BIOLOGICAL MONITORING
PROBLEMS OF BLOOD LEAD LEVELS

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A B S T R A C T

Blood lead levels pose problems that involve ethical, technical, toxicological, and societal considerations. Workers may legitimately object to periodic blood sampling to monitor their work environments, and technical problems and inherent errors associated with procedures reduce the accuracy of blood samples in evaluating toxic potential for workers. The inadequacy of blood lead for measurement of occupational exposures was demonstrated in a small population of lead workers in which those with blood lead concentrations below 80 µg/100 ml of blood were found to have unequivocal biochemical effects when a more sensitive testing method was used.* The co-existence of such abnormalities with acceptable blood lead levels casts doubts on the value of the entire blood lead measurement as a reliable index of hazardous exposure to and absorption of lead.

Almost all procedures for the detection and diagnosis of lead poisoning rely heavily, sometimes almost exclusively, on a determination of the concentration of lead in blood. In the criteria document for a recommended standard for occupational exposure to inorganic lead,[1] blood is offered as the better of two acceptable biological monitors; the other is urine analyses. Urinary lead, however, is considered less reliable, less well correlated with either air levels or biochemical indices, and is further confounded by the problems of differing specific gravities, diurnal variations, or the fact that spot samplings are not representative.[2-5]

While blood lead levels are less troubled by these difficulties, there are still some fairly formidable problems associated with their determination and interpretation. In addition to considerations that are essentially technical or toxicological, ethical and societal matters, while not necessarily the major concern of this conference, must be considered, however briefly, when any biological monitoring program is proposed.

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**With two exceptions, all of the 27 employees tested showed blood lead concentrations below 80 µg/100 ml. Yet in this small population, more sensitive tests demonstrated clear and unequivocal biochemical effects; EDTA mobilizations showed inordinately high body burdens of lead; and four cases of lead nephropathy were uncovered, even though only eight workers were adequately examined for renal disease.*

On quite legitimate moral grounds, a worker may object to being sampled periodically to serve, much like a guinea pig, as a monitor of the safety of the work environment provided for him. The Occupational Safety and Health Act guarantees for every work, "safe and healthful working conditions." All the personnel and the extensive apparatus and paraphernalia of OSHA and NIOSH essentially are in business to implement this mandate.

Emphasis on the safety of the work environment is clear, both as written into law, and as demanded by good preventive medical practice. Is it not then an admission of some technical weakness when reliance must be placed on human monitoring to establish safety in a work environment? A worker might well ask, "If biological specimens are needed, why not use real guinea pigs, or rats, or mice? Why me?" How many individuals would agree to being sampled regularly to serve as monitors of the ambient air quality in their residential communities? In viewing the overall record of laboratories performing blood lead analyses, one might well be tempted to suggest that guinea pigs might just as well be used.

Various techniques are now in use for the collection and analysis of lead in blood.[6] These include micro and macro procedures; finger sticking, venepuncture, ear lobe piercing; chemical assays, most notably with dithizone; atomic absorption spectrophotometry; polarography; and emission spectrography, all with various modern refinements and modifications.

Yet the general record for proficiency of laboratories performing blood lead analyses can only be described as dismal. In interlaboratory comparisons for reliability in analyses, undertaken by the American Industrial Hygiene Association in 1968 and 1969, results were disheartening.[7] For almost all the blood specimens submitted, ranges among reports from the laboratories were of the order of several hundred fold. The smallest; (i.e., the best) range reported was from 8 to 50 µg/100 ml for a specimen with an estimated true value of 20 µg/100 ml. Differences of the order of 20 to 300 percent were common. As stated in the AIHA report, only "approximately 50 percent of the laboratories in each of the two studies and 40 percent of those in both years, reported results of acceptable precision." Stated conversely, approximately half of the laboratories in each year and 60 percent for both years were reporting unsatisfactory results.

Those comparative studies are relatively old, about 7 years; and supposedly there has been considerable improvement in analyzing for blood lead since then. The significant point here, though, is that these studies provide a measure of the performance and accuracy of laboratories during the period when much of the background data used for setting concentration limits in criteria documents were being generated; in many cases by laboratories that participated in these AIHA studies. It would be highly unlikely if unreliable data were not included in literature,

enshrined in publications, and cited thereafter as authentic references for use in development of our august criteria documents.

How much improvement has there really been since 1968? The Center for Disease Control (CDC) of the U.S. Public Health Service runs a proficiency testing program to check the performance of laboratories throughout the country which routinely analyze children's blood for lead. Three to four proficiency specimens are submitted monthly. In a quote from a statement made by the CDC, dated September 19, 1974, (only a few months ago): "The number of laboratories," and there are more than 60, nationwide participating in this program, "reporting unacceptable results is over 50 percent of the total." [8]

Is this different from 1968 when almost identical findings were reported? The CDC goes on to state, "If such a large percentage of laboratories, some of which have been performing analyses for many months, are unable to consistently perform on a proficiency test, serious questions are raised about the quality of work done on samples submitted from the field." Serious questions must indeed be raised about the quality and validity of reported blood lead values, values that might well serve to judge the safety of the work environment.

Why there are such problems of reliability in blood lead analyses it is not difficult to understand. The techniques required essentially ultra-micro trace analyses (the lead is present in less than ppm quantities) and very few chemists and still fewer laboratories, are prepared for the scrupulous care, meticulous attention to detail, painstaking avoidance of contamination, and isolation that performance of such work demands.

Leaving questions of accuracy and precision, and assuming that the numbers reported are absolutely correct, how valid is a blood lead level *per se* as an index of the toxic potential of lead and how useful is it as a guide for monitoring excessive exposure to, and absorption of lead? In this country and elsewhere some general diagnostic interpretations have been assigned to certain whole blood concentrations. See Figure 1.

µg/100 ml Pbl	
50	Normal
40-80	Acceptable
80-120	Acceptable
120	Dangerous

Figure 1 Categories of Lead Absorption[9]

These are, of course, quite broad categories. The number 80 µg/100 g whole blood, or 84 g/100 ml, has become widely adopted as an arbitrary cut-off value. Even the criteria document for inorganic lead confers some official sanction to this number;[1] 80 ug/100 ml whole blood is recommended as an upper limit, delineating acceptable from unacceptable lead absorption. Concentrations below 80 ug/100 g are considered, according to the document, as "being indicative of an insignificant risk of lead poisoning."

Recommendations of the Swedish National Board are similar, Figure 2, though a somewhat lower value, 70 µg/100 ml, is recommended as the cut-off or removal-from-work point.

µg/100 ml Pbl	
20	normal for general population
20-38	acceptable - no problems
38-70	warning - watch for changes
70	danger - remove from lead work

Figure 2 Grading Lead Workers

Adapted from Swedish Nat'l. Board of Occupational Safety and Health[10]

Regardless of whether *70 or 80* µg/100 ml is used as the demarcation value, there are at least two reservations that cast doubt on the worth of such numbers:

1. There have been too many reports of symptoms of lead intoxication in workers showing blood lead levels below 80 µg/100 ml.[11-20] These are too numerous to be dismissed or easily explained by faulty analyses, differences in individual susceptibilities, or special circumstances (i.e. a temporary removal from sources of exposure). The inadequacy of blood lead as a monitor of occupational exposure was pointedly demonstrated in our study of a small population of lead workers in New Jersey.[19] With 2 exceptions, all of the 30 employees showed blood lead concentrations below 80 µg/100 ml, Figure 3. Yet, in this small population, more sensitive tests demonstrated clear and unequivocal biochemical effects of lead; and four cases of lead nephropathy were uncovered, even though only eight workers were adequately examined for renal disease. The fact that these abnormalities could co-exist with "acceptable" blood lead levels is sufficient to cast doubt on the value of the whole blood lead measurement as a reliable index of the hazards of exposure to and absorption of lead.

With two exceptions, all of the 30 employees showed blood lead concentrations below 80 µg/100 ml, as listed in Figure 3.

LEAD SCREENING TESTS ON 30 LEAD WORKERS

TEST		B_{Pb}	ALAD	FEP	U_{ALA}	U_{Pb}	24-Hr URINE EXCRETION		
							CONTROL		EDTA
							COPRO	Pb	Pb
UNITS		µg/100 ml	µg/100 ml RBC	µg%	mg/L	µg/L	µg/d	µg/d	µg/d
Subject:	Occ.								
H.Z.	LT	29	66	71	7	138	127	135	976
M.B.	LC	94	43	129	26	---	420	---	2922
J.H.	LC	70	95	147	7	---	350	---	2176
J.P.	LC	64	57	107	3	---	610	---	1794+
J.B.	LC	34	97	4	5	---	48	---	227+
R.V.	LC	47	120	11	4	---	673	---	673
J.Bo.	LB	38	88	73	4	73	---	91	1051
R.A.	LB	48	43	95	5	68	---	81	---
G.B.	LB	68	47	242	--	66	---	145	3375
R.R.	LB	45	44	124	7	82	---	84	1477
S.N.	LB	53	50	125	2	116	---	112	---
M.S.	LB	50	27	51	--	72	---	72	1881+
C.U.	LB	44	45	101	4	44	---	103	1153+
T.G.	LB	32	88	54	4	70	---	---	---
M.A.	LB	38	77	50	5	84	8	65	819
J.Ba.	LB	46	64	45	5	106	---	127	---
S.D.	LB	46	80	71	9	142	---	138	2053
G.H.	LB	54	65	134	4	96	---	102	1988
F.C.	LB	59	52	163	15	180	---	136	2810
C.K.	LB	40	65	59	5	123	---	149	2294
R.F.	LB	52	69	138	5	92	20	43	530
J.Zi.	LB	41	51	63	5	128	---	116	2401
A.B.	LB	40	--	---	5	57	---	58	1776
O.D.	LB	39	74	151	3	84	16	99	2068
J.T.	LB	48	116	63	6	128	---	129	1793
C.E.*	LB	51	82	64	5	80	7	53	1134
R.S.*	LB	66	78	26	6	86	24	99	1590
S.B.	FR	98	67	77	18	334	737	474	4018+
F.C.**	PB	35	88	3	2	70	13	112	990
J.Z.*	SC	48	42	29	70	65	757	305	5200

*Chronic lead nephropathy
**Renal disease and hypertension of uncertain etiology
+Underestimation of 24-hr Pb excretion. Creatinine excretion <1.2 gm/24 hrs.
LT = lead-tin solder worker
LC = lead cutter
LB = lead burner
PR = firing range sweeper
PB = painted steel burner
SC = solder cream worker

Figure 3, Lead screening tests on lead workers.

2. The dynamics of the interchange of lead among the various components of blood in the body pool, Figure 4, also argues against the primacy of the whole blood lead levels as a valid indicator of the body burden, particularly as a reflection of the lead content of the more vulnerable soft tissues. The most significant component may be the diffusible plasma lead concentration. This component, the metabolically active center of the body lead pool, is but a small percentage of the total plasma lead, which itself is only about 10 percent of blood lead in the body pool. The latter is estimated to be about 2 percent of the total body burden.[5] Thus, the diffusible plasma lead, though the smallest of the lead containing components of blood (and, thus, easily lost in the error factors of whole blood lead assays) may be the most significant for diagnostic purposes. Some support for this concept has been obtained, most notably by the work of McRoberts.[21] In a small number of cases of adult lead poisoning there

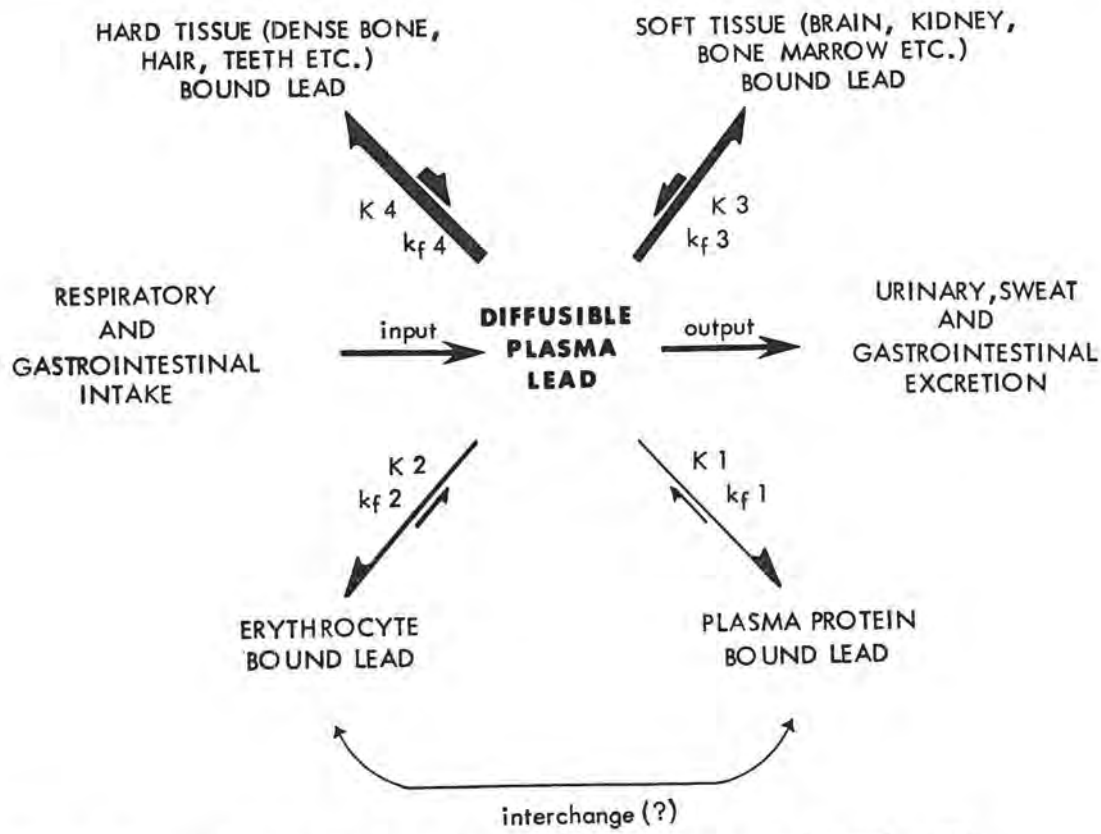

Figure 4 The dynamic interchange of the body lead pool. (5)

Adapted from: Baloh, Arch. Env. Health 27:198-208, 1974

was a shift in the partition of lead from erythrocytes to plasma, with an increase toward the plasma. A concentration of 10 g/100 ml plasma seemed to suggest itself as an upper limit for health monitoring. Determining the lead content in plasma, of course, would be considerably more difficult than for blood, and would almost certainly involve a much greater error; yet, it may prove a better index than whole blood lead.

Because of the dissatisfaction with blood lead levels as monitors of the toxic effects of lead absorption, particularly in response to the diagnostic needs of the massive childhood lead poisoning programs that have been mounted in this country, attention has been focused on measuring the metabolic effects of increased lead absorption as possible substitutes for blood lead analyses. Lead interferes with the synthesis of heme and causes alterations, both quantitatively and qualitatively, in some of the intermediates involved in this synthesis. Among such metabolites are ALA, ALAD, COPRO, and free erythrocyte protoporphyrins (FEP), Figure 5. The latter biological test - the so-called FEP test - has achieved prominence

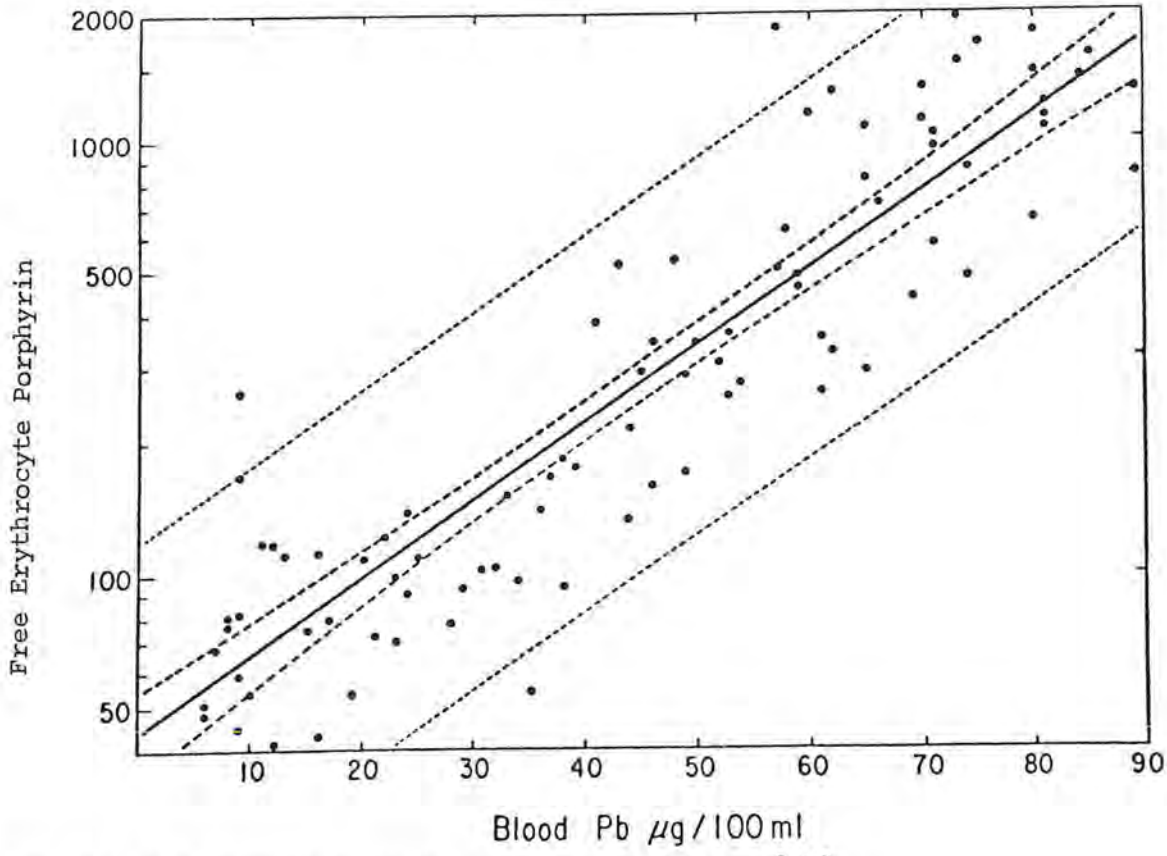

Figure 5 Relationship Between FEP and Blood Lead[22]

Adapted from Piomelli, S., et al, Pediatrics 51:254-257, 1973

with its acceptance by the Public Health Service as an alternative to blood lead testing in screening children for lead poisoning. Protoporphyrins accumulate when the insertion of iron into the protophyrin ring to form heme is blocked by lead. Their build-up in blood is roughly proportional to the blood lead level; but more important, their measurement can serve as a monitor of the toxic effects of lead absorption.

It has recently been discovered,[23] or perhaps rediscovered, that the protoporphyrin in FEP is not really free but is mostly bound with zinc to form zinc protoporphyrin (ZP). The measurement of ZP can be done simply, rapidly, without fear of contamination, directly on a drop of blood, and offers a better and more convenient test for the effects of lead toxicity than FEP. We have demonstrated this persuasively for children; and have also applied the test to adult populations of lead workers, Fig 6.

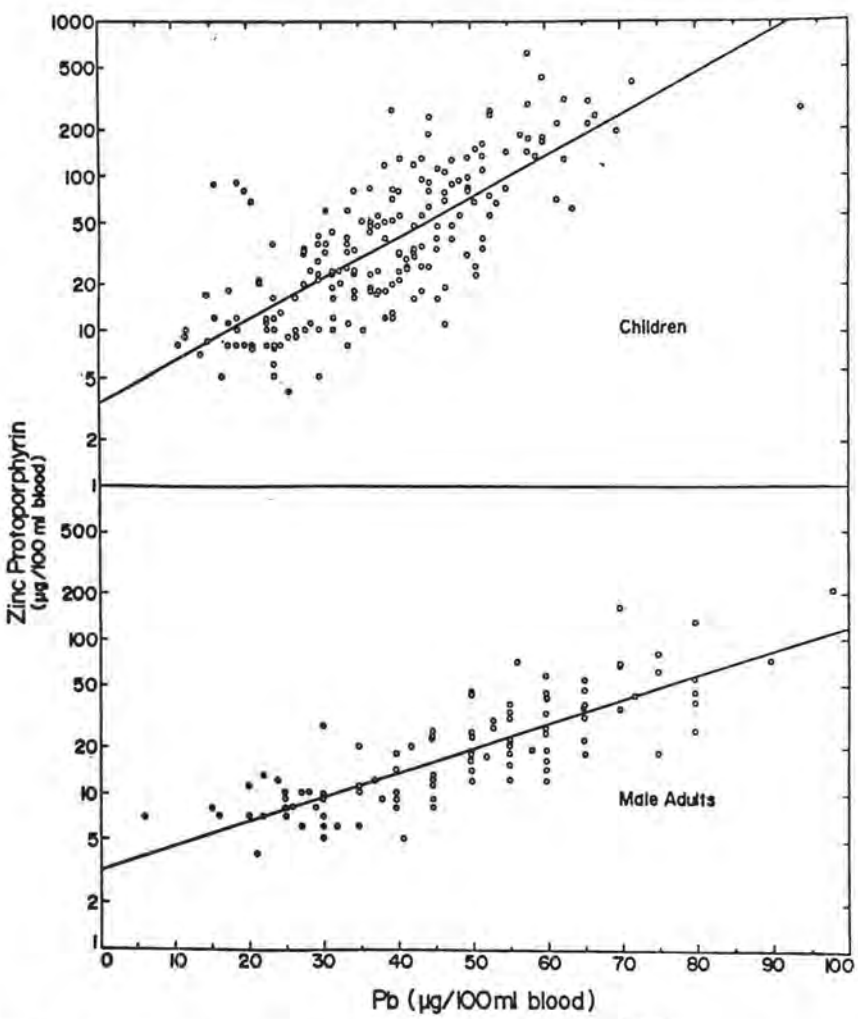

Figure 6 Relationship Between ZP and Blood Pb [23]
Adapted from Lamola, A., Joselow, M., Yamane, T.L., Clin. Chem. 21:92-97, 1973

There is the usual scatter here, characteristic for biological sampling. Children show a comparatively greater response than do adults for the same amount of lead, in keeping with the known greater sensitivity of children to lead intoxication. There is an interesting, intriguing relationship shown in Figure 6. A level of 40 ug/100 ml of blood is generally considered as the safe upper limit for children in the same sense that a level of 80 µg/100 ml has been considered as a safe upper limit for occupationally exposed adults. These lead values for both children and adults, respectively, correspond to the same ZP value of about 50 µg/100 ml.* In ZP we may have a biochemical response to lead that is more basic than any of the other indicators, and ZP may well become the method of choice, supplanting blood lead for monitoring the effects of lead absorption.

The plots in Figures 5 and 6, as well as others relating ALA or ALAD and blood lead concentration, are typical dose-response curves, with lead as the dose and the response of the organism, in terms of a biochemical change, as the ordinate. In making toxicological judgments, these particular curves are especially valuable, since they are based on human data and do not require the always uncertain extrapolation of results from animal experiments. We can apply to these data the safety factors that have become accepted as standard operating procedures in toxicology. In this case, we would apply a factor of ten to the "no-effect" dose to arrive at a judgment of a safe dose or concentration (i.e., the maximum dose of lead that elicits no response, divided by 10, as the maximum concentration that may be safely permitted in blood).

For a linear response, such as appears to be the case here, this presents something of a dilemma. Can any dose be set that will not have some measurable deleterious effect? This is a difficult question, about which there is not likely to be universal agreement among toxicologists, any more than there is agreement about the problems of setting safe limits for radiation or carcinogenic agents. However, for the moment, for blood lead concentrations, we can agree with the widespread acceptance that levels of 80 µg/100 ml whole blood should not be exceeded, since such a "dose" may be associated with overt symptoms of lead poisoning.

This, of course, is not quite the "no-effect" level we seek in toxicology. If one applies to this the safety factor of 10, the maximum allowable blood concentration of lead in the blood of adults should be 8 µg/100 ml, and about half that for children. These concentrations are, of course, beyond attainment now, and in the foreseeable future. All of us carry from birth, lead burdens considerably in excess of these levels.

When 80 µg/100 ml is offered as an acceptable concentration of whole blood lead, we are in effect ignoring the demands of toxicological protocol. We are also accepting (really asking workers to accept) some finite, though indeterminate, risk of some damage for the sake of practical expediency, or, in the euphemism of business, economic feasibility. This is, in truth, another version of the inexorable benefit/risk equation

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* Based on zinc protoporphyrin-apohemoglobin standard.

imposed by society, and raises issues of dimensions that supersede all other associated with the problems of blood lead levels.

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