INORGANIC LEAD: BIOLOGICAL INDICES OF ABSORPTION-- BIOLOGICAL THRESHOLD LIMIT VALUES

Dr. Hector P. Blejer
National Institute for Occupational Safety and Health

A B S T R A C T

Lead concentrations of 80 µg/100 ml in blood and 200 µg/1000 ml in urine traditionally have served as biological TLV's in determining "safe" levels of occupational exposure. Studies using more than one biological index have shown that metabolic and enzymatic changes and organ dysfunction and/or damage can occur from chronic lead exposures resulting in blood lead levels lower than 80 µg/100 ml. Other occupational, clinical data show that overt lead poisoning can occur among lead-exposed workers with blood lead concentrations $\leq$80 µg/100 ml. Preventive medical programs should include biological indices, in addition to blood and urinary lead determinations, and also incorporate the recognition that untoward effects, including lead poisoning can occur at lead levels below 200 µg/1000 ml of urine and 80 µg/100 ml of blood.

Introduction

The scope herein is restricted to the preventive occupational medical aspects of "Biological Threshold Limit Values for Inorganic Lead" or, as is preferable to call them, "Biological Indices of Inorganic Lead Absorption."

The definitive *primary* occupational control of lead absorption is that of maintaining the work air concentration of lead at a mimimum, that is, as low as possible below the hygienic work standard--be that a TLV, maximum allowable concentration (MAC), or time-weighted average (TWA). Thus, the preventive medical use of biological indices becomes secondary when adequate controls of lead exposures in the work atmosphere and environment are achieved. However, the situation regarding the effectiveness of such industrial hygiene engineering and other controls in the lead industries of this and other countries is generally not that good, for in many of those workplaces the TLV's, MAC's or TWA's for airborne lead are exceeded, often grossly. Until adequate controls are instituted, what can be done medically to protect the worker from such respiratory overexposures? Moreover, industrial hygiene measurements of airborne lead generally cannot quantify precisely the respiratory exposure of an individual worker, or other contributory occupational exposures such as the swallowing of airborne lead and the lead ingestion which results from poor work hygiene practices.[1] In such cases the medical use of biological indices becomes essential to protect exposed workers against undue occupational lead absorption and resultant toxic effects.

To discuss the proper preventive role of biological indices, it is necessary to review what biochemical changes or toxic effects they determine. It is also necessary to review briefly the validity of the, until recently, almost sacrosanct blood lead threshold of 80 µg/100 ml, the concentration below which supposedly nothing untoward to health happens.

Occupational use and function of biological indices

As used in an occupational medical program for lead-exposed workers, the functions of biological indices include:

1. To ensure proper medical placement of all workers;

2. To monitor where inadequate industrial hygiene engineering or other controls have allowed the occurrence of lead overexposure, over absorption and resultant toxic effects, and thus;

3. To help achieve implementation or improvement of industrial hygiene controls which will adequately prevent further over-exposure;

4. To prevent immediate (acute) or remote (chronic) toxic effects of lead overexposure;

5. To assess the degree of recovery of lead-affected workers and allow safe return to a healthful work environment.

Types of biological indices

Table I presents various biological indices. The first and third groups include tests which determine various biological effects of absorbed lead.[1,2] The second group lists indices which measure the concentration of absorbed lead in tissues and urine.

Biosynthesis of heme

A brief review of the biosynthesis of heme shows the basis for the specificity in determining the effects of absorbed lead of certain indices listed in the first group of Tables I and II.

TABLE I

INORGANIC LEAD: BIOLOGICAL INDICES OF EXPOSURE, BY TYPE

I. INTERFERENCE WITH HEME SYNTHESIS

Urinary Index

- *delta*-AMINOLEVULINIC ACID (ALA)
- COPROPORPHYRIN
- UROPORPHYRIN
- PORPHOBILINOGEN

Hematopoietic Index

- BLOOD ALA
- ERYTHROCYTE ALA-DEHYDRATASE ACTIVITY
- ETYTHROCYTE NON-HEME IRON
- ERYTHROCYTE PROTOPORPHYRIN
- ERYTHROCYTE ZINC PROTOPORPHYRIN
- BONE MARROW SIDEROBLASTS
- RETICULOCYTES (Immature Erythrocytes)
- PUNCTATE BASOPHILIA ("Stipple" Cells)
- ERYTHROCYTE LIFE SPAN (Increased Fragility)
- HEMOGLOBIN-HEMATOCRIT

II. LEAD ABSORPTION/DEPOSITION/EXCRETION

Index

- BLOOD LEAD
- URINARY LEAD
- HAIR LEAD
- NAIL LEAD
- BONE LEAD

III. OTHER TYPES OF INDICES

- BONE DENSITY (Radiographic)
- ELECTROMYOGRAPHY
- SERUM PROTEINS
- RENAL TUBULAR FUNCTION
- ENDOCRINE FUNCTION
- NEUROBEHAVIORAL FUNCTION

TABLE II

INORGANIC LEAD: BIOLOGICAL INDICES OF OCCUPATIONAL EXPOSURE BY TYPE AND SUGGESTED USEFULNESS

I. INTERFERENCE WITH HEME SYNTHESIS

Increased Concentration

- ERYTHROCYTE PROTOPORPHYRIN[a]
- ERYTHROCYTE ZINC PROTOPORPHYRIN[a]
- URINARY δ-AMINOLEVULINIC ACID (ALA)[b]
- URINARY COPROPORPHYRIN[c]

Decreased

- ERYTHROCYTE ALA-DEHYDRATASE ACTIVITY[a]
- HEMOGLOBIN[d]

Increased Count

- STIPPLE CELLS (Punctate Basophilia)[e]

II. LEAD ABSORPTION

Increased Concentration

- BLOOD LEAD[f]
- URINARY LEAD[f]

III. OTHER TYPES OF INDICES

- ELECTROMYOGRAPHY[g]
  - Motor Nerve Conduction Slowness--Extensor Muscle Weakness
- RENAL TUBULAR FUNCTION[g]
  - *Proximal Tubular Dysfunction*

[a] Specific for biochemical effect of absorption

[b] Semispecific for biochemical effect of absorption

[c] Semispecific, as above; valuable for screening

[d] Nonspecific; corroborates overabsorption

[e] Nonspecific; too variable and not useful

[f] Specific for degree of lead absorption

[g] Nonspecific; useful in early detection and diagnosis

NOTE: *See text for more precise information on footnote comments*

Fig 1 depicts a simplified schematic of the metabolism of heme.[3] Essentially, any amount of absorbed lead inhibits the activity of the enzyme δ-aminolevulinic acid dehydratase (ALAD) which is necessary to synthesize porphobilogen from two molecules of δ-aminolevulinic acid (ALA) (Stage 1, Fig 1).

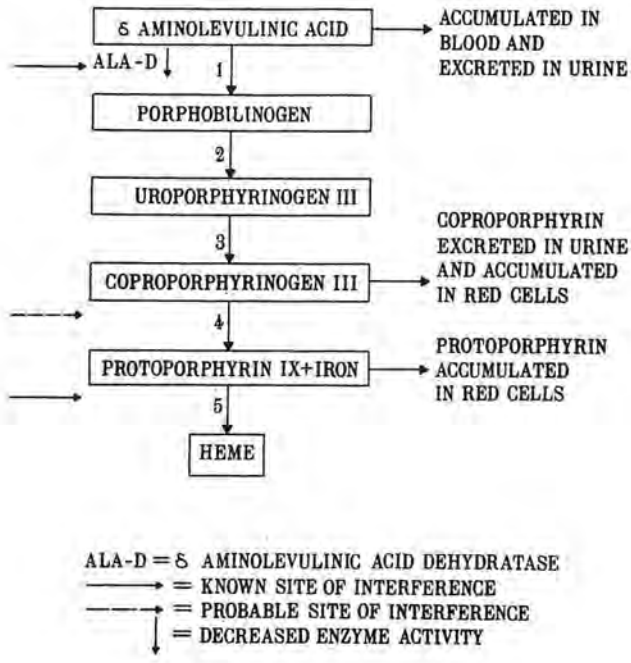

Figure 1 Biosynthesis of heme
From J.J. Chisholm, Lead Poisoning, Scientific American, 1971

As there appears to be a reserve of this enzyme, the ALAD activity needs to be sufficiently inhibited by enough absorbed lead (at blood lead levels $\geq$ 30 μg/100 g) for ALA to build up in the red blood cells (ALA-B) and be excreted in greater than normal amounts in the urine (ALA-U).[3-4] Thus, three tests of the biological response to the absorbed lead are obtained: ALA-D, ALA-B, and ALA-U.

The absorbed lead also interferes specifically with the conversion of protoporphyrin and non-heme iron into heme, so that free erythrocyte protoporphyrin (FEP), non-heme iron and also zinc protoporphyrin (ZP) accumulate in the red blood cells where each can be measured separately. Absorbed lead also acts in a poorly understood way elsewhere in the biochemical chain of heme synthesis (Stage 4) so that coproporphyrin (CP) accumulates in red blood cells and is excreted in the urine (CP-U) where it can be measured.[4]

The effects of absorbed lead on the biosynthesis or metabolism of heme are thus productive of all the changes listed under the first category in Tables I and II, including anemia, immature types of red blood cells, and bone marrow red blood cell precursors.

Occupational usefulness of selected biological indices

Indices of practical use for occupational medical monitoring are included in Table II. Urinary coproporphyrin (CP-U), blood lead (Pb-B) and urinary lead (Pb-U) determinations are the indices used most commonly by many industries to monitor lead-exposed workers. CP-U is subject to a high variance but, when done semiquantitatively, results are obtainable quickly and provide for rapid in-plant screening.[1] The value of Pb-B and Pb-U is somewhat limited, however, in that *per se* they measure only the amount of absorbed lead and do not determine its biochemical effects. Moreover, Pb-B and Pb-U results have a common disadvantage: they are subject to a frequent error of $\pm$ 10-15 percent, regardless of the analytical method used.[1] In addition, urine specimens from lead-exposed workers are often contaminated with extraneous lead.

The stipple cell count is a nonspecific test, which shows a very large variance within individuals, between individuals and between clinical laboratory observers. This test today has no occupational value by itself, even as an additional index.[5,6] Although not specific, hemoglobin or hematocrit determinations are particularly important as baseline and periodic measurements, especially when levels and effects of lead overabsorption are indicated by other indices and/or symptomatology.[5,6]

Currently, ALA-U is occupationally the most commonly used of the newer biochemical indices discussed under "Biosynthesis of Heme." At Pb-B levels greater than 40 µg/100 g or 100 ml, a good coorelation exists between ALA-U and Pb-B. As reported by Kehoe, this relationship gives the ALA-U index "an extremely useful place in the armamentarium of occupational health in the lead-using industries."[1] Moreover, its method of analysis is reliable and quick, and the results cannot be altered by contamination of the urine specimen with lead.

Other biochemical indices which indicate an interference of absorbed lead with enzymatic or other steps in the formation of heme are CP-U, already discussed, as well as ALA-D, FEP, and ZP. Presently, these last

three appear to be the most specific, reliable and sensitive indicators of related biochemical effects, especially those produced by levels of lead absorption considerably below widely accepted biological threshold limits. However, the sensitivity of ALA-D has been ascribed as too great to be of practical occupational value in differentiating between mild and severe exposure to and absorption of lead; and greatly limited in biological monitoring of workmen in the lead industries.[1]

Nonspecific and new indices of other effects of absorbed lead include measurements of certain electromyographic, behavioral and kidney function changes.[2] As discussed under "Blood Lead Threshold," these indices are uncovering subclinical and other evidence of dysfunction or damage among lead workers with Pb-B at levels below those generally considered occupationally acceptable.

Categories of biological indices

Various occupational and other categories of inorganic lead absorption have been developed in the last decade. Table III presents the tests and values listed in the "1968 British Statement" four categories: Normal, Acceptable, Excessive, and Dangerous,[5] with the cutoff between Acceptable and Excessive for Pb-B listed at 80 µg 100 ml.

TABLE III
INORGANIC LEAD:
1968 "BRITISH STATEMENT" BIOLOGICAL INDICES*

INDEX		LIMIT VALUES			
		NORMAL	ACCEPTABLE	EXCESSIVE	DANGEROUS
BLOOD LEAD	(µg/100 ml)	< 40	40 - 80	80 - 120	> 120
URINARY LEAD	(µg/100 ml)	< 8	8 - 15	15 - 25	> 25
URINARY CP	(µg/100 ml)	< 15	15 - 50	50 - 150	> 150
URINARY ALA	(µg/100 ml)	< 0.6	0.6 - 2	2 - 4	> 4

Adapted from R.E. Lane, et al, Brit Med J, 1968

In Sweden, a different approach had been taken since 1967.[7] As shown in Table IV, three occupational categories of increased lead absorption are included under Limit Values: Acceptable, Acceptable for work but with Precaution, and Unacceptable. Values for Pb-U and CP-U are not included, and the Unacceptable limit for Pb-B is any concentration greater than 70 µg 100 ml.

TABLE IV

INORGANIC LEAD:
1967 SWEDISH OCCUPATIONAL INDICES*

	LIMIT VALUES		
INDEX	ACCEPTABLE	ACCEPTABLE FOR WORK BUT WITH PRECAUTION	UNACCEPTABLE
BLOOD LEAD	< 50 µg/100 ml	50–70 µg/100 ml	>70 µg/100 ml
URINARY LEAD	< 1.5 mg/100 ml	1.5–2.5 mg/100 ml	> 2.5 mg/100 ml

**Adapted from Selander, S. and Cramer, K., Brit J Industr Med, 1970*

By contrast, Table V presents the single category of indices recommended by the 1968 Conference on Inorganic Lead[1-7] which met in Amsterdam a few days after the "British Statement" was published.[7] The single category is that of an Upper Permissible Value for occupational exposure, with a Pb-B of 70 µg/100 ml.

TABLE V

INORGANIC LEAD:
1968 AMSTERDAM OCCUPATIONAL INDICES*

INDEX	UPPER PERMISSIBLE LIMIT VALUE
BLOOD LEAD	70 µg/100 ml
URINARY LEAD	13 µg/100 ml
URINARY CP	30 µg/100 ml
URINARY ALA	1.0 mg/100 ml

**Adapted from Selander, S. and Cramer, K., Brit J Industr Med, 1970*

In 1971 the American Medical Association (AMA) developed the statement "Diagnosis of Inorganic Lead Poisoning."[6] As shown in Table VI, the categories of Normal, Acceptable, Excessive, and Dangerous recur. The AMA statement is virtually identical to the British and, except for Normal values, all the values listed under the last three categories are

lower. The AMA's cutoff between the Acceptable and Excessive values for Pb-B is 60 µg/100 ml.

TABLE VI

INORGANIC LEAD:
1971 AMA BIOLOGICAL INDICES*

INDEX	NORMAL	ACCEPTABLE	EXCESSIVE	DANGEROUS
BLOOD LEAD µg/100 ml	< 40	40 - 60	60 - 100	100
URINARY LEAD µg/100 ml	< 8	8 - 12	12 - 20	20
URINARY CP µg/100 ml	< 15	15 - 30	30 - 100	100
URINARY ALA mg/100 ml	< 0.6	0.6 -1.5	1.5 - 3.5	3.5

**Adapted from Diagnosis of Inorganic Lead Poisoning, AMA, Chicago, 1971*

TABLE VII

INORGANIC LEAD:
OCCUPATIONAL BIOLOGICAL INDICES#

INDEX	"NORMAL" VALUE	UPPER ACCEPTABLE LIMIT VALUE	DANGEROUS LEVEL
BLOOD LEAD µg/100 ml	< 30	60	> 100
URINARY LEAD µg/100 ml	< 8	12	> 20
URINARY CP µg/100 ml	< 15	30	> 100
URINARY ALA mg/100 ml	< 0.5	1.5	> 3.5

#Adapted from Diagnosis of Inorganic Lead Poisoning, AMA, Chicago, 1971 and Selander, S. and Cramer, K., Brit J Industr Med, 1970

Discussion

Different preventive occupational approaches--and at times arbitrary value judgements--are built in the various categories or risk included in Tables III through VII. Also, irrespective of which limit values are considered adequate to prevent toxic effects among lead-exposed workers, a growing body of occupational medical data is effectively challenging the scientific preciseness of all the upper acceptable values given, particularly the existence of a threshold for blood lead.

Categories of risk

Both the British and AMA Statements explicitly state that their four categories of lead absorption are arbitrary divisions.[5,6] This is most evident in the case of Excessive and Dangerous, for if a degree of lead absorption is considered excessive, then it must also be deemed dangerous. However, both statements address indirectly the concept of occupationally unacceptable lead absorption, for they define their Excessive categories partly as levels of absorption which, even in the absence of symptoms and signs, are *unacceptable* because of the possibility of toxic effects and long-term sequelae.[5,6]

In contradistinction, the Swedish categories of Acceptable, Acceptable for Work but with Precaution, and Unacceptable, address the occupational issue directly, and so does the single Amsterdam category of Upper Permissible Limit. Moreover, both of these approaches readily transmit descriptive information of pragmatic use in the biological monitoring of lead-exposed workers. Also, notable is that the Amsterdam values were not meant to indicate limits between safe and unsafe. They were recommended as guidelines, with the proviso that no undue reliance be placed on a single index.[7]

The approach shown in Table VII is essentially a hybrid which incorporates related guidelines developed in California in 1972,[8,9] the Amsterdam single-category guidelines and the AMA upper acceptable values It is an attempt by the author to overcome certain occupational shortcomings of and bridge major differences between the other four approaches.

As discussed below, however, newer data are questioning the preventive effectiveness of the limit values given in all the preceding categories of acceptable or permissible risk.

Blood lead threshold

Lately, the previously widely accepted concept of a blood lead threshold which prevented harmful effects and below which overt, clinical symptoms and signs did not occur is being challenged. As reviewed succintly and recently by Waldron,[10] there is mounting evidence which effectively questions the validity of this concept and the accuracy of presently accepted biological threshold levels--be they Pb-B of 80 µg/100 g associated most closely with Kehoe,[11] or lower limits of 70 and 60 µg 100 g.[6,7] Occupationally, these data are of two kinds. Among lead-exposed workers with Pb-B of *less* than 80 µg 100 ml subclinical effects such as neuropathy[12] neurobehavioral dysfunction[13] and nephropathy[14,15] have been demonstrated in the *absence* of any conventional clinical sign of lead intoxication. The second is the well-documented occurrence of overt, acute clinical symptoms such as lead colic in lead-exposed workers with Pb-B of less than 80 µg/100 g.[14,16] Additionally, a recent review of the California State official data

compiled from the "Doctor's First Reports of Work Innury" revealed that for the period 1968 to 1974, there were 52 cases of lead-exposed workers with Pb-B of less than 80 µg/100 ml. In 45 of these lead workers the reporting physician described acute symptomatology due to lead, diagnosed lead poisoning, prescribed specific treatment, such as chelating agents, and/or recommended removal from lead exposure.[17]

Further, as noted by Waldron, the 80 µg/100 g threshold limit for Pb-B was derived exclusively from the experience with *male* workers in lead industries.[10] As such, this occupational blood lead threshold may be inapplicable to female lead workers, especially those who can become pregnant. Waldron concluded that Pb-B in adults generally should not be permitted to rise above 50 µg/100 g, and he cautioned that even this lower limit may be higher than is consistent with health.[10]

Occupationally, the new data discussed above[12-17] strengthen Waldron's further caveat that "threshold values should not be regarded as fixed and unchangeable but must always be subject to revision in the light of new knowledge."[10]

Conclusions and summary

Although primary prevention can be achieved only by engineering controls, the medical use of biological, monitoring indices is still needed to protect workers occupationally exposed to inorganic lead. Essentially, these indices are of two types, those which measure the degree of absorbed lead and those which determine biochemical or other effects of that absorption. All have specific occupational shortcomings and, consequently, the use of one index from each of the two types is indicated (*e.g.*, Pb-B and ALA-U) in addition to special monitoring of hemoglobin.

Recent occupational data strongly indicate that the previously widely accepted blood lead "threshold" of 80 µg/100 g is too high to prevent untoward health effects among male lead workers. Moreover, other recent data appear to indicate either that a threshold level for blood lead does not exist, or that it should be set much lower, in the range of 50 to 60 µg/100 g for female and male adults, with corresponding values for other biological indices, including ALA-D and FEP. In any of these cases, a TLV or TWA of 150 µg/cu m for airborne lead does not provide an occupational exposure level at which no worker will suffer impaired health or impaired functional capacity.

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