Research Article

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Relationships among tryptophan, kynurenine, and neopterin levels and exposure to heavy metals and trace elements in e-waste recycling workers

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Abstract: The study aimed to evaluate the effects of occupational exposure on the cellular immune response by measuring neopterin release and the kynurenine pathway and to assess trace element status and heavy metal exposure. The study group consisted of 30 male e-waste recycling workers who underwent detailed occupational anamnesis and a comprehensive physical examination. Concentrations of essential trace elements (Cr, Co, Cu, Mn, Mo, Ni, Se, and Zn) and heavy metals (Sb, Cd, and Pb) were measured in whole blood or serum samples using inductively coupled plasma mass spectrometry (ICP-MS). Serum tryptophan (Trp) and kynurenine (Kyn) levels were determined by high-performance liquid chromatography (HPLC), and serum neopterin concentrations were quantified using a commercial enzyme-linked immunosorbent assay (ELISA) kit. Serum neopterin, Trp, and Kyn concentrations were 7.8 ± 0.7 nmol/L, 54 ± 2 μmol/L, and 0.5 ± 0.04 μmol/L, respectively. The estimated indoleamine 2,3-dioxygenase (IDO) activity, expressed as the Kyn/Trp ratio, was 8.8 ± 0.8 μmol/mmol. Elevated levels of individual metals, except for Pb, did not significantly alter neopterin release or kynurenine pathway activity (all, $p > 0.05$). Blood Pb levels showed positive correlations with both Sb and neopterin concentrations, whereas they were negatively correlated with Cu levels (all, $p < 0.05$). These results indicate that e-waste recycling workers are exposed to multiple heavy metals, suggesting potential inhalation exposure, and that such exposure may influence trace element status, neopterin release, and the kynurenine pathway without inducing pronounced changes. Further studies with larger populations are warranted to confirm these findings and to better characterize the health impact of multiple metal exposure. Occupational safety measures should be strengthened to minimize such exposures.

Keywords: antimony; copper; e-waste; kynurenine pathway; lead; neopterin

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1 Introduction

Tryptophan (Trp) is an essential amino acid with crucial functions in the body and must be obtained from dietary sources. In addition to its role in protein synthesis, Trp is a precursor in two critical metabolic pathways, kynurenine (Kyn) and serotonin [1]. The Kyn pathway is initiated by two pivotal enzymes, namely tryptophan-2,3-dioxygenase (TDO) and indoleamine 2,3-dioxygenase (IDO). TDO is mainly located in the liver and is induced by Trp itself or hormones like corticosteroids [2]. IDO is stimulated primarily by interferon-gamma (IFN-γ) and other cytokines and inflammatory molecules. It is present in macrophages/monocytes and several organs, such as the colon, stomach, lungs, and brain [3]. Increased levels of IDO, the rate-limiting enzyme in the Kyn pathway, result in a reduction in Trp levels and an enhancement in Kyn synthesis. Kyn is the main by-product of Trp degradation, and the increase in IDO activity is

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reflected by an elevated ratio of Kyn to Trp [1, 4]. Trp degradation and neopterin production generally correlate strongly and positively with altered cellular immunity. With the induction of IFN-γ, monocyte macrophages release significant amounts of neopterin, a nonspecific and early biomarker reflecting T helper (Th1) type immune activation [4, 5]. Many environmental pollution factors or occupational exposures, such as heavy metals, affect various systems, including the immune system, and can potentially disturb homeostasis in human organisms. Heavy metals such as lead (Pb), cadmium (Cd), and antimony (Sb) are used in various industries, including battery manufacturing and mining [6, 7]. Although Pb is a ubiquitous element found in many inorganic and organic forms in the natural environment, its exposure has become a serious concern in electronic waste (e-waste) recycling [6, 8]. Pb in an occupational environment may result in inhalational and dermal exposure of workers, and it may affect the immune system [9–11]. In laboratory animals, Pb has been shown to target macrophages and T cells, especially CD^{4+} type Th cells. With occupational exposure, Pb-associated immune changes include altered T-cell subpopulations, decreased immunoglobulin (Ig) levels, and decreased polymorphonuclear leukocyte chemotactic activity [10]. Cd is another heavy metal widely used in electronics such as switches, joints, rechargeable batteries, cables, and some coatings. Occupational Cd exposure is highly possible in e-waste recycling areas [12–14]. Cd affects the immune system in two distinct ways: it may either induce autoimmunity [15] or suppress lymphocytes and natural killer (NK) cells [16]. Sb is used mainly as a flame retardant in electronic plastic fragments. It may also be used in typical batteries to increase the resistance of Pb [17, 18]. The effect of Sb exposure on the immune system seems to change with dose and duration. Low levels but chronic exposure to Sb causes immune activation; however, on higher doses, immunodeficiency develops [19]. In electronic recycling, Pb, Cd, and Sb are widely used in electronic devices, and occupational exposure may occur through fumes, dust, soil, and water. Especially inappropriate recycling processes can release significant amounts of heavy metals along with other toxic substances, and combined exposure is highly possible. This study, therefore, aimed to investigate whether inhalation exposure to heavy metals in recycling areas disrupts trace element homeostasis and alters neopterin levels and kynurenine pathway activity.

2 Materials and methods

2.1 Study group

The study recruited male workers within the e-waste recycling industry during periodic health surveillance at workplaces, who were referred to the hospital by occupational physicians for further examination. All workers were invited to the study between April and June 2021. Detailed occupational anamnesis was obtained for each participant, a standard systemic physical examination was performed, and 30 volunteered workers were included in the study. Demographic data of the participants are presented in Table 1. Blood samples were collected early in the morning before the work shift started. Twenty of the participants were smokers, and smoking was prohibited for at least 8 h before the sampling time.

2.2 Measurements

Routine biochemistry measurements of all participants were examined in the hospital biochemistry laboratory. Pb, Cd, Sb, manganese (Mn), and chromium (Cr) in whole blood samples and zinc (Zn), copper (Cu), selenium (Se), molybdenum (Mo), nickel (Ni), and cobalt (Co) in serum samples were quantified using the inductively coupled plasma-mass-spectrometry (ICP-MS) technique, employing an Agilent 7,700× device. Samples were treated with high-purity acid and microwave degradation before analysis. High-purity argon and helium gases were used to avoid interferences. The part of collected blood samples was centrifuged at 3,000 rpm, and aliquots of serum were stored at −20 °C for the analysis to detect serum neopterin, Kyn, and Trp concentrations. Serum Trp and Kyn levels were simultaneously determined using the verified high-performance liquid chromatography (HPLC, Agilent 1,200 Series, Austria) method described before [20]. Serum neopterin levels were quantified using a commercially available ELISA kit (IBL, Germany), following the manufacturer's instructions.

Table 1: The demographics of the study participants.

Workers (male, *n* = 30)	Mean ± SD	Minimum	Maximum
Age (years)	33 ± 8	21	51
Body mass index (kg/m^2)	24 ± 4	17	32
Working duration (months)	29 ± 34	5	156

3 Statistics

Demographic information and data obtained from the measurements were evaluated using the IBM SPSS 23 statistical software. Variables were presented as mean and standard deviation (SD)/error (SEM). All measured values, including those outside the laboratory reference ranges, were included in the statistical analyses. No data points were excluded or treated as outliers. As the data for most variables deviated from a normal distribution, nonparametric tests were employed. Relationships between the measured parameters (trace elements, heavy metals, and immune biomarkers) were analyzed using Spearman's rank correlation coefficient. Homogeneity was evaluated with *Levene*'s test. The alpha value was chosen as 0.05.

Informed consent: Informed consent has been obtained from all individuals included in this study.

Ethical approval: The research related to human use has been complied with all the relevant national regulations, institutional policies and in accordance the tenets of the Helsinki Declaration, and has been approved by the authors' Institutional Review Board or equivalent committee. The University Clinical Research Ethics Committee approved the study protocol with decision #2021/17–27.

4 Results

4.1 Demographic characteristics and signs

As shown in Figure 1, the most frequently reported symptoms (with a prevalence ≥10 %) were body pain, sleep disturbance, fatigue, dermatitis, gastric problems, hearing loss, numbness, dyspnea, anemia, weight loss, cardiac problems, skeletal problems, and impotence. However, no significant association was found between elevated metal or trace element levels and individual symptoms in workers when assessed using the Mann–Whitney U test (all, $p > 0.05$). The effect of the working duration in the same sector was not correlated with any of the measured parameters (all, $p > 0.05$). There was no effect of smoking status on any of the measured metal, trace element, or immune biomarker levels ($p > 0.05$).

4.2 Concentrations of trace elements and heavy metals

As shown in Table 2, there were nine cases exceeding upper laboratory limits in five of the measured metals/elements (Sb, Pb, Cd/Mn, and Zn), while there were six cases below the lower limits in three of the detected metals/elements (Zn, Cu, and Se). The mean whole-blood Pb concentration was markedly elevated compared to typical population reference values, while the levels of other metals and trace elements showed more variable distributions relative to their reference/laboratory ranges.

4.3 Levels of neopterin, tryptophan, kynurenine, and IDO activity

Serum neopterin, Trp, and Kyn concentrations and the estimated IDO activity (Kyn/Trp ratio) are presented in Table 3.

4.4 Correlations of the measured parameters

Spearman's correlation analysis was performed to test all possible pairwise relationships between the measured heavy metals, trace elements, and immune biomarkers (neopterin, Trp, Kyn, Kyn/Trp). Also, a visual summary of these correlations is provided in the heatmap (Figure 2), and the statistically significant correlations ($p < 0.05$) are separately reported in Table 4. Notably, blood Pb levels showed a significant positive correlation with Sb concentrations ($R = 0.518$, $p = 0.004$) and with serum neopterin levels ($R = 0.410$, $p = 0.027$). Furthermore, a significant negative correlation was observed between Pb and Cu levels ($R = -0.377$, $p = 0.048$).

5 Discussion

5.1 Heavy metal exposure and health effects

E-waste recycling involves the recovery of valuable metals and other reusable materials from discarded electronic components. However, this process also releases various hazardous substances, including heavy metals and persistent organic pollutants, posing occupational and environmental health risks. Workers may be exposed to these toxicants through inhalation, ingestion, or dermal contact, and the diversity of e-waste materials makes exposure profiles complex and variable between sites and workers [21–23]. Most previous studies on metal exposure among e-waste workers have been conducted in Asian and African regions (e.g., China, Ghana, Taiwan), documenting elevated

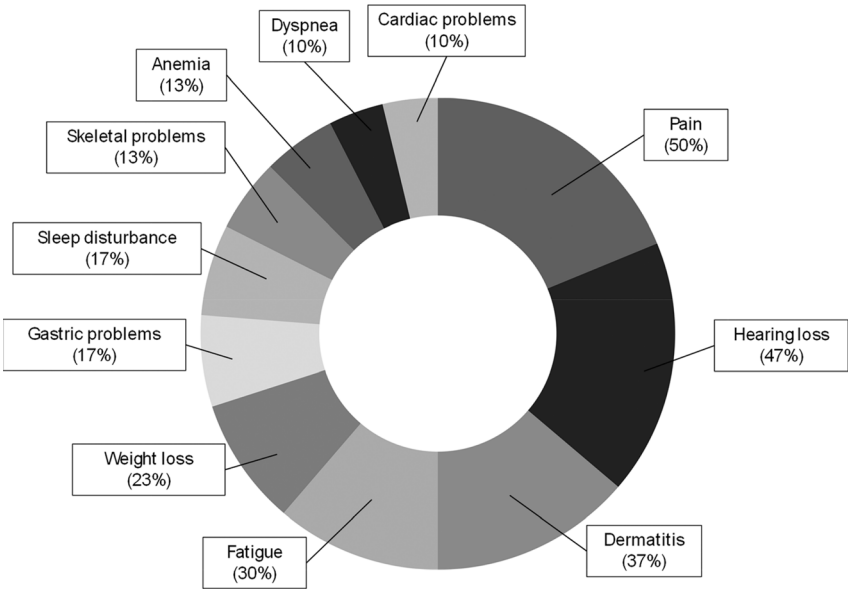

Figure 1: Prevalence of self-reported symptoms among e-waste recycling workers (n = 30).

Table 2: Blood and serum concentrations of trace elements and heavy metals in e-waste recycling workers.

Result (Unit)	Mean ± SD	Minimum	Maximum	Laboratory reference[a]
Whole blood Pb level (µg/dL)	71 ± 31	32	202	0–5
Whole blood Cd (µg/L)	2.3 ± 1.6	0.02	6	0–5
Whole blood Sb (µg/L)	2.9 ± 1.7	0.1	7	0–6
Whole blood Mn (µg/L)	16.7 ± 6	5.8	29	4.7–18.3
Whole blood Cr (µg/L)	2.4 ± 1.2	0.7	6.1	0.7–28
Serum Zn (µg/dL)	83 ± 15	56	115	66–110
Serum Cu (µg/dL)	87 ± 12	70	107	75–145
Serum Se (µg/L)	90 ± 13	56	109	60–150
Serum Mo (µg/L)	0.9 ± 0.5	0.3	1.9	0.3–2
Serum Ni (µg/L)	1.1 ± 1.1	0.1	3.8	0–10
Serum Co (µg/L)	0.2 ± 0.1	0.1	0.5	0–1
Hemoglobin (g/dL)	14.6 ± 1.6	9.5	17.7	12.2–16.2
RDW (%)	14.5 ± 1.6	12.5	19.5	11.6–17.3
WBC (10^{39}/µL)	7.43 ± 1.96	3.7	13	4.6–10.2
CRP (mg/L)	1.8 ± 1.6	0.1	6.9	0–5
Glucose (mg/dL)	96 ± 16	74	148	70–100
Iron (µg/dL)	85 ± 32	21	148	60–180

[a]The normal reference range provided by the clinical laboratory where the analyses were performed; RDW, red cell distribution width; WBC, white blood cell; CRP, C reactive protein.

Table 3: Measured serum neopterin, tryptophan, and kynurenine levels and the estimated IDO activity.

Parameter (Unit)	Mean ± SEM	Minimum	Maximum	Median [IQR]
Neopterin (nM)	7.8 ± 0.7	0.5	16	8.2 [3.7]
Tryptophan (µM)	54 ± 2.0	39	69	53.6 [12.5]
Kynurenine (µM)	0.5 ± 0.04	0.01	0.9	0.49 [0.35]
Kyn/Trp (µmol/mmol)	8.8 ± 0.8	0.2	20.3	9.5 [6.1]

IQR, interquartile range.

blood Pb, Cd, and Sb levels and associated health effects [8, 11, 13, 18, 24–27].

In a study performed by Wang et al. [28], the genotoxic effects of metal exposure were investigated, and blood Pb levels were found to be positively correlated with the results. Similarly, Zhang et al. [29] also found a positive correlation between urinary levels of all 13 metals studied (aluminum, arsenic, Sb, Co, Cd, Mn, mercury, Pb, Se, thallium, tin, and Zn) in local-residents and urinary 8-hydroxy-deoxyguanosine levels. Chen et al. [30] studied hospitalized exposed and nonexposed groups and found positive correlations between blood Pb, Cd, and abnormal liver function. In this study, the mean whole-blood Pb concentration was 71 µg/dL, approximately 17 times the reference limit, indicating substantial occupational exposure. Pb was positively correlated with Sb, consistent with their joint use in alloys, solders, and batteries

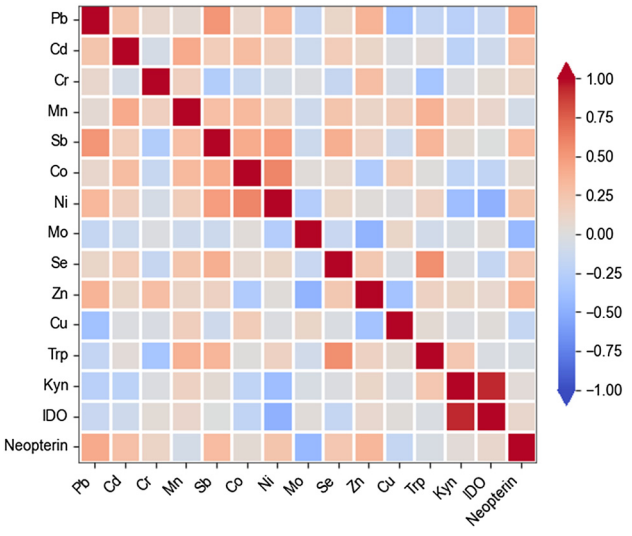

Figure 2: Spearman correlation matrix visualized using Python with SciPy and Seaborn.

Table 4: Significant correlations among measured parameters of e-waste workers.

Category	Parameters	Correlation coefficient	*p*-Value
Metal–metal correlations	Pb–Cu	−0.377	0.048
	Pb–Sb	0.518	0.004
	Cd–Mn	0.411	0.027
	Co–Ni	0.592	0.001
	Ni–Sb	0.481	0.008
	Sb–Co	0.405	0.029
	Sb–Se	0.389	0.037
Metal–immune biomarker correlations	Pb–neopterin	0.410	0.027
	Mo–neopterin	−0.431	0.020
	Ni–Kyn/Trp	−0.478	0.010
	Ni–Kyn	−0.413	0.029
	Se–Trp	0.552	0.002
Other significant correlation	Mo–Zn	−0.470	0.012

[13, 27]. Previous studies have demonstrated that Pb exposure can alter T-cell differentiation, suppress immunoglobulin production, and impair macrophage function [9–11]. Sb exposure, although less studied, has been linked to altered lymphocyte subpopulations and reduced cytokine production [19, 31]. In a study, the workers from an Sb production plant were found to have decreased T and B lymphocyte counts as well as decreased or delayed functions [19]. In another study by Kim et al. [31], serum IgG1, IgE, and IFN-γ levels of Sb-exposed workers were found to be decreased independent of the dose exposed. The results were interpreted as Sb exposure led to a potential human immunosuppression. Pathak and Khandelwal [32] demonstrated a significant decrease in Cd-exposed cytokines in BALBc mice. Th1-derived cytokines (IL-2 and IFN-γ) were found to be more declined than Th2-derived cytokines. Cd levels in the workers were not abnormal, and only three workers had Cd levels slightly exceeding the limit in the present study. Notably, we found no significant association between smoking status and the levels of the heavy metals analyzed, suggesting that occupational exposure, rather than smoking, was the primary source in this cohort.

5.2 Relationship between neopterin and kynurenine pathways

The present findings of a significant positive correlation between Pb and neopterin (R = 0.410, p = 0.027) support the hypothesis that Pb induces macrophage activation and a Th1-type immune response, which is reflected by elevated neopterin production. Neopterin and kynurenine are both markers of cell-mediated immune activation regulated by IFN-γ. However, in this study, while Pb exposure correlated with neopterin levels, no corresponding change was observed in the kynurenine pathway or IDO activity. This dissociation suggests that Pb exposure may trigger oxidative or inflammatory signaling sufficient to stimulate macrophage neopterin release but not enough to fully induce IDO enzymatic activity [4, 5, 33, 34]. Alternatively, Pb might directly inhibit tryptophan catabolism by interfering with heme-dependent dioxygenase enzymes [35–37].

5.3 Coexposure and trace element homeostasis

Inhalational exposure to multiple metals can disturb trace element balance. In our cohort, Cu levels were negatively correlated with Pb, possibly due to competitive absorption or binding to metallothioneins [38, 39]. Cd and Mn were positively correlated, suggesting coexposure or linked metabolic handling. Such imbalances may affect antioxidant defenses and immune homeostasis, since enzymes like superoxide dismutase (Cu/Zn-dependent) are critical for redox regulation [40, 41].

5.4 Comparison with previous occupational studies

Previous reports of Pb-exposed workers (mean = 63.5 µg/dL) showed neopterin levels around 2.7 nmol/L [42], whereas the current study found higher neopterin (7.8 nmol/L) despite

similar Pb exposure, likely due to additional mixed-metal exposure and possible synergistic immune modulation. Conversely, the Kyn/Trp ratio was markedly lower than in single-metal exposure studies [43], reinforcing the notion that multimetal exposure may produce a complex immune effect, combining both activation (via Pb) and suppression (via Cd or Sb) mechanisms [44].

5.5 Implications and future directions

The findings highlight that e-waste workers experience simultaneous exposure to several heavy metals, which may exert differential effects on immune biomarkers. The altered neopterin–kynurenine relationship could serve as an early warning indicator of immune dysregulation before clinical toxicity appears. Future work should include larger cohorts, longitudinal monitoring, and cytokine profiling (e.g., IFN-γ, IL-6, TNF-α) to better elucidate causality [4, 45, 46].

6 Conclusions

Since any amount of Pb in the blood means lead exposure, the authorities regulate, control, and point out to use blood Pb levels in workers [47]. The American Conference of Governmental Industrial Hygienists (ACGIH) has set biological exposure indices for blood lead at 30 µg/dL [48]. The mean blood Pb level (71 µg/dL) far exceeds the biological exposure index confirming significant occupational exposure. Blood Sb levels were reported as 0.9–5.0 µg/L in workers, and 0.4 µg/L in unexposed workers [49]. In the present study, Sb levels in some workers exceeded the biological reference value, indicating concerning exposure to this metal as well, while blood Cd levels were mostly within the biological exposure index (5 µg/L) [50]. The elevated Pb burden, along with detectable levels of Sb, Cd, Ni, Mn, and Co, is consistent with inhalational exposure to multiple metals among e-waste recycling workers. Although no dramatic alteration was detected in kynurenine metabolism, the Pb-associated increase in neopterin suggests early immune activation. Our study provides evidence of immune dysregulation in e-waste workers, characterized by a specific activation of the neopterin pathway in response to lead exposure, independent of kynurenine pathway activation. This suggests that neopterin may serve as a sensitive biomarker for monitoring immune effects in this population. The results also support the need for regular biomonitoring of immune and oxidative stress markers in exposed populations and for stricter occupational safety standards in informal recycling settings. Additionally, the results obtained in this study point to a metabolomics study to understand which other systems, parallel to the immune system, are affected by those working in e-waste recycling.

7 Limitations

The main limitation of this study is the small sample size. Although 30 participants are acceptable for a pilot study, it may have limited the power to detect subtle immunological correlations. Furthermore, the absence of a control group limits the ability to firmly establish whether the observed levels of heavy metals and alterations in immune parameters are solely attributable to occupational exposure.

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Conflict of interest: Authors state no conflicts of interest.
Data Availability Statement: The datasets generated during and/or analyzed during the current study are available from the corresponding author on reasonable request.

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