



Oxidative Stress and Antioxidant Status in Nigerian E-waste Workers: A Cancer Risk Predictive Study

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Authors' contributions

This work was carried out in collaboration between all authors. The authors contributed to the intellectual content of this paper in the areas of concept and design; data acquisition; analysis and interpretation as well as drafting and reviewing of the article. All authors read and approved the final manuscript.

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ABSTRACT

Introduction: In Africa, Nigeria has been reported as the largest destination for unregulated volume of electronic waste (e-waste). Currently, e-waste management practices in Nigeria remain completely primitive, taking place essentially in the informal sector. Recent report indicates that the majority (88.8%) of Nigerian e-waste workers have exposure burden of ≥ 6 hours per day; ≥ 6 days per week, and reportedly worked without personal protective devices. These crude management practices enhance the workers' exposure to electronic waste borne toxic and carcinogenic metals

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and chemicals through almost all body cavities.

Objective: Concisely, this study aimed at evaluating the status of enzymatic and non-enzymatic oxidative stress biomarkers as cancer risk indices in Nigerians occupationally exposed to e-waste.

Methods: Serum levels of malondialdehyde (MDA), uric acid (UA), albumin (ALB), total bilirubin (TBil) and conjugated bilirubin (Cbil.) and activities of enzymatic antioxidants [glutathione reductase (Gr), catalase (Cat), superoxide dismutase (SOD) and glutathione peroxidase (GPx)] were determined in Nigerian e-waste workers (n=63) and in age-matched unexposed participants (n=41), using standard colorimetric methods.

Results: Significantly elevated lipid peroxidation and raised uric acid levels were indicated in e-waste workers. Further to this, CAT, SOD and GPx were significantly reduced in e-waste workers compared with the unexposed human population. Comparatively different observations were not registered in the activity of GR and levels of ALB, TBil. and CBil. between exposed and unexposed participants.

Conclusion: This study provides evidence that the oxidative stress observed in the studied population could be associated with occupational exposure to e-waste chemicals and may be a predictive mechanism for chemical carcinogenesis in Nigerians involved in primitive e-waste management.

Keywords: E-waste; Nigeria; Antioxidants; Oxidative stress; Chemical carcinogenesis.

1. INTRODUCTION

Environmental challenges in Africa especially issues of chemicals and wastes are on the increase with cross-cutting impacts, of which magnitude is yet to be fully assessed and recognized, bearing in mind the connection between waste, climate change and human health.

Electronic waste, e-waste, e-scrap, or waste electrical and electronic equipment (WEEE) describe discarded electrical or electronic devices. The term may broadly be defined as discarded computers, office electronic equipment, entertainment device electronics, mobile phones, television sets and refrigerators. This definition includes used electronics which are destined for reuse, resale, salvage, recycling, or disposal [1].

Informal processing of electronic waste in the developing countries may cause serious health and pollution problems, though these countries are also most likely to reuse and repair electronics. E-waste disposal is especially problematic when humans and the environment are exposed to hazardous chemicals during the process of dismantling electronic products. E-waste contains approximately 1,000 chemicals; key among which are mercury, lead oxide, cadmium, and polyvinyl chloride, which are especially hazardous to human health [2].

Greenpeace, a global Environmental Protection Agency, in a publication highlighted that e-wastes contain such health-threatening substances as Mercury, Lead, Arsenic and

Cadmium. Others are Beryllium, Hexavant Chromium, Bromated flame retardants (BFRs) and Polyvinyl chloride (PVC); as well as Phthalates (phthalate esters) and Organotins. Some of these substances are carcinogenic, and listed as restricted hazardous substances in WEEE [3,4].

The Bamako Convention made the trade in hazardous e-waste illegal in sub-Saharan African countries, yet the e-waste trade continues to thrive in Nigeria. Although Nigeria ratified the Basel Convention on May 24, 2004, it still has not ratified the Bamako Convention, and the country remains a dumping ground for e-waste from European and Asian markets [5,6]. It is estimated that 500 containers of second-hand electronics are imported into Nigeria every month from Europe, with each container holding 500 computers [7]. About three-quarters of these imported products are reported to be junk that cannot be reused and are dumped in landfills [8].

Humans can become exposed to heavy metals in dust through several routes which include ingestion, inhalation, and dermal absorption [9,10]. In dusty environments, very common in many developing countries, it has been estimated that adults could ingest up to 100 mg dust/day [10-12]. Exposure to high levels of heavy metals can result in acute and chronic toxicity, such as damage to central and peripheral nervous systems, blood composition, lungs, kidneys, liver, and even death.

There is a serious association between heavy metal and chemical toxicants, and high cancer

risk [14]. China is known to be the largest e-waste dump yard in the world. The emergence of China Cancer villages is well-documented [13-15], and this may not be unconnected with the reported heavy chemical pollution, including toxicants in e-wastes. Lack of operation system of environmental law of China has been reported as a contributory factor to the emergence of China Cancer Villages [14].

With the unregulated heavy inflow of e-waste into Nigeria, coupled with other widespread health-threatening pollution, the emergence of Nigerian Cancer villages is not impossibility.

In the theory of cancer development, the involvement of chemical toxicants and oxidative stress, as well as oxidative DNA damage are well reported [8,16-18].

The etiology for many cancers are still unknown, however, there are risk factors which are either modifiable or non-modifiable. The modifiable factors include tobacco use, physical inactivity, unhealthy diet, obesity, ultraviolet radiation and infectious agents like Human papilloma virus (HPV), hepatitis viruses (HBV, HCV) and Helicobacter pylori. The non-modifiable factors include heredity, sex, ethnicity, immunosuppression and ageing [19,20]. Moreover, due to the epidemiological shift, increase in ageing population, high rate of infections and entrenchment of the modifiable risk factors [21], cancers will yet pose significant challenge to Nigeria and other developing countries which currently lack cancer control programs directed at reducing cancer incidence and mortality and to improve the quality of life [19]. There are very few human and material resources for cancer control in developing countries where cancers occur at younger ages; 70% of cancer deaths occur and only 5% of global funds for cancer control are available [22].

The prevalence of cancer in Nigeria has grown over the years. Reports from the National Cancer Prevention Agency, courtesy of Ibadan Cancer Registry and Abuja Cancer Registry, showed that incidence rate of cancer in Nigeria in 2012 stood at 66.4 per 100 000 men and 130.9 per 100 000 women [23].

The present study was aimed at evaluating lipid peroxidation and antioxidant status as cancer risk indices in Nigerians occupationally exposed to WEEE and compare with non-exposed human population.

2. PARTICIPANTS AND METHODS

2.1 Study Design

The investigation was designed as a comparative study between occupationally exposed and unexposed groups.

2.2 Study Area

The study was carried out in the Metropolitan City of Benin, Edo State, Nigeria, formerly Mid-western but now South-south Nigeria. Benin City is the current capital of Edo State with an estimated average population of 1,147,188 in the 2006 general census.

2.3 Study Population

2.3.1 Exposed group

Male Waste Electric and Electronic Equipment (WEEE) Workers (n = 63, Mean age of 31 years) working and living in Benin City, formed the exposed group. The states of origin of the exposed subjects comprised of Edo, n = 32 (50.8%); Imo, n = 15 (23.8%); Delta, n = 7 (11.1%); Anambra, n = 3 (4.8%); Ekiti, n = 2; (3.2%); Enugu, n=2 (3.2%) and Abia, n=2 (3.2%). Only subjects with a minimum of 5 years of occupational exposure to toxic substances in WEEE were enrolled into the study.

2.3.2 Unexposed group

Age-matched apparently healthy male participants (n =41), with minimal or no occupational exposure to toxic substances in WEEE, recruited from the Ugbowo Campus Community of the University of Benin formed the non-exposed group in this study.

2.4 Inclusion Criteria

- a) Exposed subjects comprised of Electronic Technicians carrying out informal (primitive) e-waste recycling, processing, repair and dismantling repair of electronic and electrical equipment. Subjects who were occupationally exposed to e-waste for a period of five years and above at the time of sample collection were considered eligible for the study.

Five years duration of exposure is based on the E-waste Risk Assessment Report of Adaramodu, et al. [24].

- b) Control subjects were apparently healthy male individuals with minimal or no occupational exposure and with no hobby involving e-waste exposure. The unexposed participants had no previous demographic and medical history of incidence of cancer.

2.5 Exclusion Criteria

E-waste workers who are not exposed to e-waste for a period up to five years at the time of sample collection were not considered eligible for the study. Subject with history of any form of cancer, tobacco smoking and alcohol ingestion were excluded from the study. Tobacco smoking and alcohol consumption also served as the basis of exclusion for recruiting the apparently healthy control subjects.

2.6 Ethical Approval

The protocol for this study was approved by the Health Research Ethics Committee of the University of Ibadan/ the University College Hospital, Ibadan, Nigeria, with the reference number UI/UCH EC Registration Number: NHREC/05/01/2008a.

2.7 Informed Consent

Participants for this study were all adults who were adequately briefed about the research protocol and informed consent was obtained prior to sample collection. The informed consent form used for this study was explicitly explained to the participants in English and in their local dialect.

2.8 Sample Collection

Approximately 5 milliliters of venous blood was collected from test subjects (e-waste workers) and control subjects using standard phlebotomy techniques. Blood samples obtained were dispensed into plain (anticoagulant-free) specimen bottles to obtain serum after clotting and centrifugation at 3000 revolution per minute for 3 minutes. Analysis of samples for the generation of data was carried out using the well-preserved and labeled samples.

2.9 Laboratory Analysis

Concentrations of MDA in the samples were estimated by the thiobarbituric acid reactive

substance (TBARS) assay. Assay of TBARS was carried out according to the method of Varshney and Kale [25]. Activity of serum catalase was assayed according to the kinetic method of Cohen et al. [26]. GPx assay was done according to the kinetic method described by Flohe and Gunzler, [27]. Assay of GR was done according to the method described by Ellman, [28]. Activity of serum superoxide dismutase enzyme was assayed according to the kinetic method of Misra and Fridovich, [29]. Total and conjugated bilirubin levels were determined using diagnostic kits manufactured by Randox Labs, United Kingdom, based on the colorimetric method described by Jendrassick and Grof [30]. Plasma uric acid concentration was determined using diagnostic kits manufactured by Randox Labs, United Kingdom. Serum albumin concentration was determined using Bromocresol Green reagent.

All biochemical assays were carried out in the Clinical Chemistry laboratory of the Department of Medical Laboratory Science, University of Benin, Benin City.

2.10 Statistical Analysis

Statistical analyses including descriptive statistics were carried out using the Statistical Package for Social Sciences (SPSS, Chicago, IL) version 17.0. All values were expressed as Mean \pm Standard Error of the Mean (SEM). The Independent Student's t-test was used to determine significant differences between exposed and unexposed groups and *P* value <0.05 was accepted.

3. RESULTS

Oxidative stress biomarkers as indices for cancer risk prediction in Nigerian e-waste workers and in unexposed participants are shown in Tables 1 and 2.

Elevated lipid peroxidation activities (as indicated by MDA concentration) and uric acid levels in the e-waste workers compared with the unexposed group and the difference was significant ($P<0.05$). In addition, CAT, SOD and GPx were significantly reduced in e-waste workers compared with the unexposed population. Comparatively different observations were not observed in the activity of GR and levels of ALB, TBil and CBil between exposed and unexposed participants.

Table 1. Enzymatic antioxidant biomarkers in Nigerians occupationally exposed to e-waste and in the unexposed population

Variables	Mean \pm SEM		P value	Level of significance
	Exposed subjects (n=63)	Non-exposed subjects (n=41)		
Glutathione reductase (U/g/dL)	0.23 \pm 0.00	0.28 \pm 0.00	0.080	Not significant
Catalase (μ mol/min/mL)	178.04 \pm 11.95	271.10 \pm 21.20	0.000	highly significant
Superoxide dismutase (μ mol/min/mL)	220.03 \pm 24.24	577.70 \pm 77.82	0.000	highly significant
Glutathione peroxidase (μ mol/min/mL)	32.89 \pm 1.51	40.70 \pm 2.46	0.005	Highly significant

*SEM: Standard Error of Mean; *P \leq 0.05: Significant; *P>0.05: Not significant

Table 2. Non-enzymatic biomarkers of oxidative stress in Nigerians occupationally exposed to e-waste and in the unexposed population

Variables	Mean \pm SEM		P value	Level of significance
	Exposed subjects (n=63)	Non- exposed subjects (n=40)		
Malondialdehyde (nmol/dL)	59.41 \pm 3.64	41.59 \pm 3.29	0.001	Highly significant
Uric acid (mmol/L)	0.56 \pm 0.02	0.40 \pm 0.01	0.000	Highly significant
Albumin (g/L)	47.63 \pm 0.34	48.75 \pm 0.59	0.084	Not significant
Total bilirubin (μ mol/L)	10.40 \pm 0.65	9.09 \pm 1.12	0.280	Not significant
Conjugated bilirubin (μ mol/L)	6.15 \pm 0.44	5.41 \pm 0.43	0.256	Not significant

*SEM: Standard Error of Mean; *P \leq 0.05: Significant; *P>0.05: Not significant

4. DISCUSSION

In the theory of cancer development, the involvement of chemical toxicants and oxidative stress, as well as oxidative DNA damage are well reported [8,16-18]. E-waste contains approximately 1,000 chemicals; including mercury, lead oxide, cadmium, and polyvinyl chloride, some of which are carcinogenic, and listed as restricted hazardous substances in WEEE. Metal-induced oxidative damage is a known mechanism of carcinogenesis [31], and this may offer some explanatory evidence predictive of cancer risk study in chronic occupational exposure of the Nigeria e-waste workers enrolled into this study.

Our observation in this study, among others indicates high degree of exposure to toxic e-waste chemicals, particularly due to the occupational lifestyle of e-waste workers which shows high level of primitiveness and near zero safety practices. Oxidative stress indicators as reflected by the enzymatic antioxidant biomarkers (GR, CAT, SOD and GPx) were significantly reduced in e-waste workers compared with the unexposed population.

The differences in the activities of CAT, SOD, and GPx between the studied groups were highly significant ($P\leq 0.005$). Glutathione reductase activity was reduced in exposed group compared with the unexposed group, the difference was however not significant ($P=0.08$).

In the mechanism of metal-induced oxidative stress, metals are classified into two: redox-active and redox-inactive groups. Redox active metals include; Fe, Cu, Cr, Mn and other transition metals. Redox inactive metals include; Pb, Cd, Hg, As. Both of these groups deplete the cells' major antioxidants by different mechanisms. Redox-active metals are able to undergo Fenton-like reaction to exaggerated oxidative stress while redox-inactive metals deplete antioxidants especially thiol-containing antioxidants and enzymes [32].

The exposed subjects in this study are occupationally exposed to both redox-active and redox-inactive metals reported to be present in WEEE, and it is therefore conceivable that oxidative stress may occur through any of the above mechanisms.

Redox-inactive metals can directly interfere with the activity of GR due to the presence of disulphide bond in its structure. Other antioxidant enzymes which remove peroxides superoxide radicals including GPx, CAT and SOD are also potential target of metals such as lead, which is a component of WEEE and also often used by WEEE workers for soldering.

Glutathione reductase catalyzes the reduction of glutathione disulfide (GSSG) to the sulfhydryl form glutathione (GSH), which is a critical molecule in resisting oxidative stress and maintaining the reducing environment of the cell [33]. Glutathione plays a key role in maintaining proper function and preventing oxidative stress in human cells. It can act as a scavenger for hydroxyl radicals, singlet oxygen, and various electrophiles. Reduced glutathione reduces the oxidized form of the enzyme glutathione peroxidase, which in turn reduces hydrogen peroxide (H_2O_2), a dangerously reactive species within the cell. Glutathione reductase does not play a central role as an antioxidant enzyme per se, it only catalyzes the reduction of oxidized glutathione (GSSG) to reduced glutathione (GSH). However, another antioxidant; alpha lipoic acid (ALA) has been shown to recycle GSH in the same way GR catalyzes the reduction of GSSG. Dihydroxy lipoic acid (DHAL) has been shown to be more potent than ALA. DHAL was reported to recycle oxidized ascorbate, glutathione, coenzyme Q and vitamin E to their active forms as antioxidants [34]. DHAL is responsible for the ability of ALA to increase intracellular GSH level; and of importance is its ability to regenerate GSH [35]. This function of ALA might have preserved GR activity since they appear to work synergistically to prevent oxidative stress; probably explaining why the GR level in these exposed subjects was not significantly depleted unlike other antioxidant enzyme activities observed in this study.

Catalase catalyzes the decomposition of hydrogen peroxide to water and oxygen [36]. It is a very important enzyme in protecting the cell from oxidative damage by reactive oxygen species (ROS). Superoxide dismutases are important antioxidant defense systems in nearly all cells exposed to oxygen, they are proteins co-factored with copper and zinc, or manganese, iron, or nickel. In biological systems, the main reactions of superoxides are with itself (dismutation) or with another biological radical such as nitric oxide (NO) or with a transition-

series metal. The superoxide anion radical (O_2^-) spontaneously dismutates to O_2 and hydrogen peroxide (H_2O_2) quite rapidly (approximately $10^5 M^{-1}s^{-1}$ at pH 7). SOD is necessary because superoxide reacts with sensitive and critical cellular targets to cause pathological conditions. Reduced SOD activity is observed in oxidative damage [37].

GPx is a selenium dependent enzyme with peroxidase activity whose main biological role is to protect the organism from oxidative damage. The biochemical function of glutathione peroxidase is to reduce lipid hydroperoxides to their corresponding alcohols and to reduce free hydrogen peroxide to water. GPx requires selenium for its activity, but in lead toxicity; lead may form a complex with selenium, resulting in GPx activity decrease [38,39]. This may account for the reduced activity of GPx in the e-waste workers studied. Treatment of human fibroblasts with sodium arsenite slightly decreases GPx activity and significantly decreased CAT activity; as reported by Lee et al. [39,40].

Also lead exposure may account for the significant reduction of SOD activities in exposed subjects. Animal studies demonstrated reduced erythrocyte SOD activity was reduced in lead-exposed rats [41,42].

WEEE contains Cd, a carcinogen and an inducer of oxidative damage [31]. Cadmium has been reported to affect the activities of antioxidant enzymes especially CAT and SOD [43]. Administration of Cd-acetate to liver and kidney in-vitro causes inhibition of SOD activity and high level of lipid peroxidation was found in these tissues [43].

Copper is a cofactor for SOD, unavailability of copper causes decrease SOD activity. Involvement of mercury (a component of e-waste) in oxidative stress may be due to its ability to displace copper from its binding site. It has been suggested that mercury increases intracellular copper only by increasing influx from extracellular medium which could particularly increase oxidative stress [44,45].

In addition, this study demonstrates significantly raised non enzymatic oxidative stress indicators (MDA and UA) in exposed subjects compared with non-exposed group. Metal toxicity exacerbates oxidative stress which causes different pathological processes including lipid peroxidation. Malondialdehyde (MDA) is a

product of lipid peroxidation and provides a means of assessing the extent of lipid peroxidation. Many studies have confirmed lipid peroxidation secondary to heavy metal toxicity. In the work of Yiin et al. [46], lipid peroxidation was assessed by MDA analysis; and it was observed that lipid peroxidation increases in lead toxicity. MDA concentration was found to increase in liver and kidney after cadmium exposure [47].

The significantly raised MDA concentration in the e-waste exposed group in this study directly reflects increased lipid peroxidation and oxidative damage, a mechanism that contributes to carcinogenesis. Serum uric acid (UA) has been shown to have antioxidant activity. Ames et al. [48], demonstrated that urate reduces the oxo-haem oxidant formed by peroxidation reaction with haemoglobin, and protects erythrocytes from peroxidative damage which leads to lysis. Also, urate was reported to be as effective an antioxidant as ascorbate in scavenging hydroxyl radicals [49,50].

Furthermore, this study demonstrates that UA level in the exposed subjects was significantly higher than levels obtained in non-exposed subjects, despite the evidence of oxidative stress in the exposed subjects. Acting as systemic antioxidant, UA level is expected to have been lowered in oxidative stress due to depletion.

This elevation of UA in the exposed subjects enrolled in this study may be due to the effect of reactive oxygen species on DNA or may be attributed to toxic metal- induced renal dysfunction. It may be an up-regulation, a consequence of increased ROS burden. Uric acid, being an end product of purine (Adenosine and Guanosine) metabolism; adenosine and guanosine are released from DNA in their triphosphate forms [51]. In-vitro study in plants exposed to various environmental stresses such as salinity has been shown to enhance DNA degradation. Oxidative attack on DNA results in deoxyribose oxidation, strand breakage, removal of nucleotides, variety of modification in the organic bases of the nucleotides and DNA-protein crosslink [52]. The increased release of adenosine and guanosine phosphates from damaged DNA may be responsible for the elevated UA level in the exposed subjects of this study.

In another light, uric acid is excreted by the kidney; thus renal dysfunction may also cause elevated UA. Cadmium is a known

nephrotoxicant and heavy metal toxicity has been shown to cause renal damage [53].

Albumin has been shown to exert specific antioxidant function due to its multiple ligand-binding capacities and free-radical trapping properties, both closely related to its structure [54,55]. In this study, the ALB concentration in the exposed subjects was less than, but not significantly different from unexposed participants. This observed difference may be attributed to the depletion of ALB due to its antioxidant properties. Also, since metal toxicity affects liver function; the slight decrease may be due to reduced production by the liver.

Bilirubin has been reported to exhibit antioxidant function. Bilirubin when bound to human albumin and at concentrations found in normal human plasma, protects albumin-bound linoleic acid from peroxy radical-induced oxidation in-vitro [56]. Stoker et al. [56] also showed that one mole of albumin-bound bilirubin can scavenge two moles of peroxy radicals and that small amount of plasma bilirubin is sufficient to prevent oxidation of albumin-bound fatty acids as well as of the protein itself.

In this study, the values for Total bilirubin (TB) and Conjugated bilirubin (CB) were slightly higher (not significantly different) in exposed subjects compared with the unexposed group. Increase in both TB and CB in the exposed subjects may be as a result of haemolytic processes which may be secondary to erythrocyte membrane lipid peroxidation, an accompaniment of the prevailing oxidative stress. It has been reported that some metals such as gold, mercury, copper and lead (also part of WEEE) cause lipid peroxidation [57]. Increased release of haemoglobin from haemolysis of erythrocytes may explain the higher values of the two forms of bilirubin in the exposed subjects.

Taken together, the present study provides evidence of increased oxidative stress and lipid peroxidation in the exposed group studied; this may predisposed to cancer development. The mechanism for this predisposition may be complex and multifactorial but related to the effects of oxidative damage and lipid radicals on biological systems. Lipid radicals which are products of lipid peroxidation can diffuse through membranes, thus modifying the structure and function of the membranes and resulting in the loss of cell integrity and homeostasis. In addition,

lipid peroxides may interact with cellular DNA and cause the formation of DNA-MDA adducts [58]. Proteins are also easily attacked by reactive oxygen species (ROS) directly or indirectly through lipid peroxidation. Protein radicals can be rapidly transferred to other sites within the protein structure, this can result in further modification of enzyme activity (stimulation or inhibition) [59,60]. Changes to receptor proteins and gap junction proteins may also modify signal transduction in cells. In selective cases alteration of protein structure may allow the target protein to be further attacked by proteinases [61]. Thus, protein oxidative damage can result in the modifications in structure, enzyme activity, and signaling pathways. Activation of transcription factors is an important signaling pathway for the regulation of gene transcription by ROS [62]. Transcription factors regulate the transcription of genes involved in the development, growth, and aging of cells [63]. Nuclear factor kappa B and AP-1, by direct oxidation and phosphorylation, are two transcription factors that are modulated by oxidative stress [64]. Reactive oxygen species can cause activation of AP-1 as well as new synthesis of AP-1 [65]. By activating AP-1, ROS can stimulate cell proliferation and the persistent proliferation due to chronic oxidative stress would make the rate of cell production to exceed the rate of apoptosis. This is a hallmark of cancer development and malignancy, resulting in subsequent tumor.

Furthermore, ROS or their by-products of lipid peroxidation, MDA, through direct reaction with DNA forms oxidative DNA adducts. The presence of oxidative DNA adducts generated by chemical carcinogens suggest an interactive role of ROS in initiation of cancer. ROS, therefore, can have multiple effects in the initiation stage of carcinogenesis by mediating carcinogen activation, causing DNA damage, and interfering with the repair of the DNA damage [66]. Cancer results when defective DNA molecules are incorporated into the DNA of developing cells during cell proliferation.

5. CONCLUSION

In conclusion, the present study demonstrates that the oxidative stress arising from increased lipid peroxidation and lowered antioxidant defenses observed in the studied population may be associated with chronic occupational exposure to e-waste chemicals and could be a key mechanism for chemical carcinogenesis in Nigerian e-waste workers and may be predictive of cancer in these individuals.

COMPETING INTERESTS

Authors have declared that no competing interests exist.

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