Oxidative Stress and Arsenic Exposure Among Copper Smelters

Thesis

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By

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Abstract

Introduction: Copper is widely used in industry. It has been associated with several health hazards among exposed workers.

Aim: The aim of this work is to measure the indicators of oxidative stress as malondialdehyde and superoxide dismutase enzyme activity levels in blood and their association with copper and arsenic levels among secondary copper smelter workers.

Subjective and methods: This study was conducted on forty (40) male workers in a secondary copper smelting factory, who were occupationally exposed to copper. They were compared to forty (40) male non-exposed individuals. Full history was taken, clinical examinations were done. Laboratory investigations in the form of: CBC, serum copper, serum arsenic, urinary arsenic, malondialdehyde and superoxide dismutase blood levels were measured. Environmental measurements of copper and arsenic dusts and fumes were carried out at selected different workplaces.

Results: Environmental measurements in the workplace were within the normal permissible limits in Egypt. Statistically significant ($p<0.05$) differences were found between exposed and control as regards the prevalence of the respiratory and neurological symptoms. Compared to the control group, serum copper, serum arsenic, urinary arsenic and blood malondialdehyde level (Cu=148.4±15.6, serum As=2.6±1.2, urinary As=38.7±14.2, MDA=5.6±1.9) were significantly increased among exposed worker. Superoxide dismutase activities in blood (185.5±19.8) were significantly decreased and negatively correlated with duration of the employment ($r=-0.750$; $p<0.001$). Also malondialdehyde in blood were significantly increased and positively correlated with the duration of employment ($r=0.830$; $p<0.001$).

Conclusion: The oxidative stress biomarker as malondialdehyde (MDA) was significantly increased with exposure to copper dusts and fumes. It was positively related to copper and arsenic levels. While superoxide dismutase enzyme activity was significantly reduced, and it was negatively related to copper and arsenic levels. The disruption of hemostasis induced by oxidative stress may promote the development of health hazards with continued occupational exposure to copper fumes.

Recommendation: from the present study we recommend :Pre-employment and Periodic medical examination for smelters workers including clinical examination and laboratory investigations as measuring serum copper, urinary arsenic, serum arsenic. Malondialdehyde and superoxide dismutase blood levels can be used as indicators of oxidative stress among exposed workers.

Key words: Copper smelters, Arsenic, Malondialdehyde (MDA), Superoxide dismutase (SOD).

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List of Abbreviations

ACGIH:	American Conference of Governmental Industrial Hygienists
AP-1:	Activator protein-1
AsV:	Arsenate
AsIII:	Arsenite
AsH_3:	Arsine gas
As-GSH:	arsenic-glutathion complexes
$As^{+3}MT$:	Arsenic (+3 oxidation state) methyltransferase
As_2S_3:	Orpimen
As_4S_4:	Realgar
ATG:	Arsenic triglutathione
ATRA:	All-trans retinoic acid
BFD:	Black foot disease
BER:	Base excision repair
CAT:	Catalase
CAT:	Chronic arsenic toxicity
cc:	cubic centimeters
CCI_3:	Carbon-centered free radical
Cd:	Cadmium
$(CH_3)_2As•$:	dimethylarsinic radical
$(CH_3)_2AsOO•$:	dimethylarsinic peroxyl radicals
$ClCH=CHAsCl_2$:	Lewisite (2-chlorovinyl-dichloroarsine)
Cu:	Copper
Cu-ZnSOD:	Copper-Zinc superoxide dismutase
Cu^{+1}:	Cuprous

Cu^{+2} :	Cupric
DMA:	Dimethylarsenate,
DMAIII:	Dimethylarsonic acid
DMAV:	Dimethylarsinic acid
DMAG:	Dimethylarsinic glutathione
DMDTAV:	Dimethyldithioarsinic acid
DMMTAV:	Dimethylthioarsinic acid
DMSA:	Dimercaptosuccinic acid
EC-SOD:	Extracellular superoxide dismutase
EPA:	Environmental Protection Agency
EW:	Electro wining
FDA:	Food and Drug Administration
Fe:	Iron
$FeSiO_3$:	Ferrous silicate
FEV1:	forced expiratory volume measured in 1 sec
FVC:	forced vital capacity
GSH:	Reduced glutathione
GPx:	Glutathione peroxidase
GR:	Glutathione reductase
GSSG:	Oxidized glutathione
GSTO1-1:	Glutathione S-transferase omega 1-1
hCtr1	The human homologue copper-transport protein1
hCtr2:	The human homologue copper-transport protein2
Hg:	Mercury
HNE:	4-Hydroxinonenal
HNO_2 :	Nitrous acid

H_2O_2 :	Hydrogen peroxide
HOCl:	Hypochlorous acid
HSA:	Human serum albumin
IARC:	International Agency for Research on Cancer
KCI:	Kerman copper industries
LOO•:	Lipid peroxyl
MADG:	Monomethylarsonic diglutathione
MDA:	Malondialdehyde
MMA:	Monomethylarsenate
MMAIII:	Monomethylarsonous acid
MMAV:	Monomethylarsinic acid
MMA reductase:	Monomethylarsenate reductase
MNK:	Menkes protein
Mn:	Manganese
Mn-SOD:	Manganese superoxide dismutase
MTHFR:	Methylenetetrahydrofolate reductase
NAC:	N-acetyl-L-cysteine
NADPH:	N-acetyl diphosphate hydrogenase
NaPi-IIb:	Sodium-coupled phosphate transporter
NER:	Nucleotide excision repair
NF kappaB:	Nuclear factor-kappaB
NIEHS:	National Institute of Environmental Health Sciences Sciences
Ni:	Nickel
Ni-SOD:	Nickel superoxide dismutase
$NO^{\bullet}$:	Nitric oxide
$NO_2^{\bullet}$:	Nitrogen dioxide

$O_2^{\bullet-}$:	Superoxide
$^1O_2$:	singlet oxygen
O_3 :	Ozone
$^{\bullet}OH$:	Hydroxyl
$ONOO^-$:	Peroxynitrite
OS:	Oxidative stress
OSHA:	Organization of Safety and Health Administration
PAM:	Peptidylglycine alpha-amidating mono-oxygenase
PET:	Poistron Emision Tomography
Pb:	Lead
PLS:	Pregnant leach solution
$ROO^{\bullet}$:	Peroxyl radical
ppm:	parts per million
PUFA:	polyunsaturated fatty acids
RDAs:	Recommended dietary allowances
RH:	Activated methylene
RNS:	Reactive nitrogen species
$ROO^{\bullet}$:	Peroxyl
ROOH:	Lipid hydroperoxide
ROS:	Radical oxygen species
NRC:	National Research Council
SAH:	S-adenosyl-homocysteine
SAM:	S-adenosyl-methionine
SO_2:	Sulphur dioxide
SOD:	Superoxide dismutase
SP1:	Specificity protein1

SX:	Solvent extraction
TMAIII:	Trimethylarsine
TMAOV:	Trimethylarsine oxide
TPM:	Total particulate matter
TWA:	Time-weighted average
WND:	Wilson protein
Zn:	Zinc

Introduction

Mining and smelting of heavy metals can be traced back thousands of years ago. However, production has grown rapidly since the industrial evolution ***(Pacyna, 1986).***

The discovery of copper dates from prehistoric times. It is said to have been mined for more than 5000 years. It is one of man's most important metals. Copper occasionally occurs native (elemental copper) in ores and minerals. The most important copper ores are the sulfides, oxides and carbonates. From these, copper is obtained by smelting, leaching, and electrolysis ***(Lide, 2012).***

Um Bogma area is the most famous mineralized area in Sinai, Egypt. It is characterized by the presence of manganese, iron, and copper deposits.There are many hazardous elements such as iron, copper, manganese, lead, and zinc as well as others associating heavy metals such as arsenic, selenium, and sulfur which are dispersed in the environment ***(Khalifa and Arnous, 2012).***

Emissions from copper smelter are principally particulate matter and sulfur oxides. Copper and iron oxides are the primary constituents of particulate matter but other oxides such as arsenic, antimony, cadmium, lead, mercury and zinc may be also present along with metallic sulfates and sulfuric acid mist ***(Tasić et al., 2010).*** As the most common emissions are copper and arsenic, that is why we measured these metals.

Copper can induce oxidative stress by two mechanisms. Firstly, it can directly catalyze the formation of radical oxygen species (ROS) via a fenton-like reaction. Secondly, exposure to elevated levels of copper significantly decreases glutathione levels through binding to its thiol group ***(Speisky et al., 2009).***

Chronic exposure to inorganic arsenic involves a biotransformation process that led to the main excretion of organic methylated metabolites, such as monomethylarsinic acid (MMA) and dimethylarsinic acid (DMA), as well as the parental inorganic species ***(Marcos et al., 2006).***

At the molecular level, physio-pathological effects related to arsenic toxicity appear to involve different mechanisms and intracellular targets. Oxidative stress is

among the most documented mechanisms of arsenic toxicity and carcinogenicity. It is the result of an imbalance between radical oxygen species (ROS) production and the antioxidant defense system e.g. superoxide dismutase (SOD) and vitamin E ***(De Vizcaya-Ruiz et al., 2009).***

Radical oxygen species (ROS) production by arsenic may result in an attack, not only against antioxidant defenses and DNA, but also against membrane phospholipids, which are very sensitive to oxidation, producing peroxyl radicals and then malondialdehyde (MDA) ***(Shi et al., 2004).***

Gentry et al. (2010) highlighted the role of inhibition of DNA repair by arsenic as a mode of action for its carcinogenic effect. They analyzed data on in vitro cellular and in vivo gene expression changes following exposure to inorganic arsenic. The analysis of the data suggests the key events in carcinogenicity of arsenic include inhibition of DNA repair under conditions of oxidative stress, inflammation, and proliferative signaling. This may lead to a condition in which mitosis proceeds without maintaining the integrity of the cellular DNA.

Numerous studies showed increased incidence of lung, skin, and bladder cancer due to high exposure to arsenic ***(Ferreccio et al., 2006; Kapaj et al., 2006; Kligermanand et al., 2007; Hlubin et al., 2008).***

In regard to toxicity, the International Agency for Research on Cancer (IARC) defines arsenic as a group I known human carcinogen that also induces a wide array of other noncancer effects, leaving essentially no bodily system free from potential harm ***(IARC, 2012).***