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## **REVIEW ARTICLE**

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# The role of laboratory diagnostics in the assessment of occupational lead exposure

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#### ABSTRACT

**Introduction:** Industrialization and urbanization led to a significant increase in the environment. Lead inhibits the activity of numerous enzymes, triggers oxidative stress, and causes protein biosynthesis dysregulation. Inhalation of lead particles is the most common route of intoxication associated with occupational exposure. This study aims to evaluate laboratory methods and biomarkers in the assessment of lead exposure.

**Methods:** For non-experimental qualitative research, available scientific articles in English published in the relevant databases (MEDLINE and ScienceDirect) were used. The database search was performed using the keywords "Laboratory diagnostics", "occupational exposure", and "lead".

**Results:** Atomic absorption spectrometry (AAS) is the gold standard in laboratory monitoring of occupational lead exposure. Inductively coupled plasma with mass spectrometry is a commonly used method described as more sensitive than AAS due to its low detection limit. Lead concentrations can be determined in various samples, but blood and urine are the most commonly used in laboratory practice. The most important exposure biomarker is the enzyme  $\delta$ -aminolevulinic acid dehydratase (ALAD) in the blood, which is characterized by progressive inactivation by lead and a negative correlation with its concentration. The concentration of urinary delta-aminolevulinic acid ( $\delta$ -ALA-U) reflects the state of impaired enzyme function in heme biosynthesis. In addition, determining blood zinc protoporphyrin and urinary coproporphyrin levels significantly aids in assessing occupational lead exposure disorders.

**Conclusion:** The availability of the laboratory methods used and the biomarker specificity and sensitivity play an important role in the adequacy of lead exposure monitoring. Accurate determination of ALAD and  $\delta$ -ALA-U concentrations, along with other biomarkers, is critical for assessing individuals exposed to lead.

Keywords: Lead; occupational exposure; laboratory diagnostics; biomarkers

#### INTRODUCTION

Lead is an integral part of the earth's crust and a widespread heavy metal that is widely used in various areas of production due to its properties and ease of processing (1). As industrialization progresses and the use of lead for various purposes increases, its concentration in the environment rises, and the risk of poisoning increases due to its poor biodegradability. Today, lead is mainly used in the manufacture of car batteries and, to a lesser extent, as a pigment in paints, colored glass, weapons, jewelry, toys, traditional cosmetics, and Ayurvedic medicines (1-3).

Lead has no known biological function in the body. The International Agency for Research on Cancer classifies inorganic lead in the group of probable carcinogens (2A),

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while organic lead is classified in group 3 with no proven carcinogenic effect on human health (4). The mechanism of the toxic effect of lead is primarily based on the inhibition of the activity of certain enzymes, such as enzymes involved in the biosynthesis of hemoglobin, Vitamin D, and enzymes that help maintain the integrity of cell membranes, the induction of oxidative stress, and the dysregulation of DNA transcription, that is, protein biosynthesis itself (5). Exposure to lead can lead to symptoms such as gastrointestinal problems in the form of abdominal pain, nausea, pallor, anemia, headaches, irritability, sleep disturbances, metabolic syndrome, cardiovascular and kidney disease, and the appearance of a characteristic "lead" "line" on the gums (3,6,7).

According to a 2021 report by the World Health Organization (WHO), of the 2 million deaths reported as a result of chemical exposure, around half were caused by lead (2). The most common route of intoxication in the general population is ingestion of contaminated food and water, soil, and lead paint (2,3). For occupationally exposed

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individuals, inhalation of lead particles and dust generated during the processing of this metal is the most important route of intoxication. After inhalation, 35-40% of the lead is stored in the lungs, of which 95% is absorbed into the bloodstream. In the blood, the lead is stored in the erythrocytes or passes into mineralizing tissues such as bones and teeth, as well as into parenchymatous organs. The lead stored in the bones has a half-life of 27-30 years and is gradually released into the bloodstream, which contributes to a prolongation of exposure. Most of the lead is excreted in the urine, with a small amount excreted in hair, nails, feces, and sweat (3,8).

According to the WHO guidelines, a lead concentration of more than 5  $\mu$ g/dL in blood is considered a critical value and a sign that working conditions should be reviewed (2). The EU scientific committee on occupational exposure limits directive states that absorption spectrometry or another equivalent method should be used as the analytical method for biological monitoring of lead exposure. The blood lead level with a binding biological limit of 70 µg Pb/100 mL is determined as an indicator of exposure. However, workers with a blood lead concentration of more than 40 µg Pb/100 mL should be monitored. Certainly, other strategies for monitoring lead exposure can be developed and implemented. Other biomarkers such as urinary  $\delta$ -aminolevulinic acid,  $\delta$ -aminolevulinic acid dehydratase ( $\delta$ ALAD), and zinc propoporphyrin (ZPP) can be used for this purpose (9). The aim of this study is to evaluate laboratory methods and biomarkers for the assessment of lead exposure.

## METHODS

This article is a non-experimental qualitative research or scientific review of the literature available in the Medline and ScienceDirect databases. The search was conducted using the keywords "laboratory diagnostics," "occupational exposure", and "lead". From the articles available in the above databases, scientific papers published in English between 2013 and 2023 were selected. We focused on the scientific articles whose primary aim was to evaluate occupational lead exposure and/or health effects independent of the duration of exposure and to identify sample types, analytical methods, and applied biomarkers.

#### RESULTS

Thirty-one scientific articles were found in selected databases, and after evaluation, 17 publications were included in the further analysis (Table 1). According to the geographical listing, most of the included studies were conducted in Asia, with some in Africa and Eurasia. Specifically, four studies were conducted in India and individual studies in Libya, Bangladesh, Indonesia, Iran, Thailand, China, Turkey, and Tunisia. In five studies, the research area was not defined in the methodological approach. Three studies were published in 2019, 2/year in 2023, 2020, 2016, and 2014, and individual studies in the other years included in this review. In these studies, the majority of participants were male (94%). A total of 3160 samples from occupationally lead-exposed and unexposed participants were analyzed.

## DISCUSSION

Occupational exposure to lead is evidently an important research topic, but when looking at the geographical locations where the studies were conducted, it is noticeable that the interest of researchers in the Asian region is particularly high. According to the results presented, workers in painting, blast furnace maintenance, the batik industry, lead and zinc mines, lead battery manufacturing and maintenance, car repair shops, and tank and bridge maintenance are occupationally exposed to lead intoxication. The majority of respondents included in the study were men (94%), and only 6% were women. We assume that the reason for the apparent gender discrepancy lies in the characteristics of the above-mentioned jobs, which do not involve women as workers to any significant extent. In the context of occupational lead exposure, it is important to emphasize the role of various risk factors, namely: duration of lead exposure (37%), insufficient implementation of personal hygiene (31%), workplace and its characteristics (16%), and insufficient or incomplete use of appropriate protective equipment (16%).

In terms of laboratory diagnostics, the most frequently used sample in the present study was blood (60%), while urine (30%) was used to a lesser extent as the sample of choice. The authors emphasize that urine is a sample suitable for the assessment of acute lead exposure (24). In the studies by Nouioui et al. (24) and Christensen et al. (20), the importance of hair as an analytical sample was investigated. According to their results, hair can be considered a suitable sample for monitoring lead exposure, but the hair root must be used for this purpose. The lead concentrations in the hair root were lower and correlated with the lead concentration in the blood compared to the part of the sample above the scalp. The contamination of the upper part of the hair with lead particles from the external environment is said to be the cause of the differences in concentration (20).

The most common indicator of lead exposure was blood lead concentration (61%), but to a lesser extent, the levels of delta-aminolevulinic acid (δ-ALA) (22%), ALAD, urine lead level, hair lead level, coproporphyrin (11%), and Porphobilinogen (PBG) (6%) were quantified. Rahimpoor et al. (15) state that ZPP in blood and  $\delta$ -ALA and coproporphyrin in urine may be useful in the assessment of chronic lead exposure. Kshirsagar et al. (8) add u-PBG to  $\delta$ -ALA in urine as a good indicator of lead exposure in the body. Lead interferes with heme synthesis by inhibiting ALAD activity, which in turn leads to an increase in ALA concentration. In addition to ALAD, lead inhibits ferrochelatase and coproporphyrinogen oxidase, leading to an accumulation of heme pre-cursors such as ALA, coproporphyrin, and ZPP. The increase in U-ALA correlates positively with the increase in lead concentration (17). However, lead is negatively correlated with ALAD, i.e., increased lead concentrations reduce ALAD activity. It can therefore be concluded that ALAD can be used as a reliable indicator of lead toxicity (19).

The method most frequently used in the analysis of the samples mentioned was atomic absorption spectrometry (AAS) (43%), of which graphite furnace AAS was used in half of the investigations. The functional principle of the method is based on atomization, that is, the conversion of the analyte into free atoms. These absorb part of the light,

Authors and citation number		Country	Objective	Materials and methods	Results	Conclusion
1.	Upadhyay et al. (2021) (10)	India	To evaluate hematological and cardiovascular manifestations of chronic low lead exposure	In a cross-sectional study, 64 male workers were evaluated. BLL were assessed using GF-AAS technique. CBC was investigated using automated blood cell counter	Workers exposed to higher levels of lead had aberrant BLL, CBC and BP results in comparison to lower lead levels	Authors concluded that workers exposed to lead should be regularly monitored for early detection of cardiovascular and hematological aberrations
2.	Elhadi and Ahmed (2022) (11)	Libya	To evaluate BLL among painting workers and in control group. To evaluate its effect on hematological and cardiovascular parameters	In a retrospective cross sectional study 64 male workers were included. Blood samples were taken and used for quantification of BLL and hematological parameters (RBC, Hb, HCT, MCV, MCH, WBC)	Significantly higher BLLs in exposed workers when compared to unexposed group. Significant decrease in the RBCs, Hb, HCT, MCV, MCH and WBC was noted, as well as increase in blood pressure	Lead exposure brings about adverse hematological disturbances accompanied by cardiovascular diseases and should be evaluated
3.	Ahmad et al. (2014) (12)	Bangladesh	To measure BLL and assess its impact on health of lead acid battery workers	In a cross sectional study 118 workers were included. BLL were evaluated using stripped voltametry technique	Higher BLL were detected in workers involved in battery breaking and manufacturing, as well as workers with longer shifts. 28% of respondents were found to be anemic. Hypertension was found to be positively correlated with BLL	Prolonged and high level lead exposure in lead acid battery workers are in relation with hematological disturbances as anemia and many other illnesses
4.	Kshirsagar et al. (2015) (8)	India	To determine BLL and its effects on $\delta$ -ALAD, U- $\delta$ ALA, PBG and hematological parameters	Blood and urine samples were taken from 40 lead exposed and 38 unexposed respondents. BLL were determined using ASV, while spectrophotometry was used to evaluate δ-ALAD, U-δALA, PBG levels	Exposed subjects had higher BLL with significantly increased activated $\delta$ -ALAD/non-activated $\delta$ -ALAD ratio, as well as U- $\delta$ ALA and PBG. Their HCT, MCV, MCH, MCHC and RBC levels were decreased while WBC were significantly elevated	BLL, heme biosynthesis and hematological parameters should be regularly evaluated in order to identify numerous lead induced illnesses
5.	Dobrakowski et al. (2016) (13)	N/A	To investigate the impact of short-term occupational lead exposure on blood morphology and cytokines involved in hematopoiesis	GF-AAS was used to determine BLL in blood samples of 37 respondents. CBC were analyzed using Sysmex K-4500, while IL-7, IL-9, G-CSF, GM-CSF, HGF, SCF, PDGF and PECAM-1 levels were determinated using BioPlex 200 system	Mean BLLs were increased when compared to the levels noted before exposing respondents to lead. MCV, MCH, MCHC, PDW, P-LCR and MPV were decreased while WBC, LYM, MXD and PLT levels increased	Biomonitoring of occupationally lead exposed populations should include parameters in relation to anemia, WBC and PLT, besides lead exposure biomarkers.
6.	Oginawati et al. (2023) (14)	Indonesia	To assess dermal and inhalation lead exposure and to evaluate its effects on health of batik industry workers. To evaluate relation between lead exposure and Hb and U-δALA levels	Urine and blood samples were taken from 30 respondents. MCE filters were used in dermal exposure sampling. U- $\delta$ ALA was determined using spectrophotometry, while lead levels were determined using X-ray fluorescence	Levels of exposure positively correlate with U- $\delta$ ALA. Significant negative correlation was noted between Hb and U- $\delta$ ALA which supports their use as lead exposure biomarkers	Combined utilization of different lead exposure biomarkers is a valuable approach in evaluating lead exposure. In occupations with high air lead levels outdoor work should be implemented as a protective measure
7.	Rahimpoor et al. (2020) (15)	Iran	To assess occupational lead exposure and its impact on hematologic and kidney function parameters	In a matched case-control study, 100 male workers were included. Blood samples were used to determine BLL by AAS	In exposed group certain CBC parameters were lower when compared to unexposed group. Exposed subjects had increase in	Chronic lead exposure decreased HCT, MCV, MCH, RDW-CV and HGB. Authors suggested

## TABLE 1. Overview of research studies and outcome

(Contd...)

Aut	hors and	Country	Objective	Materials and methods	Results	Conclusion
				and B-ZPP by fluorometric detector. U-δALA and urine coproporphyrin were determined by HPLC method. CBC, blood urea and urine creatinin were also evaluated	U-ALA, U-coproporphyrin and B-ZPP. Significant relation between these markers and BLL was indicated	that the bio monitoring of occupationally exposed populations should be performed regularly by assessing blood and renal function parameters
8.	Wani et al. (2019) (16)	India	To examine blood lead and zinc levels and influence of zinc on DNA damage, blood cell morphology and oxidative stress	In total, 174 exposed participants were selected. Their blood samples were taken and used to determine BLL and zinc levels by AAS. Commet assays were performed to evaluate DNA damage, and microscopy to investigate blood morphology	Occupationally exposed workers had higher BLL and increased DNA damaged when compared to zinc exposed subjects. Echinocytes, acanthocytes, dacrocytes, shistocytes and hypochromic RBC were observed in lead exposed group	Lead absorption was significantly affected by zinc levels. This exerts its influence on DNA damage, blood cell aberration and oxidative stress induction due to lead toxicity.
9.	Patharkar et al. (2018) (17)	India	To evaluate U-δALA in garage workers as lead exposure biomarker	In a cross sectional study 72 subjects were included. Urine samples were collected and evaluated for U-δALA colorimetrically	In 73.61% subjects U-δALA levels were increa sed which is a clear indicator of chronic lead exposure. Duration of employment is positively correlated with U-δALA	High prevalence of lead exposure implicates the need to educate occupationally exposed populations as well as the need to take precautions
10.	Sudjaroen and Suwannahong (2017) (18)	Thailand	To investigate relation between hematological and biochemical markers of lead exposure and to determine the role of occupational lead exposure	Blood samples (n=63) were collected and analyzed for lead and $\delta$ -ALAD levels, CBC and reticulocyte count. AAS was used for BLL quantification, while spectroscopy was used for $\delta$ -ALAD	Significant increase in BLL and decrease in δ-ALAD was noted in battery workers. These exposure biomarkers showed inverse correlation. MCH was significantly lower in exposed groups	BLL and ALAD were useful markers in lead exposure evaluation and are in relation with hematological parameters, duration of exposure and hypertension. Authors suggest that CBC could be used as a screening test in subclinical lead exposure but also to improve sensitivity of BLL and ALAD
11.	Chiu et al. (2013) (19)	N/A	To investigate activity of δ-ALAD in relation to blood lead and other factors	ALAD levels were determined in blood samples using spectrophotometric determination. ALAD genotyping was performed using PCR-RFLP	Lead exposed workers had significantly decreased ALAD activity	ALAD activity showed potential to be used in lead exposure monitoring as a reliable lead toxicity biomarker
12.	Christensen et al. (2023) (20)	N/A	To differentiate between endogenous and exogenous lead along hair strands, to investigate the relationship between HLLs and BLLs and accuracy of lead exposure assessment using hair	Hair and blood samples were collected from 44 occupationally exposed subjects. HLL were determined using ICP-MS	Lead in hair samples below the scalp significantly predicted BLL and thus can be used and non-invasive method for lead exposure evaluation	Below-scalp hair lead levels effectively predicted BLL excess. Authors consider hair as a non-invasive alternative to blood sampling
13.	De Barbanson (2020) (21)	N/A	To investigate effectiveness of urinary lead as a recent exposure indicator	Urinary lead levels in 105 samples during 3 years were determined using ICP-MS	Mean urinary lead levels post-shift were 1,6-5 times higher when compared to pre-shift values	Urinary lead levels can be used as an exposure biomarker. Authors recommended to include this test in monitoring occupationally exposed populations.

# TABLE 1. (Continued)

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Authors and citation number		Country	Objective	Materials and methods	Results	Conclusion
						They also emphasized the need to review work conditions
14.	Wu et al. (2016) (22)	China	To analyze the dose-response relationship between occupational, cumulative lead exposure, lead poisoning and biomakers	A retrospective cohort study was conducted among occupationally exposed workers (n=1832). Urinary coproporphyrin and ZPP levels were evaluated. Lead levels in blood and urine were determined using AAS technique	Cumulative lead dust or lead fumes exposure was found to be positively correlated with workplace seniority, ZPP, blood and urinary lead	Cumulative lead exposure dose and the incidence of lead poisoning showed a significant dose-response relationship. Authors suggested that the occupational lead exposure limits need re-examination and adjustment, while occupational cumulative exposure limits should be established to better prevent occupational lead poisoning
15.	Turksoy et al. (2019) (23)	Turkey	To develop a model for early inflammation and atheroschlerosis detection in occupationally exposed workers	In total, 49 occupationally exposed subjects were paired with 50 control subjects. Blood samples were taken and IL-6, IL-10, TNF- $\alpha$ , h-FABP, VCAM-1 and lead were evaluated. BLL were determined using ICP-MS	BLLs and IL-6, IL-10 and TNF-α were positively correlated, while negative correlation was noted between BLL and WBC and Hb levels	Strong correlation between BLL and inflammatory markers confirmed pro-inflammatory potential of lead. Authors stated that oxidative stress parameters should be determined as well, in order to better understand effects of lead toxicity
16.	Nouioui et al. (2019) (24)	Tunisia	To biomonitor occupational lead exposure by measuring it in urine, blood and hair in battery worker	In total, 52 battery workers were included. Their BLL and ULL were determined using GF-AAS, HLL using ICP-MS and U-δALA using cation-exchange column	BLL and ULL significantly correlated with U-δALA. BLL and HLL significantly correlated as well which suggests usefulness of hair as analitycal sample	In medium-to-high lead levels hair could be useful sample for lead exposure monitoring. Authors emphasized the need to review working conditions, use of engineering controls, good work practices, respiratory protection and pesonal hygiene
17.	Trzcinka-Ochocka et al. (2014) (25)	N/A	To present ICP-MS and GF-AAS as methods for lead and cadmium determination	In total, 40 blood samples were collected from occupationally exposed workers. Levels of lead and cadmium were determined using ICP-MS and GF-AAS	Validation parameters were better for ICP-MS when compared to GF-AAS	Authors concluded that ICP-MS should be widely implemented and used in clinical laboratories due to it being faster and having lower detection limit in comparison with GE-AAS

Legend: GF-AAS: Grafite furnace-atomic absorption spectrometry, CBC: Complete blood count, BP: Blood pressure, RBC: Red blood cells, Hb: Hemoglobin, HCT: Hematocrit, MCV: Mean corpuscular volume, MCH: Mean corpuscular hemoglobin, MCHC: Mean corpuscular hemoglobin concentration, WBC: White blood cells, Lym: lymphocytes, MXD%: Mixed cell count, PLT: Platelets, PDW: Platelet distribution width, P-LCR: Platelet-large cell ratio, ASV: Anodic stripping voltametry, IL-6: Interleukin 6, IL-7: Interleukin 7, IL-9: Interleukin 9, IL-10: Interleukin 10; G-CSF: Granulocyte colony-stimulating factor, GM-CSF: Granulocyte macrophage colony-stimulating factor, HGF: Hepatocyte growth factor, SCF: Stem cell factor, PDGF: Platelet-derived growth factor, PECAM-1: Platelet endothelial cell adhesion molecule-1, HPLC: High-performance liquid chromatography, PCR-RFLP: Polymerase chain reaction-restriction fragment length polymorphism, ICP-MS: Inductively coupled plasma mass spectrometry, HLL: Hair lead level, ULL: Urine lead level, TNF-α: Tumor necrosis factor-α, h-FABP: Heart-type fatty acid binding protein, VCAM-1: Vascular cell adhesion molecule 1

and the amount or intensity of light read on the detector is a measure of the lead concentration in the sample (26). AAS is the gold standard for quantifying lead concentration in human samples, but inductively coupled plasma mass spectrometry (ICP-MS) is cited as its increasingly used equivalent. ICP-MS was used for analysis in a total of 29% of the studies presented. This method is more sensitive and has a detection limit 6 times lower than AAS, indicating that it is suitable for the detection of low lead concentrations in samples. In addition, ICP-MS allows multiple analytes to be analyzed simultaneously, which is particularly important for assessing exposure to other heavy metals, and has less spectral interference and a wider dynamic range (25). In the work presented, AAS was only used for the analysis of blood samples, while ICP-MS was used for the analysis of blood, urine, and hair samples, which can be considered an additional advantage.

## CONCLUSION

The availability of the laboratory methods used and the biomarker specificity and sensitivity play an important role in the adequacy of lead exposure monitoring. Accurate determination of ALAD and urinary delta-aminolevulinic acid concentrations, along with other biomarkers, is critical for assessing individuals exposed to lead. It is clear that there is a need to increase the number of original scientific studies on the consequences of occupational lead exposure and the evaluation of the methods and samples used. This would allow a deeper understanding of the contribution and importance of laboratory diagnostics in this issue.

### **DECLARATION OF INTERESTS**

Authors declare no conflict of interests.

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