already existing mental retardation;
4. The rapidly exchangeable body burden is relatively higher;
5. The acceptable limit of PbB = 70 µg Pb/100 ml as proposed for healthy adults, probably does not apply for children; the margin of safety is probably smaller.

Future research should especially be directed at gathering data from young children: measurement of daily total uptake, body burden (also with EDTA provocation tests), biological responses; particularly long term follow up studies are needed, taking fully into account data on mental development.

7 — ACCEPTABLE BIOLOGICAL LIMITS

Environmental standards have to take into account total daily uptake; this can be measured indirectly by biological monitoring of PbB, ALAD and ALAU. Particularly for more or less homogeneous groups one may conclude to acceptable biological limits, characterised by group average and upper limit; for individuals one may present upper limits. These limits should not be regarded as fine lines discriminating innocent from nocuous environments; however, if these limits are exceeded the possibility of undue acute effects and/or chronic sequelae increases. The data as established in population groups should always be interpreted by experts, and not by the lay public as such. Single values moderately exceeding upper limits in individuals should cause awareness and caution: the measurement should be repeated. Group data have a stronger significance than individual data.

The following acceptable limits are suggested as guidelines:

For adults

	individual limit	group average	unit
PbB	⩽ 40	⩽ 25	µg Pb/100 ml
ALAU	⩽ 6	⩽ 3	mg/l urin
ALAD	⩾ 20	⩾ 30	procentual decrease from 100% (at PbB = 10 µg Pb/100 ml)

For children

	individual limit	group average	
PbB	⩽ 35	⩽ 20	as above
ALAU	⩽ 5	⩽ 3	as above
ALAD	⩾ 30	⩾ 40	as above

8 — Pb IN TRAFFIC EXHAUST

Within the Common Market recently much attention has been paid to the public health aspects of exposure to traffic exhaust. A few comments should be made:

1. There are insufficient data regarding the effect of Pb in petrol on total daily intake; as yet there are no indications that oral intake of Pb in adults has increased due to traffic exhaust. PbB levels in USA have not evidently increased in last decades (Stopps 1966) [53].
2. Regional variability in oral uptake probably exceeds variability in uptake due to traffic exhaust.
3. Traffic exhaust appears to yield a small contribution to Pb uptake in children if compared to many other sources of lead (Baltrop 1972) [5].
4. Up to the present moment there are no indications that under conditions prevailing in the Common Market health and wellbeing of adults and children has been negatively affected by lead in traffic exhaust.
5. The overwhelming attention in the Common Market to Pb in traffic exhaust yields a greatly distorted picture of the total range of negatieve effects of traffic on public health: accidents, noise, traffic congestion, traffic exhaust. The most promising and rewarding approach to tackle the problem of traffic and public health is to decrease the distance between traffic and human subjects (living quarters, working quarters, playing grounds, etc.). If available money and man-power are solely or mainly directed to restriction of Pb in petrol, we may have a somewhat cleaner environment in respect to Pb, but the much greater other risks to health and wellbeing continue to exist and to increase.
6. Much attention is being paid to direct effects of Pb on human health. However, Pb ultimately pollutes the environment, particularly the oceans. If this affects primary production, indirect effects on human health and wellbeing may occur. This field of study deserves a higher priority in allocation of funds and manpower than research on direct effects on public health.

9 — GENERAL CONCLUSION

Pb is a non-essential element; therefore presence in the human biological system should be minimised as far as possible. In this respect restriction or elimination of Pb in petrol should be promoted. However, within the total significance of traffic for public health, other measures should receive a higher priority. If these measures—politically much more difficult to achieve—are taken, the potential risks of Pb in petrol to public health will indirectly decrease at the same time.

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DISCUSSION

ABBRITTI (Italy)
Are the acceptable biological limits you propose in your paper also valid for workers occupationally exposed to lead?
In a statement published in the *British Medical Journal* (1968) the acceptable level of δ-ALA in urine of workers exposed to lead was fixed at 20 mg/day. As the increased excretion of δ-ALA and coproporphyrin means that haem synthesis is affected (whereas the decrease in ALA-D does not necessarily and always mean an impairment of haem synthesis, this enzyme being "non limiting" in the haem biosynthetic pathway), don't you believe that this limit is too high and unacceptable also for occupationally exposed people, and that also in view of the importance of haem in many fundamental functions of cells and considering the presence of other pollutants in the environment that can interfere with haem synthesis?

ZIELHUIS (Netherlands)
No. In november 1968 a working group under the auspices of the Subcom. on MAC, Perm. Comm. Int. Ass. Occ. Hlth., convened in Amsterdam and proposed the following acceptable limits:

Pb in air	150 µg/m³
in blood	70 µg/100 ml
in urine	130 µg/l
ALA in urine	10 mg/l
Coproporphyrin in urine	300 µg/l

See: *Arch. environm. Hlth*, October 1971
and R. L. ZIELHUIS, *Proceedings 16th Int. Congress Occ. Hlth.*, Tokyo, pp. 510-512, Tokyo, 1971.

CRAMÉR (Sweden)
I whole-heartedly agree with the guidelines given in your paper, although I know that it will be difficult to live up to those standards. I would only like to make the remark that your average values must represent the median values and not the mean values, as these distributions tend to be truncated to the left.

ZIELHUIS (Netherlands)
Most data in literature are presented as $\bar{x} \pm 2\sigma$, although distributions probably are skewed. For the provisional tentative guidelines I proposed average levels and maximal levels, but I agree with Dr CRAMÉR, that in the final proposal acceptable percentile levels should be given: recommendations for $\leq 50\%$, $\leq 95\%$, $\leq 99\%$ of population groups; the size of the monitor groups should also be given.

SCHLIPKÖTER (Federal Republic of Germany)
With the present-day air lead burden of large cities, man is already taking up as much lead with respiratory air as with foodstuffs.

ZIELHUIS (Netherlands)
If we assume:

— oral intake 300 µg Pb/day, 10% absorption;
— average Pb in ambient air 5 µg/m³;
— 12 hr exposure every day to ambient air outdoors;
— 12 hr exposure indoors to 1 µg Pb/m³;
— retention 50%, absorption 100%, 10 m³/12 hr outdoors, 5 m³/12 hr indoors;

then uptake/day:

— gastrointestinal	=	30 µg
— respiratory 10.5.0,5.	=	25 µg
.. 5.1.0,5.	=	2.5 µg
total		57.5 µg Pb

According to "Air lead concentrations in the Europ. Comm. April 1971 – March 1972" the assumed air lead concentration of 5 µg Pb/m³ for 12 hr/day appears to be too high for everyday exposure of the "normal" public. Also, taking into account the work of LAWTHER, the respiratory retention-absorption of 50% may be too high. Therefore, the above presented calculation—apart from being a "calculated guess"—probably presents an unrealistic picture of the long term daily intake of the "normal" public; presumably the respiratory daily absorption generally is below 50% of total daily absorption.

SCHLIPKÖTER (Federal Republic of Germany)
As long as we are uncertain whether the reduction of ALA-D activity is of importance to health, we must take into consideration this enzyme change when assessing the effect of lead.

ZIELHUIS (Netherlands)
Clinical physicians in their treatment of patients very often have to make statements, although they always have to bear in mind the possible uncertainties. However, they have to carry this burden themselves, and not burden the patient with scientific doubts. Also public health physicians have to bear a responsibility in giving statements to governments, and should not stay away from it because they still have theoretical questions.

Certainty can be given in three levels:
(a) general scientific *consensus* of dose-effects relationships,
(b) reasonable doubt: scientists discuss together *potential risks*, albeit there is not yet a certainty,
(c) *theoretical risks*: asking questions without reasonable basis in scientific hypotheses; science—being science—will never stop asking questions, neither now, nor in the future.

Acceptability should be based upon *a* and *b*; reasonable doubt is covered by a safety factor. Level *c* cannot be covered. Progress of research may lead to change in levels *a* and *b*, and therefore also of *c*. Some environmentalists say: "It does not hurt to be too safe". However, this may be a false statement, because all preventive measures use resources, and this policy may use up limited resources for the wrong cause.

SCHLIPKÖTER (Federal Republic of Germany)
Your mean blood lead values can be accepted. A blood lead level of ~ 40 µg% for individuals is too high, since such values are harmful to the health of pregnant women and sick persons.

ZIELHUIS (Netherlands)
Average group levels and maximal individual levels should be dealt with in combination. My proposal has to be discussed. Some changes may have to be made. Up to the present I do not think that levels 40 µg% (and not higher) have been proven to be harmful for pregnant women and sick persons.

LOB (*Switzerland*)
With progress in occupational medicine and medicine in general, Pb sources tend to decrease. There is only one source which is continually increasing, i.e. pollution by exhaust gases. We are obviously without any criteria for assessing the health hazards, although we have one parameter, the decrease in ALA-D activity of which we do not understand the real significance, but which is apparently a factor in cerebral activity. A reduction of the part played by exhaust gases would appear to me to be a moot question. On the other hand blood lead does not represent the total lead in the organism. Lead is stored in the bones and may be mobilised under the influence of various stresses, e.g. malaise.

ZIELHUIS (Netherlands)
There are at least two methods to reduce traffic exhaust Pb: reduce Pb in petrol, or reduce number of cars/number of people. The second method also results in a reduction of other risks to public health: accidents, noise, other exhaust gases, etc; however this reduction also has some negative effects: decrease of degrees of freedom (easy transport, holidays, etc.). There is a benefit-risk balance. Paying undue emphasis to Pb alone disregards other public health risks.
From the medical point of view there is nothing against a decrease of Pb in petrol (if this does not induce increase of other exhaust gases!), but at the same time *from the medical point of view* there is little to propose this measure as a very important contribution to public health. The relationship traffic-public health should be considered in its *total benefit-risk balance* and not in the context of one (and not the most important) factor.
Lead is stored in the bones. There is inadequate basis for the statement that this deposit—if as a result of long term low level exposure—contributes to ill health under the influence of various stresses. What is "malaise"?

PALLIES (U.S.A.)
For years in Philadelphia I have watched the growing interest in lead absorption in children. We once had a death or two a year attributed to lead, but not in recent years. It is difficult today to demonstrate clinical illness referable to lead. Yet we are devoting hundreds of thousands of dollars every year to the removal of lead from the environment of children who are living in wretched surroundings where they are severely malnourished, nibbled on by rats, breathe carbon monoxide in large quantities and are exposed to other hazards of known deleterious effect. If we succeed after the expenditure of vast efforts in removing this suspected hazard causing unknown but suspected harm we will leave these children in a totally wretched environment but a lead-free one. There is, as Prof. ZIELHUIS has said, a need for examining our priorities and devoting our efforts to helping these children rather than running scientific investigations of academic interest.

WOUTERS (O.E.S.C.)
Concerning standards to be observed for workers employed in zinc and/or lead ore processing plants, which, in your opinion, are the standards regulating
a) temporary withdrawal from work,
b) permanent withdrawal from work?

ZIELHUIS (Netherlands)
In 1968 a Working Group on inorganic lead, Perm. Cee Int. Ass. Occ. Hlth., proposed the following guidelines for occupational exposure

Pb in air	150 µg Pb/m³
Pb in blood	70 µg Pb/100 ml
Pb in urine	130 µg Pb/l
ALA in urine	10 mg/l
Coprop. in urine	300 µg/l

These guidelines should be regarded as "warning signs"; the industrial physicians should recheck levels, examine working conditions; the levels should not be regarded as sharp lines, demanding withdrawal from work. The industrial physician (adequately educated in lead toxicology!) should pay particularly attention to the health of these workers. Temporary or permanent withdrawal from work demands an experienced judgment of workers and work situation, and cannot be laid down in "standards"!

ELLISON (U.K.)
I should like to draw attention to the fact that Dr. ZIELHUIS is mistaken in stating that LAWTHER *et al.* (1972) suggest that one may presume a maximal retention x absorption of 10-12%. LAWTHER *et al.* quote the data of DAVIES and his co-workers (references below) as indicating that for tidal breathing and for insoluble monodisperse spherical particles of diameter 0.5 µm the pulmonary deposition was in this range, and further say that the experiments on which this conclusion was based were of such quality that they must be taken as indicating that for these particles the I.C.R.P. curves were too high. LAWTHER *et al.* also accept the inference that the I.C.R.P. curves were too high over that part of the size-range on either side of this, and since a large proportion of the particles observed in their electron micrographs of particles from vehicles are aggregates of about this size they conclude that deposition is considerably lower than the figures often quoted. They do not venture to put forward a figure in the paper referred to. Aerosols from industrial sources cannot be assumed to have the same particle size distribution and may therefore have very different pulmonary deposition.

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HEYDER, J. & DAVIES C.N., *Aerosol Science*, v. 2, 437-452, 1972.

BRIDBORD (U.S.A.)
My own calculations indicate that the differences (safety factor) between industrial lead exposure and general population lead exposure are considerably less than the 10-20 time factor that you quoted in your presentation. Any calculation of the difference between occupational and general population lead exposures must consider the difference in *total* lead exposures that exist between the groups. For example a worker in occupational exposures is commonly exposed to air leads of 150 µg/m³ for a 40 hour week. This is equivalent to breathing air containing approximately

$$\frac{150 \times 40 + 2 \times 128}{168} = \frac{6000 + 256}{168} = \frac{6256}{168} = 37\ \mu g/m3$$

This assumes breathing air at 2 µg/m³ when not on the job. Under the additional assumption that approximately 30% of airborne lead is retained in the lungs; that nearly 100% of this retained lead is absorbed; that an adult male breathes 20 m³ per day and has a dietary lead intake of approximately 300 µg per day of which 10% is absorbed the following table can be constructed:

	Daily lead absorption		
	Absorption from air	Absorption from food	Total
Occupational Exposure	$37 \times 20 \times 0.3 = 222$	$300 \times 0.1 = 30$	252
Community Exposure	$2 \times 20 \times 0.3 = 12$	$300 \times 0.1 = 30$	42
Relation factor or safety factor $= \frac{252}{42} = 6$			

Can you please comment.

ZIELHUIS (Netherlands)

WILLIAMS found PbB = 75 µg Pb/100 ml in workers exposed to 200 µg Pb/m³ (personal sampling), 40 hr/wk. This increases (as far as assumptions prove to be correct) the safety factor calculated by Dr BRIDBORD with $\frac{4}{3}$; it becomes 8. According to my table 4 PbB = 65-75 µg Pb/100 ml corresponds to PbA = 40 µg Pb/m³.24 hr; a safety factor = 2 in PbB corresponds to a safety factor = 8-10 in PbA = 5 µg Pb/m³ and 20 in PbA = 2 µg Pb/m³. I agree with Dr. BRIDBORD. that his method of calculation is more correct, taking into account the total (air + nutrition) exposure.
Another calculation is also possible:
worker, 150 µg Pb/m³, 8 hr, 40/wk:
respiratory absorption 5 workdays:

	150 µg/m³ × 10 m³ × 0.4 × 5 d(8 hr) =	3000 µg
	2 µg/m³ × 10 m³ × 0.4 × 5 d(16 hr) =	40 µg
resp. absorption weekend	2 µg/m³ × 15 m³ × 0.4 × 2 d(24 hr) =	24 µg
	nutrition, 7 days	210 µg
	week total	3274 µg Pb

general population, light activity, 24 hr exp. 2 µg/m³; 15 m³: respiratory absorption 7 days:

2 × 15 × 0.4 × 7 =	84 µg
nutrition	210 µg
week total	294 µg

So safety factor (between acceptable exposure in adult worker and general population): $\frac{3300}{300} = 11$.
Both safety factors, taking into account various assumptions, are of the same order of magnitude: 10. In food toxicology a safety factor of 10, covering variability in sensitivity between human subjects, generally is regarded as adequate. Moreover 150 µg/m³ is—in Western countries—regarded as an acceptable exposure already itself containing a margin of safety.
If the criticism of LAWTHER proves to be valid, then respiratory absorption of exhaust Pb is lower, say 15%, this increases the safety factor in regard to Pb from vehicle exhaust.