Epidemiological Bases for Possible Air Quality Criteria for Lead

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In at least some urban areas, population exposure to elevated atmospheric lead levels is associated with increased blood lead. No reasonable alternative explanation exists other than that the increased levels of lead pollution are causing increased lead storage in the body. The study of lead body burdens in U. S. populations indicates an increasing concentration with age in liver, spleen, pancreas, kidney, and lung. No such increase is found in samples of residents from foreign countries.

The effect of increased storage of lead on porphyrin metabolism is in urgent need of investigation. Higher levels of lead exposure may interfere with hemoglobin synthesis.

Using WHO categories for air quality guides (criteria), a level I criterion for two micrograms of lead per cubic meter of air for a long-term average can be proposed. It would apply to pollution largely derived from motor vehicular sources.

Lead is widely distributed in man's environment. It is found in his food, his water, and in the air he breathes. Some of this lead derives from the industrial and technological activities of man.

Technological uses of lead have changed over time. At present, two of the principal applications are for storage batteries and gasoline additives; substantial amounts are also used in pigments, pesticides, and plumbing. Pottery glazes and solder are important as sources of human absorption.

Almost all foods contain detectable amounts of lead. Sources include: uptake and concentration by the organism from soil or fodder; contamination through aerial fallout; use of lead compounds in agriculture and direct contamination during processing, storage, and preparation.

Lead enters drinking water from a number of sources. The most important are lead pipe, cisterns, solder, paints, atmospheric fallout into uncovered reservoirs, and industrial sewage.[1]

Routes of Exposure

For most individuals, the diet is the major source of lead exposure. While estimates vary, the average dietary intake in the United States and in Europe is usually placed at about 0.30 mg per day.[1] In some areas, drinking water may be a major source, particularly in old urban areas where lead pipes or storage cisterns may still be in use. Tobacco smoke contains lead, apparently derived from soil residues of insecticide sprays used many years ago, and this source may contribute to total body burden in smokers.[2] Until recently, community pollution was largely neglected because it was thought to contribute little to population exposures.

Since a large proportion (90–95%) of orally ingested lead is excreted in the feces, most of the ingested lead is not truly absorbed into the metabolic pool of the body. Metabolic absorption (as opposed to ingestion) may result in increased body burden regardless of the route of intake. Some of this is excreted in the urine. Increased storage is likely when exposures are persistently increased. Decreased storage occurs when exposures decrease. From what is known about turnover rates of isotopes in bone, where much of the body burden of lead is stored, the processes associated with decreases in storage may have a slower half-time than those associated with increase. This needs to be further investigated, however.

The amount absorbed by the respiratory tract is a function of particle size, solubility and route. Of inhaled lead derived from motor vehicle exhaust pollution, from 25 to 50% is thought to be absorbed; airborne lead from other industrial sources generally has a larger particle size and a smaller proportion is absorbed. Because of the difference in absorption ratios, the amounts absorbed by the body via the oral and the respiratory routes may be similar in magnitude even though the total ingested with food and water is usually several times the total inspired with air.

Health Effects of Lead

Inorganic lead in sufficient amounts is implicated as a causative agent in decreased hemoglobin synthesis, liver and kidney damage, mental retardation in children and in abnormalities of fertility and pregnancy.[1,3,4] Claims that lead is a carcinogen have not been sustained by occupational studies. Clinical observations are often used in denoting the effects of undue lead exposure and it is against the onset of clinical pathology in occupational exposure situations for adults, that blood and urine levels of inorganic lead have been established in setting presumed "normal" values.[5]

Adults who have less than 0.08 mg of lead per 100 g of blood, and excrete less than 0.15 mg of lead per liter in 24-hour urine specimens, are considered to be within "normal" limits.[6] They ordinarily do not show clinical lead intoxication even though metabolic effects of lead exposure may be reflected in blood and urine.

There is evidence that exposure to moderately low lead levels may produce abnormalities in the synthesis of porphyrins.[5] The most specific, but not the only, site of damage in porphyrin biosynthesis is the inhibition of delta-aminolevulinic acid (d-ALA) dehydrase. This inhibition leads to increased blood and urine levels of d-ALA; this increase may appear before any change is noted in blood or urine lead levels.[7,8] In one study of occupationally exposed workers, a considerable increase in d-ALA in blood was the first sign

...[9] The pathway of porphyrin synthesis, with known ... of lead inhibition, is shown in Figure 1.

...ildren are said to be more susceptible to lead intoxica... ...than adults. Encephalopathy and mental deterioration ...ead-poisoned children have been well-documented. One ...ly disclosed that 200 normal children had blood lead levels ...0.01-f to 0.030 mg per 100 g while mentally defective ...ren showed 0.04 to 0.08 mg per 100 g of blood.[10] Amino... ...linic acid levels in the blood of these latter children were ...high. While it has been assumed that the elevated lead ...el was a causal factor in mental deficiency,[11] it is possible, ...course, that the mental deficiency might have contributed ...an increased intake of lead; e.g., from pica or chewing of ...ded paint, rather than the other way around. Gordon, ...ng, and Mackay[12] did not find significantly higher blood ...d in children who were mentally deficient compared with ...ntrols.

Lead is deposited mostly in bone with lesser amounts in ...ft tissues. Once deposited, lead appears to be released at a ...w rate over extended periods of time. Lead workers re... ...oved several years from exposure still have shown high ...els of porphyrins in their blood and of d-ALA in blood and ...ine.[13] Presumably, sufficient lead was released slowly from ...cumulated reserves to sustain the interference with por... ...hyrin metabolism. Because of this equilibration with bone ...d other tissues and because direct measurement of lead ...torage is not possible, blood lead levels are generally taken ...s an indicator of total body storage for living populations, ...ven though values for an individual may fluctuate widely ...er time.

The Human Body Burden of Lead

Since one of the goals of air quality criteria for lead is to ...revent any increase in storage of this material in the body, the total body burden in relationship to lead exposure should provide an important index of this effect. Schroeder and Tipton[14] have recently reviewed the available data.

Their basic approach was to collect organ weights and samples from U.S. decedents with sudden accidental death, in cooperation with medical examiners' offices in nine major U.S. cities. The specimens were analyzed by emission spectroscopy. Specimens from foreign countries were also obtained, but only about half were from deaths due to accident. However, only tissues showing no gross pathology were analyzed for both U.S. and foreign subjects. Unfortunately, not all organs from all locations could therefore be used. Otherwise, comparable sampling and analytical procedures were used throughout.

Table I shows the basic source and variation of data for the U.S. accidental death group. Table II shows the geographical comparison between U.S. populations and foreign ones. African samples were mostly (41 out of 54) from decedents who had lived most of their lives under primitive conditions. Switzerland data shows the lowest body burden of all. Although the number of samples is small, they are of particular interest because lead additives for gasoline were not used in Switzerland until 1947, while in U.S. and many other countries, they were used since 1923.

In liver, spleen, pancreas, kidney and lung, there is an increase in lead concentration with age up to the fifth decade in the U.S. sample but no such increase was found in foreign samples. Both U.S. and foreign samples showed increased aortic lead concentrations with age. This suggests that foreign adult subjects were in a steady state whereas the U.S. subjects continued to add to lead storage in soft tissues. Similar increases were observed with age in bone lead concentrations up to the fourth decade in U.S. populations; with increasing age beyond 40 years, however, it declined.

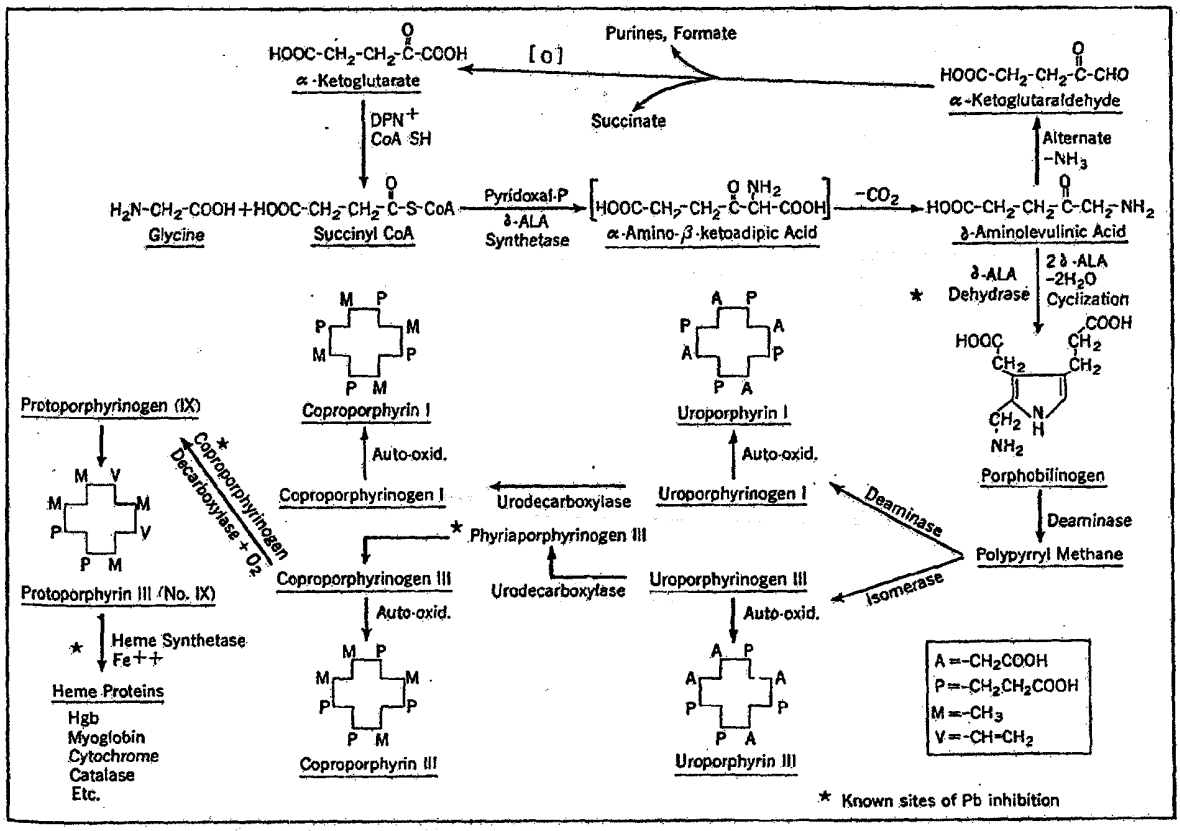

Figure 1. Pathway of porphyrin synthesis.

Table I. The body burden of lead, adult tissues from United States 150 accidental deaths, wet weight.

Tissue	Organ weight (g)	Total in organ: Mean (mg)	Total range[a] (mg)	80% Range[b] (mg)
Muscle	28 000	1.7	0–179.2	0–5.9
Fat	12 500	0.60	0.1–1.5	0.22–3.6
Skeleton	10 000	110.0	7.5–195	48–170
Blood	5500	1.4	0.22–2.7	0.3–2.4
Skin	4900	1.5	0–11.8	0.4–4.8
Dense connective tissue	2300	1.08	0–4.8	0–5.5
Liver	1800	3.1	0.72–13.5	1.3–6.3
Brain	1430	0.14	0–8.8	0–2.0
G. I. tract	1200	0.15	0–3.1	0.05–0.52
Lungs	1000	0.39	0.05–6.1	0.09–0.86
Heart	350	0.02	0–0.4	0–0.07
Kidneys	310	0.34	0.003–2.0	0.14–0.74
Spleen	180	0.06	0–2.2	0.02–0.24
Pancreas	100	0.06	0–1.1	0.02–0.17
Aorta	100	0.22	0.15–1.0	0.04–0.55
Hair	15	0.75	0.05–1.5	0.06–1.3
Other	315	0.08	0–0.2	0–0.1
Total body (ppm)	70 000	121.59	9.55–434.9	50.7–205.1
		1.73	0.14–6.25	0.72–2.93
Total soft tissue (ppm)	60 000	11.59	2.05–239.9	2.7–35.1
		0.19	0.03–4.0	0.05–0.59

[a] Total range of 258 cases.
[b] Range of 150 cases.
Source: Arch. Environ. Health, 17, December 1968.

The authors conclude: "Therefore, Kehoe's hypothesis of a balance between absorption and excretion appeared to hold for most foreign subjects but not for Americans. This idea is not valid for bone and aorta in either group."

Mathematical Distribution of Blood Lead Levels

Published epidemiologic data on blood lead levels generally show the mean but not the distribution of the observations; means for nonoccupationally exposed populations are usually between 0.015 and 0.025 mg per 100 g of blood. Estimated standard deviations, when given, are highly variable, but are usually proportional to the mean. Proportionality between mean and standard deviation is characteristic of log-normal distributions, commonly encountered in biological work, and logarithmic scales have been recommended for analysis of this type of data.[15–17] A range of 0.015 to 0.040 mg per 100 g has been considered to be average for nonoccupationally exposed persons.[5]

A recent study of Los Angeles County residents by Thomas, *et al.*[18] provided a striking demonstration of the relation between blood lead and place of residence which presumably reflects respiratory exposure for nonoccupationally exposed groups. Blood lead levels were measured for persons living near freeways (within 250 feet) and for persons near the coast (at least one mile from a freeway). Blood lead levels in the former group were markedly higher than those in the latter group but were higher, though not significantly so compared with the population values previously obtained from inland Los Angeles County, where atmospheric lead levels are generally high (Table III, Figure 2).

Goldsmith and Hexter[19,19a] have presented data including that of Thomas, *et al.* which they feel demonstrates that, for population groups, blood lead levels are epidemiologically related to estimated respiratory exposure in areas with high levels of motor vehicle pollution. This is based on epidemiological studies of general and occupational groups and the relation is similar to that from experimental exposures.[20] This relationship assumes generally similar dietary and beverage ingestions in the several populations[19,20] (Tables III and IV, Figure 3). This, in turn, implies that total body burden is, in part, a function of respiratory exposure. A reasonable interpretation of this epidemiological and experimental data is that continued respiratory exposures to ambient air levels already attained in some cities could result in increased body storage as indicated by blood lead.

Table II. Lead in adult human tissues according to geographical area median values, ppm ash.

	Nine U.S. cities	San Francisco	Switzerland	Africa	Middle East	Far East
No. cases	150	27	9	54	37	74
Aorta	140	220	32[b]	71	140	91
(%)[a]						95
Liver	130	160	59	64[b]	70[b]	97
(%)						99
Kidney	98	54	45	36[b]	62[b]	62
(%)				96		
Pancreas	49	65	42	24	34[b]	39
Lungs	47	38	32	28[b]	42	43
(%)				98		99
Testes	12	20	23	29	32[b]	35[b]
(%)	95					
Heart	5	10	14	5	24[b]	19[b]
(%)	57			65	95	
Brain	5	5	5	5	14[b]	10
(%)	69	96		71	88	81
Spleen	27	44	20	21	40	33
(%)	96			80		95
Bone	43				26[b]	30[b]
(%)					95	94
Total body (mg)[c]	121.6	137.2	61.9	63.2	78.4	93.7

[a] Percent of samples in which lead was found. When blank, lead was present in all samples. Data calculated from Tipton, et al.[12]
[b] Differs from nine U.S. cities, $P < 0.001$.
[c] Estimated by comparison of values.

Table III. Blood lead levels and estimated ambient air and occupational exposures of selected populations[a]

Type of population	Estimated exposure (μg/m³): Occupational	Ambient	Average[b]	Mean blood lead (μg/100 g): Male	Female
Populations without known occupational exposures					
Remote California mountain residents		0.12		12	9
Los Angeles residents near ocean		0.34		16	10
Composite rural U.S.		0.5		16	10
Suburban Philadelphia		1.0		13	13
Composite urban U.S.		1.0		21	16
Los Angeles aircraft workers		1.9		19	17
Pasadena city employees		2.2		19	12
Downtown Philadelphia		2.4		24	18
Los Angeles residents near freeway		2.5		23	17
Populations with known occupational exposures					
Cincinnati policemen (all)	4.7	1.4	2.1	25	
Cincinnati traffic policemen	12.8	1.4	3.8	30	
Cincinnati auto test lane inspectors	14.8	1.4	4.2	31	
Los Angeles traffic policemen	16.5	2.2	5.2	21	
Cincinnati garage workers	21.1	1.4	5.5	31	
Boston Sumner Tunnel employees	44.5	1.1	6.3	30	

[a] Source: U.S. Public Health Service, Survey of Lead in the Atmosphere of Three Urban Communities, Publication No. 999-AP-12, January 1965. State of California, Department of Public Health, Environmental Hazards Evaluation Unit.
[b] For populations with known occupational exposures, the average is a weighted average of presumed occupational and ambient exposure. Ambient exposures are estimated only and were not necessarily measured at the same times and places at which the populations were exposed.

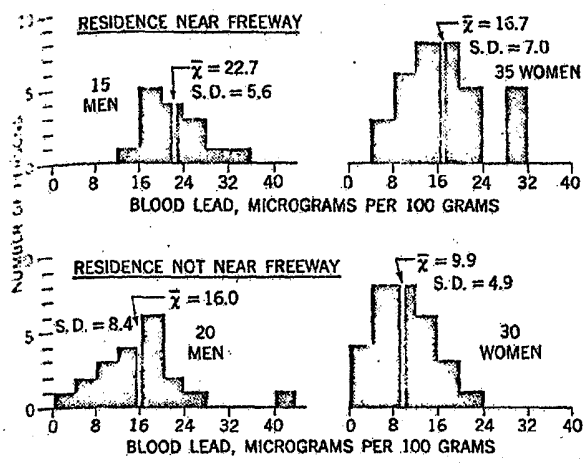

Figure 2. Frequency distribution of sample population by blood lead, sex and residence: Los Angeles County, 1966.

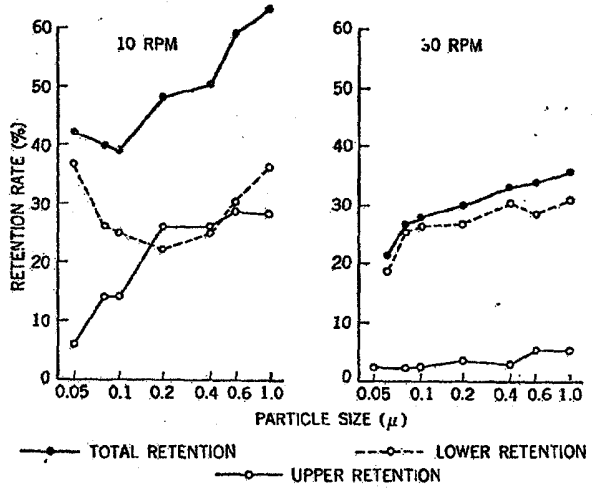

Figure 4. Relation between particle size and retention rate, total and regional retention for respiration rate. Source Nozaki, K.

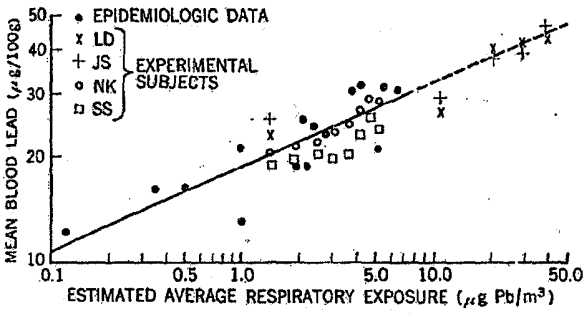

Figure 3. Mean blood lead for epidemiologic and experimental respiratory exposures with regression from epidemiologic data only.

Another experimental study which is highly relevant to epidemiology is of the relation of particle size to respiratory retention[21] (Figure 4). The importance of this derives from the particle size distribution of community airborne lead (Table V).

An experimental study of human respiratory exposure provides evidence that hematopoiesis is altered by respiratory exposures somewhat greater than those likely in community air pollution. Two subjects inhaled a mist containing dilute lead acetate solution through a special nebulizer, with doses of 0.589, 1.120, and 1.389 mg of lead per day for 61, 31, and 50 days, respectively. The amounts of lead inhaled, expired, and residual (in saliva) were measured and the net respiratory dose was found by difference. Over 80% retention was noted for this soluble salt, compared to 25–50% estimated for the

Table IV. Mean blood lead for experimental exposures to atmospheric lead (ug lead per 100 g of blood).

Respiratory exposure			Observed blood lead				
Exposure level (μg Pb/m³)	Number of hours per week	Estimated average[a] (μg Pb/m³)	Average blood lead (μg/100g)	Number of periods[b]	Average blood lead (μg/100g)	Number of periods[b]	Expected blood lead[c] (μg/100g)
			Subject NK		Subject SS		
10	0	1.4	20.4	7	18.6	5	20.2
	10.5	1.9	21.4	4	19.3	6	21.7
	21.0	2.5	21.7	6	20.2	4	23.1
	31.5	3.0	23.2	4	19.8	4	24.1
	42.0	3.6	24.6	4	20.2	4	25.1
	52.5	4.1	26.5[d]	4	23.0[e]	4	25.9
	63.0	4.6	28.5	4	25.5	4	26.6
	73.5	5.2	28.5	4	23.8	4	27.4
			Subject LD		Subject JS		
150	0	1.4	22.4	21	24.5	13	20.2
	10.5	10.7	26.0	4	28.5	4	32.4
	21.0	20.0	39.2	4	38.2	4	37.4
	31.5	29.3	40.8	4	39.8	4	40.9
	42.0	38.6	43.5	4	44.8	4	43.6

[a] Estimated average for each experimental period assumes 1.4 μg of lead per m³ in ambient air between experimental exposure sessions.
[b] Each period consists of 28 days with eight determinations of blood lead; only the average for these eight determinations was shown in the source. The averages given here are the averages of the period averages.
[c] Expected blood lead in μg per 100 g of blood calculated from the regression derived from the Three-City Study data ($\log_{10}$ blood lead = 1.271 + 0.2323 $\log_{10}$ atmospheric exposure).
[d] A 14-day "vacation" interrupted exposure just prior to this experimental period.
[e] A 21-day "vacation" interrupted exposure just prior to this experimental period.
Source: Kehoe, R. A., "Criteria for Human Safety from the Contamination of the Ambient Atmosphere with Lead," Proc. XV Congr. Intern. Med. Travail, Vienna, 1966, Vol. III, p. 83. State of California, Department of Public Health, Environmental Hazards Evaluation Unit.

Table V. Lead content of atmospheric particles by size, Berkeley, 1960.[a]

Median equivalent diameter (μ)	Percent of total atmospheric lead (by weight)
Total, all sizes	100
20	2-4
9	2-6
4	3-6
3	1-6
1.5	4-25
1	2-15
<1	50-80

[a] Source: State of California, Department of Public Health, Air and Industrial Hygiene Laboratory.

finely divided, but insoluble, inorganic lead particles from automobile exhaust. The daily absorbed dose for the first dosage level was about 0.50 mg; this produced a noticeable decrease in red blood cell count and hemoglobin count within two months, while urine coproporphyrin rose sharply within two weeks.[3]

This work re-emphasizes the importance of urinary excretion of d-aminolevulinic acid in study of lead exposed populations. So far, the sensitivity of this test has been shown for industrially exposed populations[22] (Figure 5), but not for populations with community exposures. This should be considered a high priority problem for investigation.

It is proposed that air quality criteria should include a criterion based on d-ALA excretion if and when it can be shown to be related to community air pollution exposure.

Possible Criteria

Reference is made to the report of the WHO Expert Committee on Atmospheric Pollution, WHO Technical Report Series No. 271 (1964), which suggested four levels of concentrations and exposure times for air quality criteria[23]:

"In the light of present knowledge, guides to air quality may be presented as four categories of concentrations, exposure times and corresponding effects. These four categories are defined by limiting values which may vary for a given pollutant according to the anticipated effect or the criteria used and in relation to other co-existing pollutants and the relevant physical factors, and which take into account the varying responses of different groups of human beings. The Symposium agreed to define the four categories in terms of the following levels:

"Level I. Concentration and exposure time at or below which according to present knowledge, neither direct nor indirect effects (including alteration of reflexes or of adaptive or protective reactions) have been observed.

"Level II. Concentrations and exposure times at and above which there is likely to be irritation of the sensory organs, harmful effects on vegetation, visibility reduction, or other adverse effects on the environment.

"Level III. Concentrations and exposure times at and above which there is likely to be impairment of vital physiological functions or changes that may lead to chronic diseases or shortening of life.

"Level IV. Concentrations and exposure times at and above which there is likely to be acute illness or death in susceptible groups of the population."

Using these criteria as guides, there are several questions which may be appropriate for consideration:

1. What constitutes an effect? Is storage an effect?
2. Should "effect" be defined in terms of altered blood or urine levels of porphyrins, delta-aminolevulinic acid, or other metabolites? What constitutes an altered level?
3. Does an altered level of a metabolite indicate an impairment of a vital physiological function?
4. Is it possible, or desirable, to define a concentration and exposure time corresponding to Level II?
5. Should adoption of numerical guides await further population studies, such as studies to determine the relationships, if any, between blood and urine levels of lead and of d-ALA in population groups exposed to varying intensities of urban air pollution? What groups? By whom should these studies be carried out?

In considering these questions, it is suggested that:

1. Definitions of criteria for Level I might be amended by adding, "significantly increased storage in the body of potentially toxic materials," as an example of a direct or indirect effect.
2. Definitions of criteria for Level II might be amended by adding, "significant alteration of an essential metabolic process (such as porphyrin metabolism)." Alternatively, this might be considered to be an example of a direct or indirect effect, in Level I.
3. Significant alteration in hematopoiesis be considered an example of an impairment of a vital physiological function, in Level III.

In view of the available data, and the above suggestions, it appears that a reasonable numerical guide for a Level I criteria would be long-term average exposure to 2.0 μg of lead per cubic meter of air, where pollution is largely from motor vehicular sources.

There may not be sufficient data to support numerical guides for criteria at higher levels.

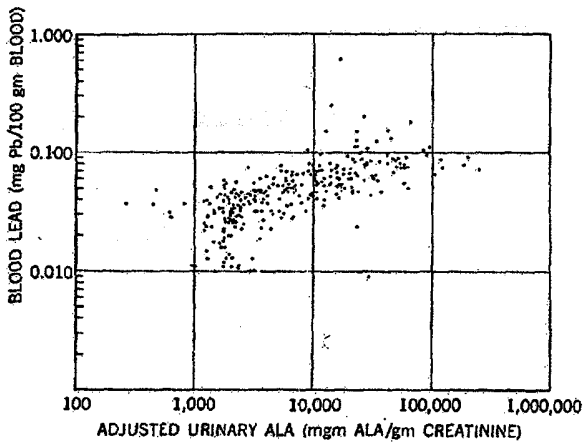

Figure 5. A group of men occupationally exposed to lead in various industries in California had blood and urine samples taken. Since the urine samples varied in their dilution, the urinary concentration of d-ALA was corrected for the amount of creatinine in the urine. The logarithmic relation is represented by a correlation coefficient of $R = +0.67$. Source: Bureau of Occupational Health and Environmental Epidemiology Unit, and Air and Industrial Hygiene Laboratory, California State Department of Public Health.

Acknowledgment

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Discussion

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Dr. Goldsmith states quite correctly that lead is widely distributed in man's environment, and that probably the diet is the major source of lead exposure; but it is not an element present only in the urban diet because lead is part of the earth's crust and is present in almost all food. This results in a certain base line level of lead being found in all human beings wherever they were sampled. We at Du Pont have been able to analyze the blood of groups of people in remote portions of the world, far removed from cities and man-made sources of lead. In South America, we were fortunate to obtain specimens from the Caraja tribe in the Xingu National Park area of central Brazil. Eleven male Indians had blood samples drawn and analyzed and the average blood lead concentration of these 11 subjects was found to be 23 μg per 100 g of blood. In southeastern Peru, on the eastern slopes of the Andes, live, tribes of Indians who have seldom seen a white man. They are completely self-sufficient in regard to their food supply and are hundreds of miles away from any man-made sources of air pollution other than their wood fires used for cooking. Samples obtained from 39 Indians had an average blood-lead level of 18 μg per 100 g of blood. Moving from South America to the bushmen of the Kalahari region of Bechuanaland now called Botswana, 63 bushmen from widely-scattered family groups had blood samples taken and the average blood-lead value was found to be 16 μg per 100 g of blood. Moving east and north from the Kalahari Desert, we were fortunate to find an expedition that was seeking out pockets of primitive people as yet largely untouched by Western civilization. From these people in portions of Kenya, Malawi, and Rhodesia, 63 blood specimens were obtained and the lead concentration was found to be 12 μg per 100 g of blood. Even further west we were able to obtain 28 samples of blood from Elcho Islanders off the northern coast of Australia. These people have little or no contact with white people, being from an isolated group of islands in Eastern Arnhem Land. A total of 28 blood samples were analyzed and the average blood lead concentration was found to be 17.5 μg per 100 g of blood.

These blood lead levels from persons living in remote areas with very little or no local exposure to artifactual lead,

range from 12 to 23 μg per 100 g. In North America, using the same laboratory for the analyses and the same analytical technique, over 6000 working men and women are being sampled on a yearly basis at 25 different locations ranging from Michigan to Florida and New York to Los Angeles. The average blood lead value for these men in 1968 was 20 μg per 100 g of whole blood; and for the women in the same year was 17 μg per 100 g of whole blood. This data is presented because it suggests that there are no gross differences between the blood lead levels of persons living in remote areas of the world away from automobiles and those of an industrial population, most of whom live in cities and commute to work by car. These figures also suggest, to the somewhat limited extent that remote primitive tribes resemble our own ancestors, that such blood lead levels have been present in man for long periods of time.

Dr. Goldsmith then goes on to mention drinking water, and tobacco smoke as possible sources of lead. In the case of drinking water, this is an unimportant source in North America, and is rapidly becoming so in other parts of the world. In the case of tobacco smoke, I will have more to say about this as a source of lead later in the discussion. In discussing ingested lead, Dr. Goldsmith points out that lead taken in by mouth is largely excreted in the feces and in a topological sense has not entered the body; and in a similar fashion, lead which has entered the lung and has not yet been absorbed into the blood through the alveolar wall, can also be regarded as outside the body. The amount of lead that will be absorbed into the blood from that deposited or retained in the lung, is a function of the particle size, density, solubility, and concentration. Because of the difficulties of experimentation, very little is known about the amount of lead aerosol retained in the lung under realistic conditions; and even less about the amount of lead absorbed from the lead so retained, since lead, like any other particle coming to rest in the lung, can be removed from the lung by phagocytosis or by ciliary action, or by a combination of the two. From a review of the literature, it appears that the quantity of lead deposited in the lung from the type of aerosol produced by the automobile is probably less than had been previously thought. The amount of lead deposited rises with increasing volume of air taken in with each breath and falls as the rate of breathing increases.

D.C.F. Muir and C.N. Davies, reporting in *Ann. Occupational Hyg.*, V 10, 161–174 (1967), found that during exercise, the fraction of deposition of 0.5 μ diameter particles is about 10% of the inhaled concentration at all work loads. At slower breathing frequencies, increased deposition is found in accord with the concept that the particles are slowly diffusing and sedimenting and that the chances of a particle encountering the wall of an airway increase with time. These workers found that the fractional deposition remained virtually constant and that the total weight of material deposited in the lung is directly proportional to the minute ventilation. The particle size having the minimal retention in the lung is of the order of 0.2 μ mass median diameter; and this is also the approximate mass median diameter of the lead aerosol found in the atmosphere. At the lower respiratory rates associated with nonexercising subjects, the total deposition of particles in the 0.2 μ mass median diameter size range varies with different experimental techniques, but ranges between 20 and 30% of the amount of aerosol inhaled. The higher total retention rates for lead fume in the paper by Nozaki, quoted by Dr. Goldsmith, may be due to factors: The use of carbon dioxide in the exhaled air as a tracer for partitioning dead space in alveolar air as this technique has been shown to probably over-estimate the retention of aerosols. All of the work which has dealt with the retention and absorption of particulate lead aerosols has been conducted with lead sesquioxide or lead from industrial sources; and there is reason to believe that the lead in the urban atmosphere might be less readily absorbed due to its particular mass median equivalent diameter, which leads to minimal retention in the lung and its relatively poor solubility in water.

In dealing with the health effects of lead, Dr. Goldsmith states that metabolic effects of lead exposure may be reflected in the blood and urine at blood and urine lead levels that are considered to be within normal limits. This statement is naturally disturbing because if it is true, it means that we cannot place reliance on the blood and urine lead levels to guide us in assessing the health risk from exposure to lead. In the context of Dr. Goldsmith's paper the metabolic disturbance to which he is referring is the depression of delta-aminolevulinic acid dehydrase with the consequent blocking of the condensation of two molecules of delta-aminolevulinic acid to form porphobilinogen. This block in the synthetic pathway of hemoglobin leads to an increase of delta-aminolevulinic acid in the blood and subsequently a spill-over of this material into the urine. This process has been well studied in animals and the time course of these events in both animals and man is fairly well understood. If the level of inorganic lead intake by the body is substantially raised above the normal level, first the urine and later the blood will reflect this increased intake by showing an increased concentration of lead. After this rise in blood lead has occurred, and if it is sufficiently great, the level of delta-aminolevulinic dehydrase will be depressed and this in turn is followed by a rise in the ALA levels in the blood and urine. If now the lead intake is reduced to normal, the blood and urine values will return to their normal values at a rate which is dependent upon the degree and duration of the previous elevation. The enzymatic depression will take longer to return to normal and will lag behind the fall in the blood and urine lead values. If the lead levels have been elevated for a period of months or years, the ALA levels may remain elevated for several months to a year after the lead levels have fallen to normal. With this background, if we reexamine Dr. Goldsmith's statement we can see that high ALA levels could be found in the presence of normal blood and urine lead values, if the person had previously had a fairly severe lead exposure. The confusion on this point has probably arisen because most of the studies of ALA levels have been carried out in populations with an abnormal exposure to lead. This point is illustrated in Figure 1 which superimposes two sets of data, one from lead-exposed workers, and one from office workers with no occupational lead exposure. It can be seen that for the same range of urine lead values, the lead-exposed workers tend to have higher ALA values. A further point worth making about studies of the relationship of gradually increasing levels of lead intake to an index of metabolic derangement such as urinary and ALA concentrations, is that such relationships tend to be curvilinear, so that there is a range of lead intake which has no biologically significant effect on the ALA level and then as the level of lead intake rises above this "no effect"

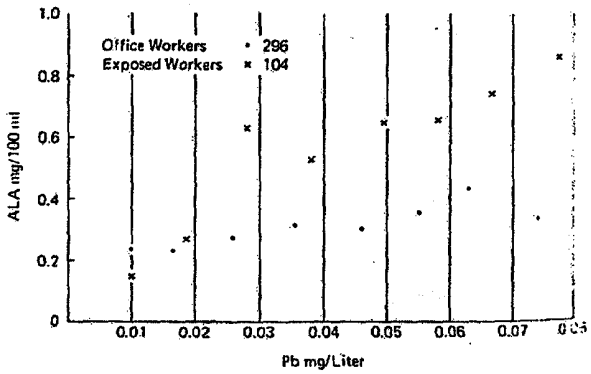

Figure 1. Relationship of ALA to lead in the urine.

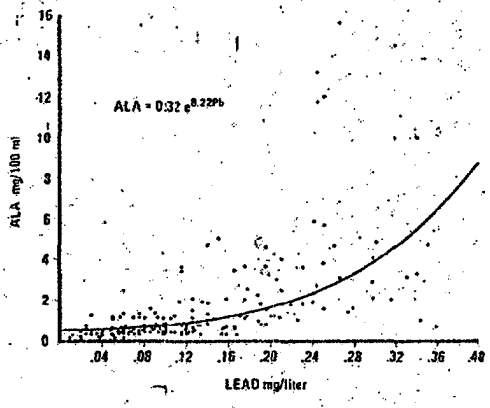

Figure 2. 193 men exposed to inorganic lead regression: ALA on lead in the urine.

region, a rise in ALA concentration takes place at a rate greater than the rate of increase of the lead intake. This concept of a level of lead intake below which no biologically significant effect occurs is open to some philosophical arguments; but as a practical guide in regulating the use of food additives in controlling pollutants and in setting safe levels of chemical exposures in industry, it has served us well.

Figure 2 shows the type of curve derived from measurements made on lead-exposed workers, with the virtually horizontal portion of the curve covering the range of lead values found in the normal population. A curve of a somewhat different nature is shown in the paper by Dr. Goldsmith, which relates estimated 24-hour air lead levels to blood lead levels of groups of persons in different parts of North America. This curve may be a true representation of the relationship between average air lead concentration and blood lead level, but in the absence of evidence that the individual groups used in constructing the regression line were properly investigated to see whether group averages could, in fact, be used; judgment on the value of the Goldsmith Hexter line must be deferred. To allow such group averages to be used to calculate a linear regression line, individual regression lines should have been fitted to each of the groups of data points comprising the population representing each subpopulation. These individual regression lines should then be subjected to the following three tests before a single regression line can be fitted: (1) the variance about each of the regression lines must be similar; (2) the slopes of the regression lines must be the same, that is to say, they can be considered parallel; (3) the separate parallel lines must be shown to be segments of one straight line. To perform these three tests, the individual data points are required. It is a much more powerful statistical technique to use all of the individual data points at one time rather than to take group averages. This statistical argument is not to deny that there is a relationship between high levels of lead in the air and blood lead levels. Such a relationship has been demonstrated and used for years in safeguarding the health of industrial populations. What seems more open to question is the form of the relationship in persons exposed only to the relatively low levels of lead encountered in the community air. To further illustrate the difficulty of making general statements about the relationship between the quantity of lead inhaled and the amount absorbed, it has been generally assumed for some years that smoking cigarettes caused an elevation of blood lead levels.

In 1967, however, G. Lehnert (*Intern. Arch. Gewerbepathol. Gewerbehyg.*, 23, 358–363) published a paper showing no difference in the blood lead levels of 116 men between 20 and 22 years of age living under identical environmental conditions and eating similar foods. Seventy-one of the subjects were smokers and 45 were nonsmokers. The average blood lead levels for the nonsmokers was 16.3 μg of lead per 100 g of blood; and for the smokers 16.4 μg of lead per 100 g of blood. Since the average number of cigarettes smoked was 17, this would give an average value of 13.64 μg of lead inhaled in the smoke; therefore an appreciable amount of lead was presented to the lungs in a very finely divided form, but this did not result in an increase in the blood lead level. Being intrigued by these results, we investigated the smoking habits of our industrial population referred to earlier and attempted to correlate the smoking habits with the blood lead levels. The lead level of smokers was 19.71 μg of lead per 100 g of blood and the lead level of nonsmokers was 19.78. Thus we have confirmed that in our series there is no difference between smokers and nonsmokers in blood lead level and that this holds whether a person smokes four packs of cigarettes per day or none at all. In a similar fashion, pipe and cigar smoking was found to be without effect on the blood lead level. These results run counter to those found in the Three Cities Survey and no immediate explanation is apparent; but if confirmed, it suggests that amounts of inhaled lead originating from cigarettes, up to about 64 μg per day, for the four pack per day smoker, have no effect on the blood lead level. This result is in contrast with the apparent effect on the blood lead level of living near a freeway in Los Angeles, with an average lead concentration of 2.5 μg per m^3. Such a person might breathe between 15 and 20 m^3 of air per day, giving a daily intake of between 37.5 and 50 μg of lead. This digression into the effects of smoking is intended to underline the apparent importance of the form and composition of the lead aerosol in determining absorption. Dr. Goldsmith has demonstrated that an aqueous lead acetate aerosol is easily absorbed, as one would predict, but we still know far less than we need to know about the retention and absorption of finely-divided solids in the lungs.

Dr. Goldsmith's proposal that air quality criteria should include a criterion based on ALA excretion, if and when it can be shown to be related to community air pollution exposure, sounds to the author suspiciously like a man who has made up his mind that the present level of lead in the community air is harmful; and that if the ALA levels of the population are not affected by it, then ALA levels as a criterion should be rejected and the search continued for some index that is influenced by the present level of lead in the air. I hope I am doing Dr. Goldsmith a disservice in drawing this conclusion and that he is more open-minded than my interpretation would suggest.

With regard to the suggestion that increased storage by itself be a criterion; this seems illogical, since body lead levels appear in general to follow the environmental lead levels in a passive manner and since lead has presumably always been present in the diet, a range of blood lead values must therefore be considered normal. If one accepts this premise, then an increase of storage may be perfectly acceptable if it occurs within the normal range; but at some point above this range an effect on health will occur. It is the level of this transition zone between safe and unsafe levels which causes so much debate. The debate drags on because we lack vital data on the long-term effects of various tissue levels of lead or disturbances of porphyrin metabolism. Here, the epidemiologists who numbered Dr. Goldsmith amongst their number must help by studying populations with moderately elevated ALA levels and comparing the health of such groups with those without raised ALA levels. If there is no difference in the health of the two groups, I can see no reason to use a slightly elevated ALA level as a criterion for setting an air quality standard. Of course, the problem I have posed, is the measurement of health, and this is not really such a semantic slough of despond that some would have us believe; and in fact, is the daily bread and butter of the epidemiologist. What is important here is that we keep our eyes firmly fixed on the functioning of the whole man rather than on individual enzyme systems.

In conclusion, since I must reject the premise upon which Dr. Goldsmith bases his air quality standard, I must also reject the number he offers.