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Original Research Article

Effects of Lead on Haem Biosynthesis and Haematological Parameters in Battery Manufacturing Workers of Western Maharashtra, India

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ABSTRACT

Lead inhibits enzymes of haem biosynthesis and alters haematological parameters of battery manufacturing workers (BMW). The main aim of this study is to know the present status of blood lead (PbB) levels and its effect on haem biosynthesis related parameters such as erythrocytes δ-aminolevulinic acid dehydratase (δ-ALAD), urinary δ-aminolevulinic acid (U-δALA) and porphobilinogen (PBG) and haematological parameters of BMW. *Material and Methods:* Forty BMW from Western Maharashtra, India, having age group between 19-42 years were selected as study group and compared with age matched 38 healthy male subjects (control group). From both group subjects, 10 ml blood sample was drawn by puncturing the anteriorcubital vein and the PbB, erythrocytes δ-ALAD, urinary δ-ALA and PBG and haematological parameters were measured by using standard methods. Statistical analysis: Between controls and BMW group was carried out by students 't' test. Blood lead levels of BMW showed significant elevation ($p<0.001$, 1050%) as compared to controls. Activated δ-ALAD ($p<0.001$, -58.88 %), non-activated δ-ALAD ($p<0.001$, -62.06 %) showed significant decrease and ratio of activated to non-activated δ-ALAD ($p<0.05$, 29.26 %) revealed significant increase in BMW as compared to controls. Urinary δ- ALA ($p<0.001$, 161%) and Urinary-PBG ($p<0.05$, 45.3%) concentrations showed significant increase in the study group as compared to the control group. In battery manufacturing workers, Hb ($p<0.001$, -16.67%) PCV ($p<0.001$,-20.31%) MCV ($p<0.05$, -4.27%) MCH ($p<0.05$, -5.66), MCHC ($p<0.001$, -7.16%) and RBC count ($p<0.001$, -10.39 %) revealed significant decrease, while a significant elevation was seen in the total WBC count ($p<0.001$, 20.47%) as compared to the controls. Blood lead levels continue to remain high in BMW, in spite of modern techniques used to reduce the lead exposure which inhibits haem biosynthesis and alters haematological parameters.

Keyword: Battery manufacturing workers (BMW); Blood lead; δ-Aminolevulinic acid dehydratase; Urinary δ-ALA and PBG, Haematological Parameters

INTRODUCTION

Lead is a ubiquitous and versatile metal that has been used by mankind for over 9000 years and is today one of the most widely distributed toxins in the environment. Lead enters in the environment from either natural or anthropogenic sources. Lead is a soft, silvery grey metal, melting at 327.5°C, highly resistant to corrosion, pliable, having high density, low elasticity, high thermal expansion, low melting point, easy workability, easily recycled, excellent antifriction metal, and inexpensive. Due to these properties, lead is used for various purposes. Lead is mainly used in acid batteries, colour pigments, jewellery industries, petrol additives (tetra ethyl and tetra methyl), and ship construction, seams of cans used to store food, soldering water distribution pipes, ceramic glazes, paper industries and printing press. Lead and its compounds can enter the environment at any point during mining, smelting, processing, use, recycling, or disposal [1, 2].

The routes of exposure for inorganic lead are inhalation and ingestion. Lead fumes and soluble respirable dust are almost completely absorbed by inhalation. Adults absorb approximately 15% of an ingested dose through the gastrointestinal (GI) tract in contrast to 50% GI absorption in children. Gastrointestinal absorption is generally inversely proportional to particle size and directly proportional to the solubility of the lead compounds. Dietary factors, nutritional status, and the chemical form of the metal and patterns of food intake affect absorption. Once absorbed, lead is found in all tissues, but eventually **>** 90% of the body burden accumulates (or is redistributed) into bone, where it remains with a half life of 27 to 30 years. Lead is excreted primarily through the urine (**>** 90%), lesser amounts are eliminated via the faeces, sweat, hair, and nails. [1-4].

Lead has been shown to cause adverse effects in several organs and organ systems, including the hematopoietic, nervous, renal, cardiovascular, reproductive, and immune and it is also mutagenic. The biological effects of lead depend upon the level and duration of exposure. Lead inhibits enzymes of heme biosynthesis [3, 4]. It affects erythrocyte formation by impairing globulin and heme synthesis and depresses serum levels of erythropoietin. Lead also decreases erythrocyte survival through its inhibition of membrane-bound Na+-K+-ATPase, resulting in decreased hemoglobin synthesis and anemia in children andadults.[1-3]

Early symptoms are often subtle, nonspecific, and/or subclinical, involving the nervous system (restlessness, fatigue, irritability, sleep disturbance, headache, difficulty in concentrating, decreased libido), GI system (abdominal cramps, anorexia, nausea, constipation, diarrhea), or musculoskeletal system (arthralgia, myalgia). Other less common conditions include tremors, toxic hepatitis, or acute gouty arthritis (saturnine gout). In general, the number and severity of symptoms worsen with increasing blood lead levels. A high blood lead level of intoxication may result in delirium, coma, and seizures associated with lead encephalopathy, a life threatening condition [1-4].

Occupational exposure to lead is entirely unregulated in many developing countries, and little monitoring is conducted in developed countries. In battery manufacturing industries the metallic lead is mainly used for the making grids, bearings, and solders. Manufacturing processes are usually manual and involves the release of lead particles and lead oxide that can cause severe poisoning and environmental pollution. Battery recycling is an important source of exposure to inorganic lead vapours, particles, and debris [1-4].

The high blood Lead affects almost all organs and systems and impairs the normal functions of the body, a fact which is well documented in literature, However, we must know the present scenario of blood lead level and its effects on

lead exposed population mainly BMW. Since its noted that now days battery industry owners are using modern techniques to reduce the lead exposure. Hence, the aim of this study is to estimate the blood lead level and to see its effects on haem biosynthesis and haematological parameters of occupational lead-exposed population mainly battery manufacturing workers of Western Maharashtra (India).

MATERIAL AND METHODS

The study group included non-lead exposed healthy male subjects and lead exposed battery-manufacturing workers of Kolhapur city in the Western Maharashtra state of India. The lead exposed groups consisted of 40 male battery-manufacturing workers (BMW) and the non-lead exposed control group consisted of 38 healthy male subjects. The control group subjects were mainly staff of Krishna Institute of Medical Sciences University, Karad. All the study group subjects were in the range of 19–42 years of age. All the study and control group subjects were non alcoholic and non smokers. Only healthy male subjects were included and those on medication for minor and major illnesses were excluded. Before blood collection, both study and control group subjects were informed about the study objectives and health hazards of lead exposure and its toxicity and written consent was obtained from subjects of both groups. Demographic, occupational and clinical data were collected by using questionnaire and interviews. Majority of battery manufacturing workers had major complaints of loss of appetite, intermittent abdominal pain, nausea, diarrhea, constipation and myalgia. The socioeconomic status of all subjects of both groups was average. Dietary intake and food habits of all subjects were normal. The experimental protocol was approved by the institutional protocol committee and also ethical clearance was obtained from institutional ethics committee. Utmost care was taken during the experimental procedure according to the Helsinki declaration of 1964 [5]. A blood sample of 10 ml was drawn by puncturing the anticubital vein and 5 ml blood was transferred in tube containing heparin and the rest 5 ml was taken in EDTA bulb for biochemical parameters assays included in the study. All the biochemical parameters were measured by standard methods. Blood lead level was estimated using lead Care II blood lead analyzer.The lead care II system uses an electrochemical technique called Anodic Stripping Voltammetry (ASV) to determine the amount of lead in a blood sample. Blood was mixed with lead care treatment reagent and the red blood cells (RBC) were lysed which release lead that was bound to the RBC wall. A negative potential was applied to the sensor to accumulate lead atoms on the test electrode. The potential is rapidly reversed releasing the lead ions. The current produced was directly proportional to the amount of lead in the sample [6]. Erythrocyte–δ-Aminolevulinic acid dehydratase (ALAD) was estimated by the method of Julian Chisolan et al [7]. Erythrocyte - δ-ALAD acts on δ-aminolevulinic acid (ALA) to form porphobilinogen, which is further reacted with modified Ehrlich's reagent to form pink colored compound measured on spectrophotometer at 555 nm. Hg-TCA solution stops the reaction by precipitating the proteins.

δ- ALAD activity was estimated by using the following formula:

δ-ALAD activity
(μmol ALA utilized/min/L of erythrocytes)=
Net absorbance×100×2×35/
(% Hematocrit×60×0.062)

Where,

2 = Conversion factor for ALA to PBG

35 = Dilution factor

60 = Incubation time (min)

0.062 = Micromolar absorptivity of modified Ehrlich's reagent and PBG chromogen.

Activated and non-activated ALAD ratio (Act/Non-act) was determined. δ - aminolevulinic acid (ALA) was estimated in urine samples by the method of Osamu W. et al. δ-ALA reacts with acetylacetone and form pyrrole substance, which reacts with p-dimethyl amino benzaldehyde. The colored complex was measured spectrophotometrically at 555nm. The results were measured in mg/L [8]. Estimation of porphobilinogen in urine was estimated by Mauzerall & Granick 1956. Porphobilinogen (PBG) from urine reacts with p-dimethyl aminobenzaldehyde (DMAB, Ehrlich's reagent) in acid solution to form a red compound, which was measured at 555 nm exactly after 5 minutes and the value were calculated according to Rimington formula [9,10].

Urinary PBG (mg/L) = Optical Density
× Numbers of times the urine diluted / 70.85

All the hematological parameters were measured by using fully automated Hematology analyzer Sysmax K-4500. Statistical comparison between controls and battery manufacturing workers groups was done by using Graph Pad Instant Demo-[DATASET-1, ISD] software. Statistical analysis between controls and BMW group was carried out by students 't' test. The mean difference was considered significant at $p< 0.05$.

RESULTS

Blood lead levels of battery manufacturing workers (BMW) showed significant elevation ($p<0.001$, 1050%) as compared to control subjects. The δ-ALAD enzyme is activated by Zn acetate and measured the activated, non-activated δ-ALAD and calculated the ratio of activated to non-activated δ-ALAD. Activated δ-ALAD ($p<0.001$, -58.88 %), non-activated δ-ALAD ($p<0.001$, -62.06 %) showed significant decrease and ratio of activated to non-activated δ-ALAD ($p<0.05$, 29.26 %) revealed significant increase in battery manufacturing workers as compared to control subjects. Urinary **δ-** Aminolevulinic Acid (U-δ-ALA) ($p<0.001$, 161%) and Urinary Porphobilinogen (U-PBG) ($p<0.05$, 45.3) concentrations showed significant increase in BMW as compared to the control group (Table 1 and Fig. 1). In battery manufacture workers, Hb ($p<0.001$, -16.67%) PCV ($p<0.001$,-20.31%) MCV ($p<0.05$, -4.27%) MCH ($p<0.05$, -5.66), MCHC ($p<0.001$, -7.16%) and RBC ($p<0.001$, -10.39 %) revealed significant decrease, while a significant elevation was seen in the total WBC count ($p<0.001$, 20.47%) as compared to the controls (Table 2 and Fig. 2).

Table 1. Blood Lead and Parameters Related to Heme Biosynthesis in Battery Manufacturing Workers & Control Group

Sr. No.	Biochemical parameters	Control Subjects (N= 38)	Battery Manufacturing Workers (N= 40)
1	PbB µg/dl	5.21 ± 3.27 (3.30-16.10)	59.93 ± 9.57*** (30.20- 65)
A	**Heme Biosynthesis**		
2	Ery δ-ALAD (µ mol δ-ALA utilised)/ (Min/L of erythrocytes)		
I	Activated δ-ALAD	30.1 ± 13.7 (10.57- 62.83)	12.38 ± 7.18*** (2.43-43.77)
II	Non-activated δ-ALAD	23.7 ± 10.4 (6.79 -45.11)	8.99 ± 6.12*** (1.37-31.89)
III	Activated / Non-activated Ratio of δ-ALAD	1.23 ± 0.268 (0.69-1.84)	1.59 ± 0.834* (1.02 -5.5)
3	U-δ-ALA mg/L	5.49 ± 1.38 (3.99-10.59)	14.33 ± 9.02*** (5.30-39.73)
4	U- PBG mg/L	14.9 ±13.5 (6.38-94.5)	21.65 ± 6.0** (8.9-34.02)

Figures indicate Mean ± SD values and those in parenthesis are range of values.
*** P< 0.001, ** P< 0.01, * P< 0.05 (Significant level as compared to controls)

PbB – Blood Lead, A- δ-ALAD- Activated δ- Aminolevulinic Acid Dehydratase, NA- δ-ALAD- Non activated δ-Aminolevulinic Acid Dehydratase, A- δ-ALAD / NA- δ-ALAD – Ratio of Activated δ-Aminolevulinic Acid Dehydratase to Non activated δ-Aminolevulinic Acid Dehydratase, U-δ-ALA- Urinary δ- aminolevulinic acid, U-PBG - Urinary Porphobilinogen

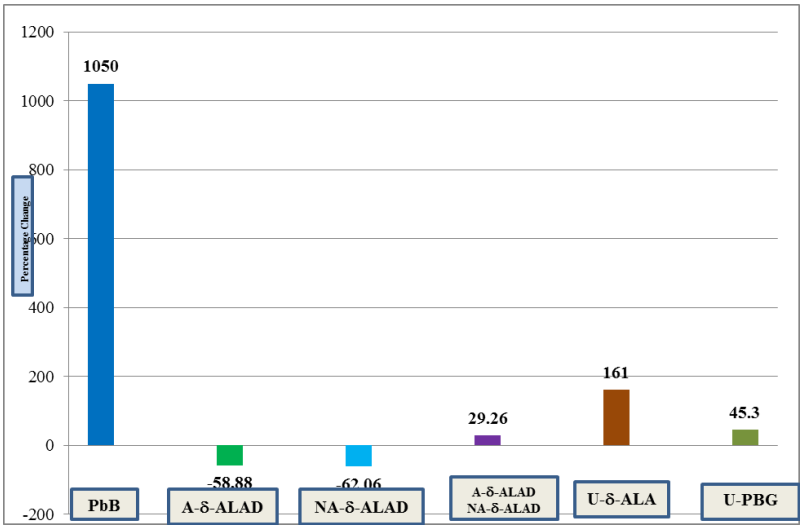

Fig. 1: Percentage Change of Blood Lead and Parameters Related to Heme Biosynthesis in Battery Manufacturing Workers with respect to Control Group

PbB – Blood Lead, A- δ-ALAD- Activated δ- Aminolevulinic Acid Dehydratase, NA- δ-ALAD- Non activated δ-Aminolevulinic Acid Dehydratase, A- δ-ALAD / NA- δ-ALAD – Ratio of Activated δ-Aminolevulinic Acid Dehydratase to Non activated δ-Aminolevulinic Acid Dehydratase, U-δ-ALA- Urinary δ- aminolevulinic acid, U-PBG - Urinary Porphobilinogen

Table-2: Hematological Parameters in Battery Manufacturing Workers & Control Group

Sr. No.	Hematological Parameters	Control Subjects (N =38)	Battery Manufacturing Workers (N =40)
1	Hb (gm/dl)	14.27 ± 1.59 (10.3- 16.0)	11.89 ± 1.43*** (8.6-15.4)
2	HCT (%)	45.58 ± 5.27 (30.2-56.6)	36.32 ± 3.97*** (28.3-46.0)
3	MCV (fL)	79.21 ± 7.37 (60-89.9)	75.82 ± 6.99* (53.9–84.9)
4	MCH (pg)	26.48 ± 3.52 (20.4-33.3)	24.98 ± 2.66* (17.5-29.33)
5	MCHC (gm/dl)	31.97 ± 2.35 (27.9-36.4)	29.68 ±2.86*** (24–33.2)
6	RBC count (million/µl)	5.29 ± 0.50 (4.48-6.3)	4.74 ± 0.63*** (3.5-6.8)
7	WBC count (/cumm)	6.35 ± 1.42 (3.6-9.9)	7.65 ± 1.68*** (4.8-12.8)

Figures indicate Mean ± SD values and those in parenthesis are range of values.
***. P< 0.001, ** P< 0.01, * P< 0.05 (Significant level as compared to controls).

Haemoglobin (Hb), Hematocrit (HCT), Mean Corpuscular Volume (MCV), Mean Corpuscular Hemoglobin (MCH), Mean Corpuscular Hemoglobin Concentration (MCHC), Red Blood Cells (RBC) count and White Blood Cells (WBC)

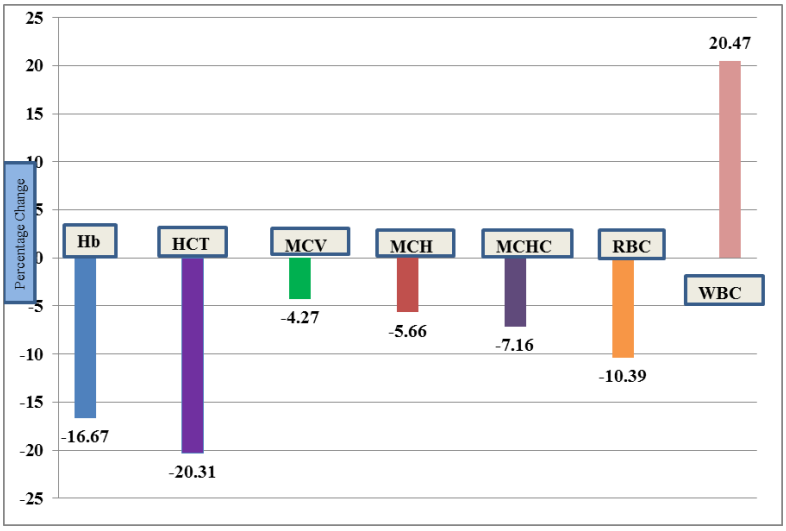

Fig.2: Percentage Change of Hematological Parameters of Battery Manufacturing Workers with Respect to Control Group

Haemoglobin (Hb), Hematocrit (HCT), Mean Corpuscular Volume (MCV), Mean Corpuscular Hemoglobin (MCH), Mean Corpuscular Hemoglobin Concentration (MCHC), Red Blood Cells (RBC) count and White Blood Cells (WBC)

DISCUSSION

Blood lead levels of battery manufacturing workers (BMW) revealed significant elevation as compared to control subjects (Table 1 and Fig. 1) which indicate greater absorption of lead in case of battery manufacturing workers. Battery manufacturing workers are mainly involved in opening and breaking of old lead battery, melting recovered lead, casting and moulding lead plates, trimming plates, applying lead oxides to the plates, and forming, acidification, and assembling of new battery. This process is usually manual and continuous release of lead into environment results into lead poisoning. Poor hygiene and inappropriate protection may be the common cause for increased blood lead levels in battery manufacturing workers [3, 4, 11].The level of blood lead depends on the equilibrium of storage and excretion. The excessive lead exposure can leads to their accumulation in the bones and soft tissues [1, 2, 12-14].

Erythrocytes δ-Aminolevulinic acid dehydratase (δ-ALAD) activity was measured from the study and control groups. The δ-ALAD enzyme is activated by Zn acetate and measured the activated, non-activated δ-ALAD and calculated the ratio of activated to non-activated δ-ALAD. Activated and non-activated δ-ALAD showed significant decrease, while ratio of activated to non-activated δ-ALAD revealed significant increase in battery manufacturing workers as compared to control subjects (Table 1 and Fig. 1) indicating the inhibition of erythrocytes δ-aminolevulinic acid dehydratase by lead in population exposed to high lead levels i.e battery manufacturing workers (BMW). The δ-ALAD (E.C.4.2.1.24) catalyses condensation of two molecules of δ-ALA to form the mono-pyrrole porphobilinogen. The δ-ALAD is a zinc-dependent metalloenzyme and zinc partly protects this enzyme against the adverse effect of lead in vitro [15] and possible also in vivo [16].

The level of δ-ALAD is decreases as early as the 4th day after the exposure begins. Once the δ-ALAD level is reduced, persistence of abnormality correlates with the amount of lead in body tissues (body burden), so that the δ-ALAD level remains reduced as long as significant quantities of lead remain. Therefore, after chronic lead exposure, low δ-ALAD values may persist for years even though exposure has ceased. The level of δ-ALAD is also very sensitive indicator of lead toxicity and is usually reduced to 50 % or less of normal activity when blood lead values are in the 30-50 μg/dl range, unfortunately, the δ-ALAD level reaches a plateau when marked reduction take place, so it cannot be used to quantify degree of lead exposure [1].

Decreased δ-ALAD activity caused by lead can be reversed by adding Zn or dithiothreitol (DTT) or by heating [17, 3, 4]. Possible mechanism of reactivation includes reduction of sulfhydryl groups, which are essential for enzyme activity, or, in the case of DTT, chelation of lead from binding sites on the enzyme. In human and experimental mammals a highly significant negative correlation between blood lead concentration and δ-ALAD activity in circulating erythrocytes is shown by several studies [18-24]. Exposure to lead does not decrease the concentration of δ-ALAD in erythrocytes, but substantially decreases δ-ALAD activity [25], as well as in other tissues [26]. Thus, in vitro reduction of δ-ALAD activity in peripheral erythrocytes may reflect inhibition of δ-ALAD activity in other tissues, making this enzyme a potential biological indicator of the effects of lead exposure.

Measurement of δ-ALAD activity in the erythrocytes offers a good and simple method of evaluation of lead poisoning. Lead in the blood is said to be rapidly incorporated into RBCs and probably affects δ-ALAD by directly inactivating to sulfhydryl groups necessary for its activity [27]. In lead poisoned rabbits the

activity of the enzyme δ-ALAD was impaired in the brain, liver, Kidney and bone marrow. This inhibition was also largely due to interference with the sulphydryl groups of the enzyme [28].

Non-activated δ-ALAD activity alone is considered as a predictor of blood lead concentration, as in the European standardized and other similar δ-ALAD assay methods [7]. Several studies have reported that the erythrocyte δ-ALAD activity is increased in individuals with anaemia and sickle cell disease [29, 30]. but not in subjects with β-thalassemia. Therefore, the use of the activated / non-activated δ-ALAD activity ratio appears to be good marker for lead toxicity. In this study, δ-ALAD was activated by using zinc acetate and the activated, non-activated values were measured. The ratio of activated / non-activated of δ-ALAD ($P<0.001$, 29. 26 %) revealed significant increase in BMW as compared to the controls. It confirms that the δ-ALAD activity was decreased or inhibited by the lead in the BMW as compared to the controls.

Urinary δ- Aminolevulinic Acid and Porphobilinogen concentrations have shown significant increase in BMW as compared to the control group (Table 1 and Fig. 1) indicating the inhibition of haem synthesis by lead. Lead inhibits the activity of three enzymes of haem biosynthesis i.e., δ-Aminolaevulinic acid dehydratase (δ-ALAD), coproporphyrinogen oxidase and ferrochelatase. Increase in the activity of δ-ALA synthase occurs as a consequence of feedback regulation by haem [31]. Since δ-ALA synthase is the rate–limiting enzyme in haem biosynthesis. As a result, there is increased production and excretion of the haem precursors i.e. δ-ALA, coproporphyrin and Zinc protoporphyrin.

The immediate effect of the inhibition of δ-ALAD will be an increased level of δ-ALA in the blood, which will then lead to its increased excretion in urine. The plasma levels of δ-ALA are elevated in the presence of higher lead levels [32-34, 3, 4]. In several studies, it has been reported that the urinary concentration of porphobilinogen showed an increase in case of lead poisoning [1-4]. Similar results are also reported in lead–poisoned rabbits [32]. Thus it appears that lead has discernable effects on the urine levels of δ-ALA at a blood lead level of around 35 μg/dl. Therefore, estimation of urinary δ-ALA and PBG are the good indicators of body lead burden.

The present study measured haematological parameters such as Hb, HCT or PCV, MCV, MCHC, RBC counts and WBC counts from the study and the control groups. In battery manufacture workers, Hb HCT, MCV, MCH, MCHC and RBC have shown significant decrease, while total WBC count has shown significant increase as compared to the controls (Table 2 and Fig. 2) indicating that the mild anaemia in BMW may be due to impairment caused by lead in the rate of incorporation of iron into mature and immature RBCs [35, 36]. or its effect on the haematopoietic system. However, it could also be due to decreased haem and globin synthesis or erythrocyte formation and function. In experimental lead-poisoned rats, it is observed that the globin synthesis is inhibited by lead in bone marrow cells at concentration as low as 1 μmol/L [37] and this may decrease the erythrocyte formation. Erythrocyte survival also decreases by lead due to inhibition of membrane bound Na+-K+-ATPase [38]. Erythrocyte formation is regulated by erythropoietin hormone and the serum level of this hormone is decreased by the lead [1,2]. Lead anaemia has many of the features of a typical sideroblastic anaemia, for example hypochromia, impaired maturation, and defective haemoglobonization of RBCs, raised serum iron, rapid plasma iron clearance with decreased cell uptake of ^{59}Fe and erythroblasts containing iron staining inclusion bodies [39]. Lead poisoning may be associated with a hypochromic, microcytic anaemia,

although more commonly, there is a normochromic, normocytic anaemia. Anaemia has been commonly associated with the adverse effects of occupational lead exposure. It is an effect that is easily diagnosed clinically and is recognised as a marker of lead toxicity. The pathogenesis of the anaemia is not properly understood. However, owing to the effect of lead in various enzymes catalysing glycolysis and certain steps in the synthesis of haem, retarded maturation or RBCs and haemoglobin deficiency must be important features [1, 2]. The lack of response of haemoglobin and other hematological indicators of anaemia at a blood lead level of 50 μg/dl and less is also in agreement with previous reports [40, 41, 3, 4]. Therefore, the determination of hematological parameters appears to be convenient for screening the high lead exposure persons such as battery manufacture workers. These parameters also have prognostic value in monitoring adverse effects of lead in occupational lead exposure during subsequent years of their employment.

Now days, the owners of battery manufacturing industry are taking all precautions such as providing special aprons, goggles, shoes, lead removal soaps and cool air blow on workers to reduce the lead exposure. In spite of all these precautions, lead exposure still is very high and it decreases the haem biosynthesis and alters the haematological parameters.

CONCLUSION

Regular monitoring of blood lead level, haem biosynthesis related and haematological parameters are useful to identify hazards of lead exposure, in order to reduce them by shifting of work place and considering chelation therapies to decrease the body burden of lead and its adverse effects of BMW and thus improving the health of workers exposed to high lead level.

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CONFLICT OF INTEREST STATEMENT

The authors declare that they have no conflict of interest.

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