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Determination of Heavy Metals and Nicotine in Tabacoo Leaves Collected from Western Sudan

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Abstract: **Sudan is one of largest countries that are planted Tabaco aseptically in western Sudan. The nomenclature in Sudan country is Toombak. This paper provides a description of the toxicological evaluation of tobacco leaves.**

Tobacco use is one of the major preventable causes of premature death and disease in the world. Tabaco is one of very harmful plant to human health, They are many methods uses of tobacco, like smoking, with oral and nasal passages, etc. Tobacco pastes or powders are used in a similar manner and placed on the gums or teeth. Fine tobacco powder mixtures are usually inhaled and absorbed in the nasal passages. There is sufficient evidence that the use of smokeless tobacco causes cancer in humans. Smokeless tobacco contains carcinogens, which contribute to cancers of the oral cavity and the risk of other head and neck cancers. Smokeless tobacco use also causes a number of noncancerous oral conditions and can lead to nicotine addiction similar to that produced by cigarette smoking.

Tobacco use has been associated with a number of adverse effects on the growth, cognitive development, and behavior of the exposed child. The use of tobacco products is detrimental to oral health. Cigarette smoking is associated with increased alveolar bone loss. A level of 4-aminobiphenyl-hemoglobin adducts in smokers of blonde (flue-cured) and black (air-cured) tobacco has been found to be proportional to bladder cancer risk. And damage the hemoglobin. Tobacco use increases susceptibility to bacterial infection. And it harmful to the heart.

Tobacco contains many kinds of heavy metals .The toxicity of heavy metals is a problem for ecological, evolutionary and environmental reasons. Heavy metals such as lead and cadmium mercury, Cobalt, Zinc, Copper, chromium, Cobalt, Manganese, copper ,and Nickel. Are highly toxic pollutants as they are added in the environment through automobile exhausts. Inhibition of germination and retardation of plant growth are commonly observed due to lead toxicity. Heavy metals are naturally occurring elements that have a high atomic weight and a density at least 5 times greater than that of water. Their multiple industrial, domestic, agricultural, medical and technological applications have led to their wide distribution in the environment; raising concerns over their potential effects on human health and the environment. Their toxicity depends on several factors including the dose, route of exposure, and chemical species, as well as the age, gender, genetics, and nutritional status of exposed individuals. Because of their high degree of toxicity, arsenic, cadmium, chromium, lead, and mercury rank among the priority metals that are of public health significance. These metallic elements are considered systemic toxicants that are known to induce multiple organ damage, even at lower levels of exposure. They are also classified as human carcinogens (known or probable) according to the U.S. Environmental Protection Agency, and the International Agency for Research on Cancer.

Tobacco-related diseases can be attributed to the inhalation of many different toxins, including heavy metals, which have a host of detrimental health effects. The current study reports the high levels of arsenic (As), cadmium (Cd), chromium (Cr), nickel (Ni), and lead (Pb) in tobacco participating in this survey the mean As, Cd, Cr, Ni, Co, Mn and Pb it very important .

These metallic elements are considered systemic toxicants that are known to induce multiple organ damage, even at lower levels of exposure. They are also classified as human carcinogens (known or probable) according to the U.S. Environmental Protection Agency, and the International Agency for Research on Cancer. This review provides an analysis of their environmental occurrence, production and use, potential for human exposure, and molecular mechanisms of toxicity, genotoxicity, and carcinogenicity.

For that reasons this research aims to illustrate the risks of tobacco use. This study aims to determine the amount of nicotine and heavy metals in tobacco from Shagra area in western Sudan, because there are many peoples used this kind of tobacco in Sudan, and to demonstrate the side effect of its content . In this research used the national leave of plant collected from the farm before fermentation and analyzed it. The results show that they are very amount of heavy metals in the sample. And the percentage of nicotine it is very high. For that the research recommends for this sample can cause dangers risks to humans who used it.

Keywords: **Heavy metals, Nicotine, toxicity, Tobacoo Leaves, production and use, human exposure, carcinogenicity.**

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1. INTRODUCTION

1-1 Introduction:

According to the data of WHO – in the 20th century, 100 million people have died from tobacco use. At the same time, studies were focused on quantitative and qualitative analyses of tobacco constituents potentially responsible for the negative health effects. More than 4,000 chemicals have been isolated from tobacco (hydrocarbons, aldehydes, ketones, aromatic hydrocarbons, heavy metals .Tobacco causes a variety of diseases, primarily lung tumors and deficiencies of the respiratory and cardiovascular system. This research study some of harmful contain in tobacco, nicotine and some of heavy metals. Including lead and arsenic, cadmium, mercury, Cobalt, Zinc, Copper and chromium are classified as carcinogenic to humans or possibly carcinogenic to humans (group 1 or 2) (1 ,2 14) .

Human population is exposed to heavy metals from many sources (air, water, soils, foodstuffs, and anthropogenic sources).

The heavy metals are widely dispersed in the environment, and at excessive levels, are very toxic to humans. Chronic exposure to these substances may also be hazardous. Although these metals occur naturally, exposure may be increased by human activities that release them into the air, soil, water and food, and by- products that contain heavy metals. Certain plants also have the ability to accumulate heavy metals that have no known biological function .Tobacco plant is amenable to absorb and accumulate heavy metal species from the soil into leaves .Tobacco plants transport metal ions from the soil through the roots into the leaves . Trace amounts of heavy metals accumulate in the leaves, and they are known to transfer in trace quantities from the cured and processed tobacco to mainstream cigarette smoke. These metals include cadmium, lead, arsenic, iron, copper, chromium, nickel, and selenium. The most abundant redox inactive metals in cigarette smoke generally are cadmium, lead and arsenic (3, 13,24).

Industrialization has contributed to the burden of trace metals in soils in urban areas. Metals that are added from the application of sewage sludge, pesticides, lime, irrigation waters and fertilizers have threatened the quality of agricultural land . Heavy metals are critical in this regard because of their easy uptake into the food chain and bioaccumulation processes.

Toxic heavy metal can cause dermatological diseases, skin cancer and internal cancers (liver, kidney, lung and bladder), cardiovascular disease, diabetes, and anemia, as well as reproductive, Developmental, immunological and neurological affects in the human body.

Chronic exposure to lead can result in decreased neurological performance. In pregnant women, exposure to high lead levels may cause miscarriage, and chronic exposure may affect the development of the foetus. Methyl mercury may cause numbness and tingling and in the extremities, blurred vision, deafness, lack of muscle coordination and intellectual impairment, as well as adverse effects on the cardiovascular, gastrointestinal and reproductive systems.

Tobacco smoking has been identified as a major serious Public health issue and contributes to high mortality and morbidity of both smokers and passive smokers. Cigarette smoking is an established cause of urinary bladder cancer, accounting for as much as 50% of the bladder cancer in Western populations . Aromatic amines, including ABP' and 2-naphthylamine, are found in cigarette smoke and are widely recognized as human and animal carcinogens . Two case-control studies have established that smokers of black, air cured tobacco are at a greater risk of bladder cancer than smokers of blonde, flue-cured tobacco . The smoke of black tobacco cigarettes contains more aromatic amines, including ABP, than the smoke of blonde tobacco cigarettes.

A person's increased [[risk]] of contracting disease is directly proportional to the length of time that a person continues to smoke as well as the amount smoked. However, if someone stops smoking, then these chances gradually decrease as the damage to their body is repaired. A year after quitting, the risk of contracting heart disease is half that of a continuing smoker.

Tobacco, the most widely smoked substance in our society, has been studied extensively with regard to its adverse effects on the lungs (5, 16).

In a previous investigation, we found that the hemoglobin adducts of ABP were approximately 5 times higher in smokers of black tobacco and 3 times higher in smokers of blonde tobacco than in nonsmokers . In addition, when adjusted for the same nicotine uptake, smokers of black tobacco excreted twice the amount of mutagenic substances as those smoking blonde tobacco. The chemical-biological properties of these mutagens are consistent with their structures being aryl amines.

Cigarette smoking causes an acceleration of the aging process of the lung and a loss of lung reserve . The incidence of lung cancer, now the leading cause of cancer death in both men and women in the United States, is about 10 times higher in smokers compared with nonsmokers. Smoking has also been associated with increased cancer of the larynx tongue, pharynx esophagus , pancreas (, and cervix, and has been related to leukemia and myeloma, hypertension , and coronary artery disease . The use of tobacco products is detrimental to oral health. Cigarette smoking is associated with increased alveolar bone loss.

The magnitude of increased relative risk of bladder cancer among smokers of the two tobacco types, as compared to nonsmokers, is proportional to the differing concentrations of ABP adducts, consistent with an etiological role of aromatic amines in tobacco-induced bladder cancer (11,22,69).

Some surveys clarified that the contents of certain chemicals especially cadmium in fats, blood and liver tobacco smokers are much higher than those of non-smokers. Tobacco kills approximately 6 million people and causes more than half a trillion dollars of economic damage each year .

Immediate cutaneous hypersensitivity to extracts of defatted tobacco leaves has been reported previously in smokers and in nonsmokers. Harkavy has suggested that allergy to constituents of tobacco may underlie the relationship between tobacco smoking and coronary artery disease and peripheral vascular disease . In this connection, Fontana and colleagues have demonstrated that 28% of smokers with immediate cutaneous hypersensitivity to tobacco extracts had changes in peripheral circulation, as measured by change in skin temperature, when they smoked cigarettes as compared with smokers with negative skin tests of whom only 4% had changes in skin temperatures.

However, the concept of allergy to tobacco constituents has not been generally accepted because (a) many nonsmokers were also found to be hypersensitive; (b) it was not clearly demonstrated that antigens extractable from tobacco leaf were also

present in tobacco smoke or, if present, in what quantity; (c) antigens from tobacco leaves or from concentrated tobacco smoke were far from pure and may have included noxious material capable of inducing a wheal and flare reaction when injected intracutaneously.

We report here on experiments in which an 18,000 molecular weight glycoprotein was purified from saline extracts of cured tobacco leaves (N. tobacum) by (NH4)2SO4 fractionation, chromatography on Sephadex G-25, and preparative continuous- flow electrophoresis on alkaline polyacrylamide gel. This material will be referred to as tobacco glycoprotein (TGP).

Twelve of 31 human volunteers displayed immediate hypersensitivity reactions when injected intracutaneously with TGP.

Similar material was demonstrated in the four commonly used varieties of tobacco leaf. In addition, a similar glycoprotein was purified from cigarette smoke condensate, and from saline through which cigarette smoke had been bubbled. By hem agglutination inhibition, it was demonstrated that TGP and material purified from cigarette smoke condensate and from saline extracts of cigarette smoke were immunochemically similar, if not identical.

Smokeless tobacco products have been in existence for thousands of years among populations in South America and Southeast Asia. Over time, these products have gained popularity in the throughout the world. Smokeless tobacco is consumed without burning the product, and can be used orally or nasally. Oral smokeless tobacco products are placed in the mouth, cheek or lip and sucked (dipped) or chewed. Tobacco pastes or powders are used in a similar manner and placed on the gums or teeth. Fine tobacco powder mixtures are usually inhaled and absorbed in the nasal passages.

There is sufficient evidence that the use of smokeless tobacco causes cancer in humans (5, 6, 11, 29).

Smokeless tobacco contains carcinogens, which contribute to cancers of the oral cavity and the risk of other head and neck cancers. Smokeless tobacco use also causes a number of noncancerous oral conditions and can lead to nicotine addiction similar to that produced by cigarette smoking.

This compendium of fact sheets on smokeless tobacco products includes information about the brand and common names of the products, their geographic location of use, their constituents (ingredients), how the products are used, who primarily uses the products, and the processes for manufacturing the products. This information has been organized by geographic region of the world – the Americas, Europe, Asia, Africa and the Middle East.

The purpose of this research is to determine the level of selected heavy metals in tobacco and nicotine in West Region of Sudan.

Tobacco tree has several names in the world, in Sudan called toombak (33) .

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1-2 Toombak classification:

BRAND NAMES: None

COMMON NAMES: None

GEOGRAPHIC LOCATION OF USE: Sudan

PRODUCT CONSTITUENTS: tobacco, sodium bicarbonate

HOW USED: Product is rolled into a ball, weighing about 10g, called a *saffa*.

The saffa is held between the gum and the lip or cheek, or under the tongue on the floor of the mouth. It is sucked slowly for 10 to 15 minutes. Male users periodically spit, while female users typically swallow the saliva generated. The user usually rinses his/her mouth with water after the saffa is removed.1

WHO USES: About 34% of Sudanese men and 2.5% of women aged 18 years and older.1

PROCESSING / MANUFACTURING: Tobacco leaves are harvested and left in a field for uniform drying. The leaves are then tied into bundles, sprinkled with water, and stored for a couple of weeks at 30 to 45ºC to allow fermentation. The leaves are then ground up and aged for up to a year. After aging, toombak vendors (in toombak shops) place the product in bowls and gradually add sodium bicarbonate until the mixture is approximately 4 parts tobacco to 1 part

sodium bicarbonate. The mixture is blended by hand and constantly tested with the tips of the fingers until it becomes moist and hardened. The toombak is then placed in an airtight container for about 2 hours prior to sale.1

Toombak whole sale Advertisement

Toombak processed by hand

Toombak wholesale advertisement Toombak processed Fire cured tobacco Punk ash for sale in local leaves for sale

1-3 Health Effects of tobacco Products:

Besides nicotine, cigarette smoke contains more than 4,000 substances, many of which may cause cancer or damage the lungs. Cigarette smoking is associated with coronary heart disease, stroke, ulcers, and an increased incidence of respiratory infections. Smoking is the major cause of lung cancer and is also associated with cancers of the larynx, esophagus, bladder, kidney, pancreas, stomach, and uterine cervix. Smoking is also the major cause of chronic bronchitis and emphysema.

Women who smoke cigarettes have earlier menopause. Pregnant women who smoke run an increased risk of having stillborn or premature infants or infants with low birth weight. Children of women who smoked while pregnant have an increased risk for developing conduct disorders.

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Cigar and pipe smokers and users of chewing tobacco and snuff can also become addicted to nicotine. Although cigar and pipe smokers have lower death rates than cigarette smokers do, they are still susceptible to cancers of the oral cavity, larynx, and esophagus. Users of chewing tobacco and snuff have an elevated risk for oral cancer (29,31,32,46,50) .

The effect of tobacco smoke on in vitro chemo taxis of human polymorph nuclear leukocytes (PMN) , whole tobacco smoke, gas phase of smoke, and water-soluble fraction were potent inhibitors of PMN chemo taxis. Active smokers and those exposed to second hand smoke are at increased risk of bacterial infection. Tobacco smoke exposure increases susceptibility to respiratory tract infections, including tuberculosis, pneumonia and Legionnaires disease. Tobacco smoke compromises the antibacterial function of leukocytes, including neutrophils, monocytes, T cells and B cells, providing a mechanistic explanation for increased infection risk.

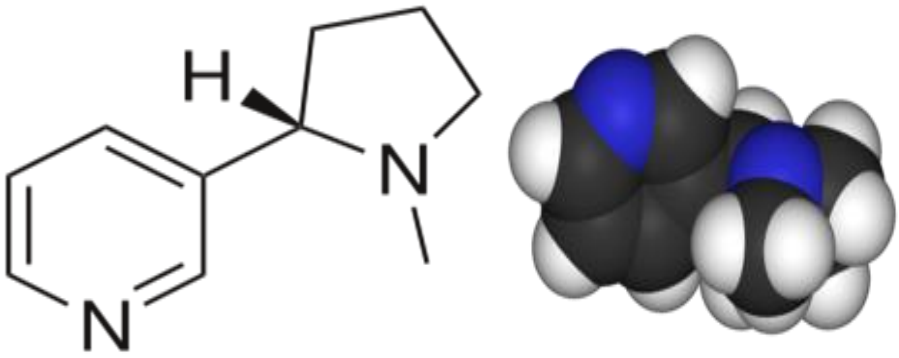
In addition, risk of bladder cancer due to exposure to occupational carcinogens is elevated in genetically determined slow acetylators. In this study of normal male volunteers, 4-aminobi- phenyl-hemoglobin adducts were found to be related to both the quantity and the type of tobacco smoked, as well as to the acetylate or phenotype (independently of smoking habits). The demonstration that both the genetically determined slow acetylate or phenotype and tobacco smoking are independently associated with levels of the carcinogen 4-aminobiphenyl in adducted hemoglobin suggests a single mechanism to explain the contribution of genetic susceptibility and environmental exposure in bladder carcinogenesis.

Tobacco is a carrier for the highly addictive drug nicotine. Once your body gets a taste for nicotine, it can quickly become a life-long addiction, with extremely fatal consequences (18, 43,51,66,71) .

Nicotine is the main drug in all forms of tobacco. Nicotine is one of the most heavily used and most addictive drugs in the world.

1-3-1 Nicotine:

Nicotine is named after the tobacco plant *Nicotiana tabacum*, which in turn is named after the French ambassador in Portugal, Jean Nicot de Villemain, who sent tobacco and seeds to Paris in 1560, presented to the French King,[113] and who promoted their medicinal use. Smoking was believed to protect against illness, particularly the plague. Tobacco is a carrier for the highly addictive drug nicotine.



Systematic (IUPAC) name : 1-[1-Methylpyrrolidin-2-yl]pyridine

Clinical data:

Trade names	Nicorette, Nicotrol

Chemical data:

Molar mass	162.23 g/mol
Chirality	Racemic mixture

Nicotine is a potent parasympathomimetic alkaloid found in the nightshade family of plants (Solanaceae) and is a stimulant drug. Nicotine is a nicotinic acetylcholine receptor (nAChR) agonist,[4][5] except at nAChRα9 and nAChRα10

where it acts as an antagonist.[4] Nicotine is found in the leaves of *Nicotiana rustica* in amounts of 2–14%, the tobacco plant *Nicotiana tabacum*, *Duboisia hopwoodii* and *Asclepias syriaca*It constitutes approximately 0.6–3.0% of the dry weight of tobaccoand is present in the range of 2–7 µg/kg of various edible plants.] It functions as an antiherbivore chemical; consequently, nicotine was widely used as an insecticide in the past[9][10] and neonicotinoids such as imidacloprid are currently widely used.

Nicotine is highly addictive. An average cigarette yields about 2 mg of absorbed nicotine, and in lesser doses of that order, the substance acts as a stimulant in mammals, while high amounts (50–100 mg) can be harmful. This stimulant effect is a contributing factor to the addictive properties of tobacco smoking. Nicotine's addictive nature includes psychoactive effects, drug-reinforced behavior, compulsive use, relapse after abstinence, physical dependence and tolerance.

Limited data is available on the health effects of long term use of nicotine. The general medical position is that nicotine itself poses few health risks, except among certain vulnerable groups.] Nicotine in the form of nicotine replacement products is less of a risk than compared to smoking. Nicotine is associated with a range of harmful effects, including potential birth defects] and at high enough-doses, poisonings. *In vitro* studies have associated it with cancer, but carcinogenicity has not been demonstrated *in vivo*. There is inadequate research to demonstrate that nicotine is associated with cancer in humans. As medicine, nicotine is used to help with quitting smoking and has good safety in this form.] During pregnancy, there are risks to the child later in life for type 2 diabetes, obesity, hypertension, neurobehavioral defects, respiratory dysfunction, and infertility. At high enough doses, nicotine is potentially lethal. It is unlikely that a person would overdose on nicotine through smoking alone. The use of electronic cigarettes, which are designed to be refilled with nicotine-containing e-liquid, has raised concerns over nicotine overdoses, especially with regard to the possibility of young children ingesting the liquids (12, 21,43,46,49) .

Nicotine, alternate molecular skeletal 2D rendering showing the 3D conformation of its ring at lowest energy in actual space.

Nicotine's mood-altering effects are different by report: in particular it is both a stimulant and a relaxant.] First causing a release of glucose from the liver and epinephrine (adrenaline) from the adrenal medulla, it causes stimulation. Users report feelings of relaxation, sharpness, calmness, and alertness.] Like any stimulant, it may very rarely cause the often uncomfortable akathisia . By reducing the appetite and raising the metabolism, some smokers may lose weight as a consequence.

When a cigarette is smoked, nicotine-rich blood passes from the lungs to the brain within seven seconds and immediately stimulates nicotinic acetylcholine receptors; this indirectly promotes the release of many chemical messengers such as acetylcholine, norepinephrine, epinephrine, arginine vasopressin, serotonin, dopamine, and beta-endorphin in parts of the brain. Nicotine also extends the duration of positive effects of dopamine and increases the sensitivity of the brain's reward system to rewarding stimuli. Most cigarettes contain 1–3 milligrams of inhalable nicotine. Studies suggest that when smokers wish to achieve a stimulating effect, they take short quick puffs, which produce a low level of blood nicotine.

Nicotine is unusual in comparison to most drugs, as its profile changes from stimulant to sedative with increasing dosages, a phenomenon known as "Nesbitt's paradox" after the doctor who first described it in 1969.

1-3-1-1Chemistry:

Nicotine is a hygroscopic, colorless oily liquid that is readily soluble in alcohol, ether or light petroleum. It is miscible with water in its base form between 60 °C and 210 °C. As a nitrogenous base, nicotine forms salts with acids that are usually solid and water-soluble. Its flash point is 95 °C and its auto-ignition temperature is 244 °C. Nicotine is readily volatile (vapor pressure 5.5 Pa at 25 °C) and dibasic ($K_{b1} = 1\times10^{-6}$, $K_{b2} = 1\times10^{-11}$).Nicotine is optically active, having two enantiomeric forms. The naturally occurring form of nicotine is levorotatory with a specific rotation of $[\alpha]_D = -166.4°$ ((−)-nicotine). The dextrorotatory form, (+)-nicotine is physiologically less active than (–)-nicotine. (−)-nicotine is more toxic than (+)-nicotine. The salts of (+)-nicotine are usually dextrorotatory. The hydrochloride and sulphate salts become optically inactive if heated in a closed vessel above 180 °C.

On exposure to ultraviolet light or various oxidizing agents, nicotine is converted to nicotine oxide, nicotinic acid (vitamin B3), and methylamine.

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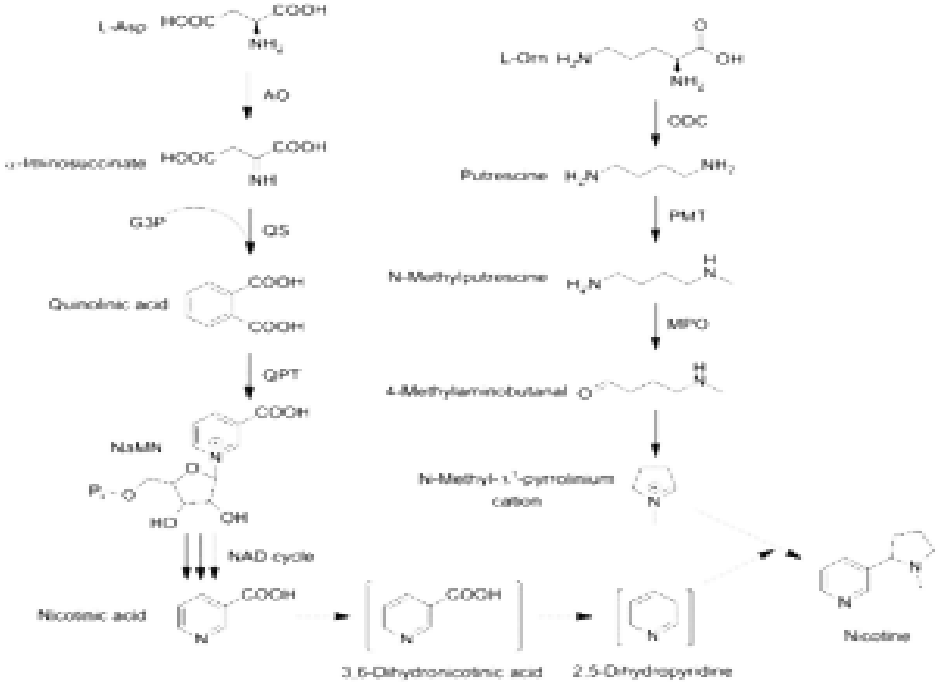
1-3-1-2 Occurrence and biosynthesis:-



1-3-1-3 Nicotine biosynthesis

Nicotine is a natural product of tobacco, occurring in the leaves in a range of 0.5 to 7.5% depending on variety. Nicotine also naturally occurs in smaller amounts in plants from the family Solanaceae (such as potatoes, tomatoes, and eggplant) (43).

The biosynthetic pathway of nicotine involves a coupling reaction between the two cyclic structures that compose nicotine. Metabolic studies show that the pyridine ring of nicotine is derived from niacin (nicotinic acid) while the pyrrolidone is derived from *N*-methyl-Δ^1-pyrrollidium cation. Biosynthesis of the two component structures proceeds via two independent syntheses, the NAD pathway for niacin and the tropane pathway for *N*-methyl-Δ^1-pyrrollidium cation. The NAD pathway in the genus *nicotiana* begins with the oxidation of aspartic acid into α-imino succinate by aspartate oxidase (AO). This is followed by a condensation with glyceraldehyde-3-phosphate and a cyclization catalyzed by quinolinate synthase (QS) to give quinolinic acid. Quinolinic acid then reacts with phosphoriboxyl pyrophosphate catalyzed by quinolinic acid phosphoribosyl transfers (QPT) to form niacin mononucleotide (NaMN). The reaction now proceeds via the NAD salvage cycle to produce niacin via the conversion of nicotinamide by the enzyme nicotinamidase .

The *N*-methyl-Δ^1-pyrrollidium cation used in the synthesis of nicotine is an intermediate in the synthesis of tropane-derived alkaloids. Biosynthesis begins with decarboxylation of ornithine by ornithine decarboxylase (ODC) to produce putrescine. Putrescine is then converted into *N*-methyl putrescine via methylation by SAM catalyzed by putrescine *N*-methyltransferase (PMT). *N*-methylputrescine then undergoes deamination into 4-methylaminobutanal by the *N*-methylputrescine oxidase (MPO) enzyme, 4-methylaminobutanal then spontaneously cyclize into *N*-methyl-Δ^1-pyrrollidium cation.

The final step in the synthesis of nicotine is the coupling between *N*-methyl-Δ^1-pyrrollidium cation and niacin. Although studies conclude some form of coupling between the two component structures, the definite process and mechanism remains undetermined. The current agreed theory involves the conversion of niacin into 2,5-dihydropyridine through 3,6-dihydronicotinic acid. The 2,5-dihydropyridine intermediate would then react with *N*-methyl-Δ^1-pyrrollidium cation to form enantiomerically pure (–)-nicotine(42,43,44,48,49) .

1-3-1-4 adverse effects:

Tobacco use is the leading cause of preventable illness and death in the United States. It causes many different cancers as well as chronic lung diseases such as emphysema and bronchitis, heart disease, pregnancy-related problems, and many other serious health problems.

Limited data is available on the health effects of long term use of nicotine because the majority of nicotine use is with products containing tobacco. Some studies of continued use of nicotine replacement products in smokers who have stopped smoking found no adverse effects from months to several years, while other studies suggest that people with cardiovascular disease are able to tolerate nicotine replacement products for up to 12 weeks. A 2013 report Cancer Research UK found that "The accepted medical position is that while nicotine is highly addictive and comparable to drugs such as heroin or cocaine, it poses little health risks except in certain vulnerable groups". Experimental research suggests that adolescent nicotine use may harm brain development. Children exposed to nicotine may have a number of lifelong health issues. Nicotine in the form of nicotine replacement products is less of a risk than compared to smoking (29,12).

1-3-1-5 Effects of Nicotine:

When a person inhales cigarette smoke, the nicotine in the smoke is rapidly absorbed into the blood and starts affecting the brain within 7 seconds. In the brain, nicotine activates the same reward system as do other drugs of abuse such as cocaine or amphetamine, although to a lesser degree. Nicotine's action on this reward system is believed to be responsible for drug-induced feelings of pleasure and, over time, addiction. Nicotine also has the effect of increasing alertness and enhancing mental performance. In the cardiovascular system, nicotine increases heart rate and blood pressure and restricts blood flow to the heart muscle. The drug stimulates the release of the hormone epinephrine, which further stimulates the nervous system and is responsible for part of the "kick" from nicotine. It also promotes the release of the hormone beta-endorphin, which inhibits pain.

People addicted to nicotine experience withdrawal when they stop smoking. This withdrawal involves symptoms such as anger, anxiety, depressed mood, difficulty concentrating, increased appetite, and craving for nicotine. Most of these symptoms subside within 3 to 4 weeks, except for the craving and hunger, which may persist for months.

Cancer: Possible side effects of nicotine.

- Smoking causes many other types of cancer, including cancers of the throat, mouth, nasal cavity, esophagus, stomach, pancreas, kidney, bladder, and cervix, as well as acute myeloid leukemia.
- Men with prostate cancer who smoke may be more likely to die from the disease than nonsmokers.

Although there is insufficient evidence to classify nicotine as a carcinogen, there is an ongoing debate about whether it functions as a tumor promoter. *In vitro* studies have associated it with cancer, but carcinogenicity has not been demonstrated *in vivo*.[There is inadequate research to demonstrate that nicotine is associated with cancer in humans, but there is evidence indicating possible oral, esophageal, or pancreatic cancer risks. Nicotine replacement products has not been shown to be associated with cancer in the real world. Nicotine as a tool to quitting smoking has a good safety history(6,10).

While no epidemiological evidence directly supports the notion that nicotine acts as a carcinogen in the formation of human cancer, research has identified nicotine's indirect involvement in cancer formation in animal models and cell cultures. Nicotine increases cholinergic signaling and adrenergic signaling in the case of colon cancer, thereby impeding apoptosis (programmed cell death), promoting tumor growth, and activating growth factors and cellular mitogenic factors such as 5-lipoxygenase (5-LOX), and epidermal growth factor (EGF). Nicotine also promotes cancer growth by stimulating angiogenesis and neovascularization. In one study, nicotine administered to mice with tumors caused increases in tumor size (twofold increase), metastasis (nine-fold increase), and tumor recurrence (threefold increase). *N*-Nitrosonornicotine (NNN), classified by the International Agency for Research on Cancer (IARC) as a Group 1 carcinogen, has been shown to form *in vitro* in amounts less than 0.01% of the active substance, when human saliva is incubated with nor nicotine .The IARC has not evaluated pure nicotine or assigned it to an official carcinogenic classification (12,28,50,52,73).

In cancer cells, nicotine promotes the epithelial–mesenchyme transition which makes the cancer cells more resistant to drugs that treat cancer (29,12).

1-3-2 How is smokeless tobacco harmful?

- Smokeless tobacco contains 28 cancer-causing agents (carcinogens).
- Smokeless tobacco is a known cause of cancer; it causes oral and pancreatic cancer.
- Smokeless tobacco is also strongly associated with leukoplakia—a precancerous lesion of the soft tissue in the mouth that consists of a white patch or plaque that cannot be scraped off.
- Smokeless tobacco is associated with recession of the gums, gum disease, and tooth decay.

- Smokeless tobacco use during pregnancy increases the risks for preeclampsia (i.e., a condition that may include high blood pressure, fluid retention, and swelling), premature birth, and low birth weight.
- Smokeless tobacco use by men causes reduced sperm count and abnormal sperm cells.
- Smokeless tobacco contains nicotine, and using it leads to nicotine addiction and dependence.

Adolescents who use smokeless tobacco are more likely to become cigarette smokers (13,49 ,54,60) .

1-4 Heavy Metals:

Heavy metals are defined as metallic elements that have a relatively high density compared to water. With the assumption that heaviness and toxicity are inter-related, heavy metals also include metalloids, such as arsenic, that are able to induce toxicity at low level of exposure .Heavy metals are also considered as trace elements because of their presence in trace concentrations (ppb range to less than 10ppm) in various environmental matrices .

There are 35 metals that concern us because of occupational or residential exposure; 23 of these are the heavy elements or "heavy metals": antimony, arsenic, bismuth, cadmium, cerium, chromium, cobalt, copper, gallium, gold, iron, lead, manganese, mercury, nickel, platinum, silver, tellurium, thallium, tin, uranium, vanadium, and zinc .Interestingly, small amounts of these elements are common in our environment and diet and are actually necessary for good health, but large amounts of any of them may cause acute or chronic toxicity (poisoning). Heavy metal toxicity can result in damaged or reduced mental and central nervous function, lower energy levels, and damage to blood composition, lungs, kidneys, liver, and other vital organs.

Long-term exposure may result in slowly progressing physical, muscular, and neurological degenerative processes that mimic Alzheimer's disease, Parkinson's disease, muscular dystrophy, and multiple sclerosis. Allergies are not uncommon and repeated long-term contact with some metals or their compounds may even cause cancer (International Occupational Safety and Health Information Centre 1999). For some heavy metals, toxic levels can be just above the background concentrations naturally found in nature. Therefore, it is important for us to inform ourselves about the heavy metals and to take protective measures against excessive exposure.

In most parts of the United States, heavy metal toxicity is an uncommon medical condition; however, it is a clinically significant condition when it does occur. If unrecognized or inappropriately treated, toxicity can result in significant illness and reduced quality of life . For persons who suspect that they or someone in their household might have heavy metal toxicity, testing is essential. Appropriate conventional and natural medical procedures may need to be pursued (1, 2,7, 14).

The association of symptoms indicative of acute toxicity is not difficult to recognize because the symptoms are usually severe, rapid in onset, and associated with a known exposure or ingestion (Ferner 2001): cramping, nausea, and vomiting; pain; sweating; headaches; difficulty breathing; impaired cognitive, motor, and language skills; mania; and convulsions. The symptoms of toxicity resulting from chronic exposure (impaired cognitive, motor, and language skills; learning difficulties; nervousness and emotional instability; and insomnia, nausea, lethargy, and feeling ill) are also easily recognized; however, they are much more difficult to associate with their cause. Symptoms of chronic exposure are very similar to symptoms of other health conditions and often develop slowly over months or even years. Sometimes the symptoms of chronic exposure actually abate from time to time, leading the person to postpone seeking treatment, thinking the symptoms are related to something else.

There are many heavy metals in our environment both naturally and from pollution. The term “heavy metal” applies to a group of metals with similar chemical properties. Some of these, including copper, iron and zinc, play important roles in our bodies. Others have no known benefit for health.

Examples of these are lead, which is found in paint in old homes as well as many other sources; arsenic, which can be found in well water and wood products; and mercury, which can build up in fish that we eat. At very high levels, most heavy metals can cause health problems. Luckily, this is very uncommon. For more information on particular heavy metals.

Their bioavailability is influenced by physical factors such as temperature, phase association, adsorption and sequestration. It is also affected by chemical factors that influence speciation at thermodynamic equilibrium, complexation kinetics, lipid solubility and octanol/water partition coefficients . factors such as species characteristics, trophic interactions, and biochemical/physiological adaptation, also play an important role (21,23,24,30,).

1-4-1 Definition of a Heavy Metal:

"Heavy metals" are chemical elements with a specific gravity that is at least 5 times the specific gravity of water. The specific gravity of water is 1 at 4°C (39°F). Simply stated, specific gravity is a measure of density of a given amount of a solid substance when it is compared to an equal amount of water. Some well-known toxic metallic elements with a specific gravity that is 5 or more times that of water are arsenic, 5.7; cadmium, 8.65; iron, 7.9; lead, 11.34; and mercury.

A heavy metal are define as a toxic metal. There is no standard definition assigning metals as heavy metals. Some lighter metals and metalloids are toxic and thus are termed heavy metals, which some heavy metals, such as gold, typically are not toxic. Most heavy metals have a high atomic number, atomic weight and a specific gravity greater than 5.0 Heavy metals include some metalloids, transition metals, basic metals, lanthanides and actinides.

It has been reported that metals such as lead, mercury, cadmium, sometimes chromium. Less commonly, metals including iron, copper, zinc, aluminum, beryllium, cobalt (Co), copper (Cu), chromium (Cr), iron (Fe), magnesium (Mg), manganese (Mn), molybdenum (Mo), nickel (Ni), selenium (Se) and zinc (Zn) and arsenic may be considered heavy metals.

They are essential nutrients that are required for various biochemical and physiological functions. Inadequate supply of these micro-nutrients results in a variety of deficiency diseases or syndromes (41).

Heavy metals are naturally occurring elements that have a high atomic weight and a density at least 5 times greater than that of water. Their multiple industrial, domestic, agricultural, medical and technological applications have led to their wide distribution in the environment; raising concerns over their potential effects on human health and the environment. Their toxicity depends on several factors including the dose, route of exposure, and chemical species, as well as the age, gender, genetics, and nutritional status of exposed individuals. Because of their high degree of toxicity, arsenic, cadmium, chromium, lead, and mercury rank among the priority metals that are of public health significance (29, 30, 35,38).

1-4-2 Occurrence:

In recent years, there has been an increasing ecological and global public health concern associated with environmental contamination by these metals. Also, human exposure has risen dramatically as a result of an exponential increase of their use in several industrial, agricultural, domestic and technological applications . Reported sources of heavy metals in the environment include geogenic, industrial, agricultural, pharmaceutical, domestic effluents, and atmospheric sources.

Environmental pollution is very prominent in point source areas such as mining, foundries and smelters, and other metal-based industrial operations . Although heavy metals are naturally occurring elements that are found throughout the earth's crust, most environmental contamination and human exposure result from anthropogenic activities such as mining and smelting operations, industrial production and use, and domestic and agricultural use of metals and metal-containing compounds.

Environmental contamination can also occur through metal corrosion, atmospheric deposition, soil erosion of metal ions and leaching of heavy metals, sediment re-suspension and metal evaporation from water resources to soil and ground water .Natural phenomena such as weathering and volcanic eruptions have also been reported to significantly contribute to heavy metal pollution. Industrial sources include metal processing in refineries, coal burning in power plants, petroleum combustion, nuclear power stations and high tension lines, plastics, textiles, microelectronics, wood preservation and paper processing plants (1, 30) .

1-4-3 biochemical and physiological functions of heavy metals:

The essential heavy metals exert biochemical and physiological functions in plants and animals. They are important constituents of several key enzymes and play important roles in various oxidation-reduction reactions. Copper for example serves as an essential co-factor for several oxidative stress-related enzymes including catalase, superoxide dismutase, peroxidase, cytochrome c oxidases, ferroxidases, monoamine oxidase, and dopamine β-monooxygenase. Hence, it is an essential nutrient that is incorporated into a number of metalloenzymes involved in hemoglobin formation, carbohydrate metabolism, catecholamine biosynthesis, and cross-linking of collagen, elastin, and hair keratin. The ability of copper to cycle between an oxidized state, Cu(II), and reduced state, Cu(I), is used by cuproenzymes involved in redox reactions . However, it is this property of copper that also makes it potentially toxic because the transitions between Cu(II) and Cu(I) can result in the generation of superoxide and hydroxyl radicals . Also, excessive exposure to copper has been linked to cellular damage leading to Wilson disease in humans .Similar to copper, several other essential elements are required for biologic functioning, however, an excess amount of such metals produces cellular and tissue damage leading

to a variety of adverse effects and human diseases. For some including chromium and copper, there is a very narrow range of concentrations between beneficial and toxic effects. Other metals such as aluminium (Al), antinomy (Sb), arsenic (As), barium (Ba), beryllium (Be), bismuth (Bi), cadmium (Cd), gallium (Ga), germanium (Ge), gold (Au), indium (In), lead (Pb), lithium (Li), mercury (Hg), nickel (Ni), platinum (Pt), silver (Ag), strontium (Sr), tellurium (Te), thallium (Tl), tin (Sn), titanium (Ti), vanadium (V) and uranium (U) have no established biological functions and are considered as non-essential metals (41,1,).

In biological systems, heavy metals have been reported to affect cellular organelles and components such as cell membrane, mitochondrial, lysosome, endoplasmic reticulum, nuclei, and some enzymes involved in metabolism, detoxification, and damage repair . Metal ions have been found to interact with cell components such as DNA and nuclear proteins, causing DNA damage and conformational changes that may lead to cell cycle modulation, carcinogenesis or apoptosis . Several studies from our laboratory have demonstrated that reactive oxygen species (ROS) production and oxidative stress play a key role in the toxicity and carcinogenicity of metals such as arsenic ,cadmium , chromium, lead ,and mercury .]. Because of their high degree of toxicity, these five elements rank among the priority metals that are of great public health significance. They are all systemic toxicants that are known to induce multiple organ damage, even at lower levels of exposure. According to the United States Environmental Protection Agency (U.S. EPA), and the International Agency for Research on Cancer (IARC), these metals are also classified as either “known” or “probable” human carcinogens based on epidemiological and experimental studies showing an association between exposure and cancer incidence in humans and animals(1,30,41).

1-4-4 Beneficial Heavy Metals:

In small quantities, certain heavy metals are nutritionally essential for a healthy life. Some of these are referred to as the trace elements (e.g., iron, copper, manganese, and zinc). These elements, or some form of them, are commonly found naturally in foodstuffs, in fruits and vegetables, and in commercially available multivitamin products Diagnostic medical applications include direct injection of gallium during radiological procedures, dosing with chromium in parenteral nutrition mixtures, and the use of lead as a radiation shield around x-ray equipment Heavy metals are also common in industrial applications such as in the manufacture of pesticides, batteries, alloys, electroplated metal parts, textile dyes, steel, and so forth. Many of these products are in our homes and actually add to our quality of life when properly used (41,30).

1-4-5 Toxic Heavy Metals:

Heavy metals become toxic when they are not metabolized by the body and accumulate in the soft tissues. Heavy metals may enter the human body through food, water, air, or absorption through the skin when they come in contact with humans in agriculture and in manufacturing, pharmaceutical, industrial, or residential settings. Industrial exposure accounts for a common route of exposure for adults. Ingestion is the most common route of exposure in children .Children may develop toxic levels from the normal hand-to-mouth activity of small children who come in contact with contaminated soil or by actually eating objects that are not food (dirt or paint chips) . Less common routes of exposure are during a radiological procedure, from inappropriate dosing or monitoring during intravenous (parenteral) nutrition, from a broken thermometer), or from a suicide or homicide attempt.

As a rule, acute poisoning is more likely to result from inhalation or skin contact of dust, fumes or vapors, or materials in the workplace. However, lesser levels of contamination may occur in residential settings, particularly in older homes with lead paint or old plumbing. The Agency for Toxic Substances and Disease Registry (ATSDR) in Atlanta, Georgia, was established by congressional mandate to perform specific functions concerning adverse human health effects and diminished quality of life associated with exposure to hazardous substances. The ATSDR is responsible for assessment of waste sites and providing health information concerning hazardous substances, response to emergency release situations, and education and training concerning hazardous substances. " The heavy metals arsenic , lead ,mercury, and cadmium , appear on this list(29,59,69).

1-4-6 What is acute heavy metal poisoning?

Acute heavy metal poisoning usually occurs when people are exposed to large amounts of a metal at one time. For example, swallowing a leaded toy can cause a large amount of lead exposure all at once. This generally does not occur from exposures that you are not aware of. Acute exposures are dangerous and can quickly cause serious health effects or death.

Some signs of acute poisoning can be confusion, numbness, nausea and vomiting, and coma.

There is growing evidence that "chronic" or long-term exposure to lower levels of heavy metals also causes health problems. The symptoms of chronic heavy metal poisoning can be severe, but are often less obvious and develop much more slowly over time than the symptoms caused by acute exposure. This is a topic of growing scientific evidence that still needs more research to clarify all the possible health effects. Chronic heavy metal poisoning can be challenging for both health care providers and patients because there are often many more questions than answers. Many of the symptoms of chronic heavy metal toxicity can include:

True chronic heavy metal poisoning is rare. More often, these same symptoms can be caused by other health problems not related to a metal exposure (59, 69).

1-4-7 Heavy metal poisoning and bio toxicity:-

The biotoxic effects of heavy metals refer to the harmful effects of heavy metals to the body when consumed above the bio-recommended limits. Although individual metals exhibit specific signs of their toxicity, the following have been reported as general signs associated with cadmium, lead, arsenic, mercury, zinc, copper and aluminium poisoning: gastrointestinal (GI) disorders, diarrhoea, stomatitis, tremor, hemoglobinuria causing a rust–red colour to stool, ataxia, paralysis, vomiting and convulsion, depression, and pneumonia when volatile vapours and fumes are inhaled .The nature of effects could be toxic (acute, chronic or sub-chronic), neurotoxic, carcinogenic, mutagenic or teratogenic.

Cadmium is toxic at extremely low levels. In humans, long term exposure results in renal dysfunction, characterized by tubular proteinuria. High exposure can lead to obstructive lung disease, cadmium pneumonitis, resulting from inhaled dusts and fumes. It is characterized by chest pain, cough with foamy and bloody sputum, and death of the lining of the lung tissues because of excessive accumulation of watery fluids. Cadmium is also associated with bone defects, viz; osteomalacia, osteoporosis and spontaneous fractures, increased blood pressure and myocardic dysfunctions. Depending on the severity of exposure, the symptoms of effects include nausea, vomiting, abdominal cramps, dyspnea and muscular weakness.

Severe exposure may result in pulmonary odema and death. Pulmonary effects (emphysema, bronchiolitis and alveolitis) and renal effects may occur following subchronic inhalation exposure to cadmium and its compounds. Lead is the most significant toxin of the heavy metals, and the inorganic forms are absorbed through ingestion by food and water, and inhalation. A notably serious effect of lead toxicity is its teratogenic effect.

Lead poisoning also causes inhibition of the synthesis of haemoglobin; dysfunctions in the kidneys, joints and reproductive systems, cardiovascular system and acute and chronic damage to the central nervous system (CNS) and peripheral nervous system (PNS) .Other effects include damage to the gastrointestinal tract (GIT) and urinary tract resulting in bloody urine, neurological disorder and can cause severe and permanent brain damage. While inorganic forms of lead, typically affect the CNS, PNS, GIT and other biosystems, organic forms predominantly affect the CNS. Lead affects children by leading to the poor development of the grey matter of the brain, thereby resulting in poor intelligence quotient (IQ) (Udedi, 2003). Its absorption in the body is enhanced by Ca and Zn deficiencies. Acute and chronic effects of lead result in psychosis.

Zinc has been reported to cause the same signs of illness as does lead, and can easily be mistakenly diagnosed as lead poisoning. Zinc is considered to be relatively non-toxic, especially if taken orally. However, excess amount can cause system dysfunctions that result in impairment of growth and reproduction .The clinical signs of zinc toxicosis have been reported as vomiting, diarrhea, bloody urine, icterus (yellow mucus membrane), liver failure, kidney failure and anemia.

Mercury is toxic and has no known function in human biochemistry and physiology. Inorganic forms of mercury cause spontaneous abortion, congenital malformation and GI disorders (like corrosive esophagitis and hematochezia).

Poisoning by its organic forms, which include monomethyl and dimenthylmecury presents with erethism (an abnormal irritation or sensitivity of an organ or body part to stimulation), acrodynia (Pink disease, which is characterized by rash and desquamation of the hands and feet), gingivitis, stomatitis, neurological disorders, total damage to the brain and CNS and are also associated with congenital malformation.

As with lead and mercury, arsenic toxicity symptoms depend on the chemical form ingested. Arsenic acts to coagulate protein, forms complexes with coenzymes and inhibits the production of adenosine triphosphate (ATP) during respiration. It is possibly carcinogenic in com-pounds of all its oxidation states and high-level exposure can cause death.

Arsenic toxicity also presents a disorder, which is similar to, and often confused with Guillain-Barre syndr-ome, an anti-immune disorder that occurs when the body's immune system mistakenly attacks part of the PNS, resulting in nerve inflammation that causes muscle weakness.

1-4-8 BIOCHEMISTRY OF TOXICITY:

The poisoning effects of heavy metals are due to their interference with the normal body biochemistry in the normal metabolic processes. When ingested, in the acid medium of the stomach, they are converted to their stable oxidation states (Zn^{2+}, Pb^{2+}, Cd^{2+}, As^{2+}, As^{3+}, Hg^{2+} and Ag^{+}) and combine with the body's biomolecules such as proteins and enzymes to form strong and stable chemical bonds. The equations below show their reactions during bond formation with the sulphydryl groups (-SH) of cysteine and sulphur atoms of methionine (-SCH_3).

1-4-8-1 COMMONLY ENCOUNTERED TOXIC HEAVY METALS:

There are 35 metals of concern, with 23 of them called the heavy metals. Toxicity can result from any of these metals. This protocol will address the metals that are most likely encountered in our daily environment. Briefly covered will be four metals that are included in the ATSDR's "Top 20 Hazardous Substances" list. Iron and aluminum will also be discussed even though they do not appear on the ATSDR's list.

1-4- 1-1 Arsenic:

Arsenic is the most common cause of acute heavy metal poisoning in adults and is number 1 on the ATSDR's "Top 20 List." Arsenic is released into the environment by the smelting process of copper, zinc, and lead, as well as by the manufacturing of chemicals and glasses. Arsine gas is a common byproduct produced by the manufacturing of pesticides that contain arsenic.

Arsenic may be also be found in water supplies worldwide, leading to exposure of shellfish, cod, and haddock. Other sources are paints, rat poisoning, fungicides, and wood preservatives. Target organs are the blood, kidneys, and central nervous, digestive, and skin systems (48, 44, 53).

1-4- 1-2 Lead;

Lead is number 2 on the ATSDR's "Top 20 List." Lead accounts for most of the cases of pediatric heavy metal poisoning. It is a very soft metal and was used in pipes, drains, and soldering materials for many years. Millions of homes built before 1940 still contain lead (e.g., in painted surfaces), leading to chronic exposure from weathering, flaking, chalking, and dust. Every year, industry produces about 2.5 million tons of lead throughout the world. Most of this lead is used for batteries. The remainder is used for cable coverings, plumbing, ammunition, and fuel additives. Other uses are as paint pigments and in PVC plastics, x-ray shielding, crystal glass production, pencils, and pesticides. Target organs are the bones, brain, blood, kidneys, and thyroid gland (International Occupational Safety and Health Information Centre 1999; ATSDR ToxFAQs for Lead).

1-4-1-2-1 Environmental Occurrence, Industrial Production and Use:

Lead is a naturally occurring bluish-gray metal present in small amounts in the earth's crust. Although lead occurs naturally in the environment, anthropogenic activities such as fossil fuels burning, mining, and manufacturing contribute to the release of high concentrations. Lead has many different industrial, agricultural and domestic applications. It is currently used in the production of lead-acid batteries, ammunitions, metal products (solder and pipes), and devices to shield X-rays. An estimated 1.52 million metric tons of lead were used for various industrial applications in the United Stated in 2004. Of that amount, lead-acid batteries production accounted for 83 percent, and the remaining usage covered a range of products such as ammunitions (3.5 percent), oxides for paint, glass, pigments and chemicals (2.6 percent), and sheet lead (1.7 percent) .

In recent years, the industrial use of lead has been significantly reduced from paints and ceramic products, caulking, and pipe solder. Despite this progress, it has been reported that among 16.4 million United States homes with more than one child younger than 6 years per household, 25% of homes still had significant amounts of lead-contaminated deteriorated paint, dust, or adjacent bare soil . Lead in dust and soil often re-contaminates cleaned houses, and contributes to elevating blood lead concentrations in children who play on bare, contaminated soil . Today, the largest source of lead poisoning in children comes from dust and chips from deteriorating lead paint on interior surfaces .Children who live in homes with deteriorating lead paint can achieve blood lead concentrations of 20µg/dL or greater(50,63 70, 75).

1-4-1-2-2 Potential for Human Exposure:

Exposure to lead occurs mainly via inhalation of lead-contaminated dust particles or aerosols, and ingestion of lead-contaminated food, water, and paints .Adults absorb 35 to 50% of lead through drinking water and the absorption rate for children may be greater than 50%. Lead absorption is influenced by factors such as age and physiological status. In the human body, the greatest percentage of lead is taken into the kidney, followed by the liver and the other soft tissues such

as heart and brain, however, the lead in the skeleton represents the major body fraction . The nervous system is the most vulnerable target of lead poisoning. Headache, poor attention spam, irritability, loss of memory and dullness are the early symptoms of the effects of lead exposure on the central nervous system.

Since the late 1970's, lead exposure has decreased significantly as a result of multiple efforts including the elimination of lead in gasoline, and the reduction of lead levels in residential paints, food and drink cans, and plumbing systems . Several federal programs implemented by state and local health governments have not only focused on banning lead in gasoline, paint and soldered cans, but have also supported screening programs for lead poisoning in children and lead abatement in housing . Despite the progress in these programs, human exposure to lead remains a serious health problem [. Lead is the most systemic toxicant that affects several organs in the body including the kidneys, liver, central nervous system, hematopoietic system, endocrine system, and reproductive system (9 75,50) ..

Lead exposure usually results from lead in deteriorating household paints, lead in the work place, lead in crystals and ceramic containers that leaches into water and food, lead use in hobbies, and lead use in some traditional medicines and cosmetics. Several studies conducted by the National Health and Nutrition Examination surveys (NHANES) have measured blood lead levels in the U.S. populations and have assessed the magnitude of lead exposure by age, gender, race, income and degree of urbanization. Although the results of these surveys have demonstrated a general decline in blood lead levels since the 1970s, they have also shown that large populations of children continue to have elevated blood lead levels (> 10µg/dL). Hence, lead poisoning remains one of the most common pediatric health problems in the United States today .Exposure to lead is of special concern among women particularly during pregnancy. Lead absorbed by the pregnant mother is readily transferred to the developing fetus . Human evidence corroborates animal findings , linking prenatal exposure to lead with reduced birth weight and preterm delivery , and with neuro-developmental abnormalities in offspring (70).

1-4-1-2-3 Molecular Mechanisms of Toxicity and Carcinogenicity:

There are many published studies that have documented the adverse effects of lead in children and the adult population. In children, these studies have shown an association between blood level poisoning and diminished intelligence, lower intelligence quotient-IQ, delayed or impaired neurobehavioral development, decreased hearing acuity, speech and language handicaps, growth retardation, poor attention span, and anti-social and diligent behaviors. In the adult population, reproductive effects, such as decreased sperm count in men and spontaneous abortions in women have been associated with high lead exposure. Acute exposure to lead induces brain damage, kidney damage, and gastrointestinal diseases, while chronic exposure may cause adverse effects on the blood, central nervous system, blood pressure, kidneys, and vitamin D metabolism (70,75) ..

One of the major mechanisms by which lead exerts its toxic effect is through biochemical processes that include lead's ability to inhibit or mimic the actions of calcium and to interact with proteins. Within the skeleton, lead is incorporated into the mineral in place of calcium. Lead binds to biological molecules and thereby interfering with their function by a number of mechanisms. Lead binds to sulfhydryl and amide groups of enzymes, altering their configuration and diminishing their activities. Lead may also compete with essential metallic cations for binding sites, inhibiting enzyme activity, or altering the transport of essential cations such as calcium [. Many investigators have demonstrated that lead intoxication induces a cellular damage mediated by the formation of reactive oxygen species (ROS). In addition, Jiun and Hseien demonstrated that the levels of malondialdehyde (MDA) in blood strongly correlate with lead concentration in the blood of exposed workers. Other studies showed that the activities of antioxidant enzymes, including superoxide dismutase (SOD), and glutathione peroxidase in erythrocytes of workers exposed to lead are remarkably higher than that in non-exposed workers. A series of recent studies in our laboratory demonstrated that lead-induced toxicity and apoptosis in human cancer cells involved several cellular and molecular processes including induction of cell death and oxidative stress , transcriptional activation of stress genes, DNA damage ,externalization of phosphatidylserine and activation of caspase-3 .

A large body of research has indicated that lead acts by interfering with calcium-dependent processes related to neuronal signaling and intracellular signal transduction. Lead perturbs intracellular calcium cycling; altering releasability of organelle stores, such as endoplasmic reticulum and mitochondria .In some cases lead inhibits calcium-dependent events, including calcium-dependent release of several neurotransmitters and receptor-coupled ionophores in glutamatergic neurons. In other cases lead appears to augment calcium-dependent events, such as protein kinase C and calmodulin (20,15,76) .

Experimental studies have indicated that lead is potentially carcinogenic, inducing renal tumors in rats and mice, and is therefore considered by the IARC as a probable human carcinogen .Lead exposure is also known to induce gene mutations and sister chromatid exchanges , morphological transformations in cultured rodent cells , and to enhance anchorage independence in diploid human fibroblasts . In vitro and in vivo studies indicated that lead compounds cause genetic damage through various indirect mechanisms that include inhibition of DNA synthesis and repair, oxidative damage, and interaction with DNA-binding proteins and tumor suppressor proteins. Studies by Roy and his group showed that lead acetate induced mutagenicity at a toxic dose at the E. coli gpt locus transfected to V79 cells . They also reported that toxic doses of lead acetate and lead nitrate induced DNA breaks at the E. coli gpt locus transfected to V79 cells. Another study by Wise and his collaborators found no evidence for direct genotoxic or DNA-damaging effects of lead except for lead chromate. They pointed out that the genotoxicity may be due to hexavalent chromate rather than lead (50, 63, 70, 57, 23).

1-4-1-3 Mercury:

Number 3 on ATSDR's "Top 20 List" is mercury. Mercury is generated naturally in the environment from the degassing of the earth's crust, from volcanic emissions. It exists in three forms: elemental mercury and organic and inorganic mercury. Mining operations, chloralkali plants, and paper industries are significant producers of mercury. Atmospheric mercury is dispersed across the globe by winds and returns to the earth in rainfall, accumulating in aquatic food chains and fish in lakes.

Mercury compounds were added to paint as a fungicide until 1990. These compounds are now banned; however, old paint supplies and surfaces painted with these old supplies still exist. Mercury continues to be used in thermometers, thermostats, and dental amalgam. Many researchers suspect dental amalgam as being a possible source of mercury toxicity . Medicines, such as mercurochrome and Merthiolate, are still available. Algaecides and childhood vaccines are also potential sources. Inhalation is the most frequent cause of exposure to mercury. The organic form is readily absorbed in the gastrointestinal tract (90-100%); lesser but still significant amounts of inorganic mercury are absorbed in the gastrointestinal tract (7-15%). Target organs are the brain and kidneys (16, 22).

1-4-1-3-1 Environmental Occurrence, Industrial Production and Use:

Mercury is a heavy metal belonging to the transition element series of the periodic table. It is unique in that it exists or is found in nature in three forms (elemental, inorganic, and organic), with each having its own profile of toxicity . At room temperature elemental mercury exists as a liquid which has a high vapor pressure and is released into the environment as mercury vapor. Mercury also exists as a cation with oxidation states of +1 (mercurous) or +2 (mercuric) . Methylmercury is the most frequently encountered compound of the organic form found in the environment, and is formed as a result of the methylation of inorganic (mercuric) forms of mercury by microorganisms found in soil and water.

Mercury is a widespread environmental toxicant and pollutant which induces severe alterations in the body tissues and causes a wide range of adverse health effects. Both humans and animals are exposed to various chemical forms of mercury in the environment. These include elemental mercury vapor (Hg0), inorganic mercurous (Hg+1), mercuric (Hg+2), and the organic mercury compounds. Because mercury is ubiquitous in the environment, humans, plants and animals are all unable to avoid exposure to some form of mercury (22).

Mercury is utilized in the electrical industry (switches, thermostats, batteries), dentistry (dental amalgams), and numerous industrial processes including the production of caustic soda, in nuclear reactors, as antifungal agents for wood processing, as a solvent for reactive and precious metal, and as a preservative of pharmaceutical products. The industrial demand for mercury peaked in 1964 and began to sharply decline between 1980 and 1994 as a result of federal bans on mercury additives in paints, pesticides, and the reduction of its use in batteries (16,22).

1-4-1-3-2 Potential for Human Exposure:

Humans are exposed to all forms of mercury through accidents, environmental pollution, food contamination, dental care, preventive medical practices, industrial and agricultural operations, and occupational operations .The major sources of chronic, low level mercury exposure are dental amalgams and fish consumption. Mercury enters water as a natural process of off-gassing from the earth’s crust and also through industrial pollution . Algae and bacteria methylate the mercury entering the waterways. Methyl mercury then makes its way through the food chain into fish, shellfish, and eventually into humans.

The two most highly absorbed species are elemental mercury (Hg0) and methyl mercury (MeHg). Dental amalgams contain over 50% elemental mercury . The elemental vapor is highly lipophilic and is effectively absorbed through the lungs and tissues lining the mouth. After Hg0 enters the blood, it rapidly passes through cell membranes, which include both the blood-brain barrier and the placental barrier . Once it gains entry into the cell, Hg0 is oxidized and becomes highly reactive Hg2+. Methyl mercury derived from eating fish is readily absorbed in the gastrointestinal tract and because of its lipid solubility, can easily cross both the placental and blood-brain barriers. Once mercury is absorbed it has a very low excretion rate. A major proportion of what is absorbed accumulates in the kidneys, neurological tissue and the liver. All forms of mercury are toxic and their effects include gastrointestinal toxicity, neurotoxicity, and nephrotoxicity (22, 21) .

1-4-1-3-3 Molecular Mechanisms of Mercury Toxicity and Carcinogenicity:

The molecular mechanisms of toxicity of mercury are based on its chemical activity and biological features which suggest that oxidative stress is involved in its toxicity. Through oxidative stress mercury has shown mechanisms of sulfhydryl reactivity. Once in the cell both Hg2+ and MeHg form covalent bonds with cysteine residues of proteins and deplete cellular antioxidants. Antioxidant enzymes serve as a line of cellular defense against mercury compounds. The interaction of mercury compounds suggests the production of oxidative damage through the accumulation of reactive oxygen species (ROS) which would normally be eliminated by cellular antioxidants.

In eukaryotic organisms the primary site for the production of reactive oxygen species (ROS) occurs in the mitochondria through normal metabolism . Inorganic mercury has been reported to increase the production of these ROS by causing defects in oxidative phosphorylation and electron transport at the ubiquinone-cytochrome b5 step .Through the acceleration of the rate of electron transfer in the electron transport chain in the mitochondria, mercury induces the premature shedding of electrons to molecular oxygen which causes an increase in the generation of reactive oxygen species (52.22).

Oxidative stress appears to also have an effect on calcium homeostasis. The role of calcium in the activation of proteases, endonucleases and phospholipases is well established. The activation of phospholipase A2 has been shown to result in an increase in reactive oxygen species through the increase generation of arachidonic acid. Arachidonic acid has also been shown to be an important target of reactive oxygen species .Both organic and inorganic mercury have been shown to alter calcium homeostasis but through different mechanisms. Organic mercury compounds (MeHg) are believed to increase intracellular calcium by accelerating the influx of calcium from the extracellular medium and mobilizing intracellular stores, while inorganic mercury (Hg2+) compounds increase intracellular calcium stores only through the influx of calcium from the extracellular medium . Mercury compounds have also been shown to induce increased levels of MDA in both the livers, kidneys, lungs and testes of rats treated with HgCl2 . This increase in concentration was shown to correlate with the severity of hepatotoxicity and nephrotoxicity .HgCl2-induced lipid peroxidation was shown to be significantly reduced by antioxidant pretreatment with selenium. Selenium has been shown to achieve this protective effect through direct binding to mercury or serving as a cofactor for glutathione peroxidase and facilitating its ability to scavenge ROS .Vitamin E has also been reported to protect against HgCl2-induced lipid peroxidation in the liver (22,16) .

Metal-induced carcinogenicity has been a research subject of great public health interest. Generally, carcinogenesis is considered to have three stages including initiation, promotion, and progression and metastasis. Although mutations of DNA, which can activate oncogenesis or inhibit tumor suppression, were traditionally thought to be crucial factors for the initiation of carcinogenesis, recent studies have demonstrated that other molecular events such as transcription activation, signal transduction, oncogene amplification, and recombination, also constitute significant contributing factors . Studies have shown that mercury and other toxic metals effect cellular organelles and adversely affect their biologic functions. Accumulating evidence also suggests that ROS play a major role in the mediation of metal-induced cellular responses and carcinogenesis (23).

The connection between mercury exposure and carcinogenesis is very controversial. While some studies have confirmed its genotoxic potential, others have not shown an association between mercury exposure and genotoxic damage .In studies implicating mercury as a genotoxic agent, oxidative stress has been described has the molecular mechanism of toxicity. Hence, mercury has been shown to induce the formation of ROS known to cause DNA damage in cells, a process which can lead to the initiation of carcinogenic processes . The direct action of these free radicals on nucleic acids may generate genetic mutations. Although mercury-containing compounds are not mutagenic in bacterial assays, inorganic mercury has been shown to induce mutational events in eukaryotic cell lines with doses as low as 0.5 µM. These free radicals may also induce conformational changes in proteins that are responsible for DNA repair, mitotic spindle, and chromosomal

segregation. To combat these effects, cells have antioxidant mechanisms that work to correct and avoid the formation of ROS (free radicals) in excess. These antioxidant mechanisms involve low molecular weight compounds such as vitamins C and E, melatonin, glutathione, superoxide dismutase, catalase, glutathione peroxidase and glutathione reductase that protect the cells by chelating mercury and reducing its oxidative stress potential .

Glutathione levels in human populations exposed to methylmercury intoxication by eating contaminated fish have been shown to be higher than normal. These studies were also able to confirm a direct and positive correlation between mercury and glutathione levels in blood. They also confirmed an increased mitotic index and polyploidal aberrations associated with mercury exposure. Epidemiological studies have demonstrated that enzymatic activity was altered in populations exposed to mercury; producing genotoxic alterations, and suggesting that both chronic and relatively low level mercury exposures may inhibit enzyme activity and induce oxidative stress in the cells. There is no doubt that the connection between mercury exposure and carcinogenesis is very controversial. However, in-vitro studies suggest that the susceptibility to DNA damage exists as a result of cellular exposure to mercury. These studies also indicate that mercury-induced toxicity and carcinogenicity may be cell-, organ- and/or species- specific (23, 22,52) .

1-4-1-4 Cadmium:

1-4-1-4 -1 Environmental Occurrence, Industrial Production and Use:

Cadmium is a heavy metal of considerable environmental and occupational concern. It is widely distributed in the earth's crust at an average concentration of about 0.1 mg/kg. The highest level of cadmium compounds in the environment is accumulated in sedimentary rocks, and marine phosphates contain about 15 mg cadmium/kg.

Cadmium is frequently used in various industrial activities. The major industrial applications of cadmium include the production of alloys, pigments, and batteries . Although the use of cadmium in batteries has shown considerable growth in recent years, its commercial use has declined in developed countries in response to environmental concerns. In the United States for example, the daily cadmium intake is about 0.4µg/kg/day, less than half of the U.S. EPA's oral reference dose. This decline has been linked to the introduction of stringent effluent limits from plating works and, more recently, to the introduction of general restrictions on cadmium consumption in certain countries (2, ,6).

Cadmium is a byproduct of the mining and smelting of lead and zinc and is number 7 on ATSDR's "Top 20 list." It is used in nickel, cadmium batteries, PVC plastics, and paint pigments. It can be found in soils because insecticides, fungicides, sludge, and commercial fertilizers that use cadmium are used in agriculture. Cadmium may be found in reservoirs containing shellfish. Cigarettes also contain cadmium. Lesser-known sources of exposure are dental alloys, electroplating, motor oil, and exhaust.

Inhalation accounts for 15-50% of absorption through the respiratory system; 2-7% of ingested cadmium is absorbed in the gastrointestinal system. Target organs are the liver, placenta, kidneys, lungs, brain, and bones (Roberts 1999; ATSDR ToxFAQs for Cadmium) (2,5,6)..

Cadmium (Cd) is a toxic environmental metal with both natural and anthropogenic sources. Cd has many important commercial uses and is also present in cigarette smoke.

Research on Cd toxicity has largely focused on occupational exposures and smoking, with experimental studies using appropriate dosing and routes of exposure, showing a broad spectrum of Cd-induced toxicities to many organ systems, including lung . Importantly, declines in smoking and environmental pollution as well as environmental remediation efforts have considerably decreased mean population exposure to Cd and associated health risks.

Inhalation of cadmium (Cd) is associated with lung diseases, but less is known concerning pulmonary effects of Cd found in the diet. Cd has a decades- long half-life in humans and significant bioaccumulation occurs with chronic dietary intake. We exposed mice to low-dose $CdCl_2$ (10 mg/L in drinking water) for 20 weeks, which increased lung Cd to a level similar to that of nonoccupationally exposed adult humans (2, 5, 17,25).

1-4-1-4 -2 Potential for Human Exposure:

The main routes of exposure to cadmium are via inhalation or cigarette smoke, and ingestion of food. Skin absorption is rare. Human exposure to cadmium is possible through a number of several sources including employment in primary metal industries, eating contaminated food, smoking cigarettes, and working in cadmium-contaminated work places, with smoking being a major contributor . Other sources of cadmium include emissions from industrial activities, including mining, smelting, and manufacturing of batteries, pigments, stabilizers, and alloys ,Cadmium is also present in trace amounts in certain foods such as leafy vegetables, potatoes, grains and seeds, liver and kidney, and crustaceans and

mollusks. In addition, foodstuffs that are rich in cadmium can greatly increase the cadmium concentration in human bodies. Examples are liver, mushrooms, shellfish, mussels, cocoa powder and dried seaweed. An important distribution route is the circulatory system whereas blood vessels are considered to be main stream organs of cadmium toxicity. Chronic inhalation exposure to cadmium particulates is generally associated with changes in pulmonary function and chest radiographs that are consistent with emphysema .. Workplace exposure to airborne cadmium particulates has been associated with decreases in olfactory function .Several epidemiologic studies have documented an association of chronic low-level cadmium exposure with decreases in bone mineral density and osteoporosis (17,6) .

Exposure to cadmium is commonly determined by measuring cadmium levels in blood or urine. Blood cadmium reflects recent cadmium exposure (from smoking, for example). Cadmium in urine (usually adjusted for dilution by calculating the cadmium/creatinine ratio) indicates accumulation, or kidney burden of cadmium . It is estimated that about 2.3% of the U.S. population has elevated levels of urine cadmium (>2µg/g creatinine), a marker of chronic exposure and body burden .Blood and urine cadmium levels are typically higher in cigarette smokers, intermediate in former smokers and lower in nonsmokers. Because of continuing use of cadmium in industrial applications, the environmental contamination and human exposure to cadmium have dramatically increased during the past century (25,5,24) .

Cadmium compounds are classified as human carcinogens by several regulatory agencies. The International Agency for Research on Cancer and the U.S. National Toxicology Program have concluded that there is adequate evidence that cadmium is a human carcinogen. This designation as a human carcinogen is based primarily on repeated findings of an association between occupational cadmium exposure and lung cancer, as well as on very strong rodent data showing the pulmonary system as a target site . Thus, the lung is the most definitively established site of human carcinogenesis from cadmium exposure. Other target tissues of cadmium carcinogenesis in animals include injection sites, adrenals, testes, and the hemopoietic system]. In some studies, occupational or environmental cadmium exposure has also been associated with development of cancers of the prostate, kidney, liver, hematopoietic system and stomach]. Carcinogenic metals including arsenic, cadmium, chromium, and nickel have all been associated with DNA damage through base pair mutation, deletion, or oxygen radical attack on DNA.Animal studies have demonstrated reproductive and teratogenicity effects. Small epidemiologic studies have noted an inverse relationship between cadmium in cord blood, maternal blood or maternal urine and birth weight and length at birth (24,6) .

Molecular Mechanisms of Toxicity and Carcinogenicity Cadmium is a severe pulmonary and gastrointestinal irritant, which can be fatal if inhaled or ingested. After acute ingestion, symptoms such as abdominal pain, burning sensation, nausea, vomiting, salivation, muscle cramps, vertigo, shock, loss of consciousness and convulsions usually appear within 15 to 30 min. Acute cadmium ingestion can also cause gastrointestinal tract erosion, pulmonary, hepatic or renal injury and coma, depending on the route of poisoning .Chronic exposure to cadmium has a depressive effect on levels of norepinephrine, serotonin, and acetylcholine . Rodent studies have shown that chronic inhalation of cadmium causes pulmonary adenocarcinomas . It can also cause prostatic proliferative lesions including adenocarcinomas, after systemic or direct exposure (42).

Although the mechanisms of cadmium toxicity are poorly understood, it has been speculated that cadmium causes damage to cells primarily through the generation of , which causes single-strand DNA damage and disrupts the synthesis of nucleic acids and proteins . Studies using two-dimensional gel electrophoresis have shown that several stress response systems are expressed in response to cadmium exposure, including those for heat shock, oxidative stress, stringent response, cold shock, and SOS. In vitro studies indicate that cadmium induces cytotoxic effects at the concentrations 0.1 to 10 mM and free radical-dependent DNA damage .In vivo studies have shown that cadmium modulates male reproduction in mice model at a concentration of 1 mg/kg body weight]. However, cadmium is a weak mutagen when compared with other carcinogenic metals . Previous reports have indicated that cadmium affects signal transduction pathways; inducing inositol polyphosphate formation, increasing cytosolic free calcium levels in various cell types , and blocking calcium channels. At lower concentrations (1–100 µM), cadmium binds to proteins, decreases DNA repair ,activates protein degradation, up-regulates cytokines and proto-oncogenes such as c-fos, c-jun, and c-myc , and induces expression of several genes including metallothioneins , heme oxygenases, glutathione transferases, heat-shock proteins, acute-phase reactants, and DNA polymerase β (69,6, 5, 24,59,56).

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1-4-1-5 Chromium $_{24}$Cr:

1-4-1-5 -1 Environmental Occurrence, Industrial Production and Use:

Chromium (Cr) is a naturally occurring element present in the earth's crust, with oxidation states (or valence states) ranging from chromium (II) to chromium (VI) Chromium compounds are stable in the trivalent [Cr(III)] form and occur in nature in this state in ores, such as Ferro chromite. The hexavalent [Cr(VI)] form is the second-most stable state .Elemental chromium [Cr) does not occur naturally. Chromium enters into various environmental matrices (air, water, and soil) from a wide variety of natural and anthropogenic sources with the largest release coming from industrial establishments. Industries with the largest contribution to chromium release include metal processing, tannery facilities, chromate production, stainless steel welding, and ferrochrome and chrome pigment production. The increase in the environmental concentrations of chromium has been linked to air and wastewater release of chromium, mainly from metallurgical, refractory, and chemical industries. Chromium released into the environment from anthropogenic activity occurs mainly in the hexavalent form [Cr (VI)] . Hexavalent chromium [Cr (VI)] is a toxic industrial pollutant that is classified as human carcinogen by several regulatory and non-regulatory agencies. The health hazard associated with exposure to chromium depends on its oxidation state, ranging from the low toxicity of the metal form to the high toxicity of the hexavalent form. All Cr (VI)-containing compounds were once thought to be man-made, with only Cr(III) naturally ubiquitous in air, water, soil and biological materials. Recently, however, naturally occurring Cr (VI) has been found in ground and surface waters at values exceeding the World Health Organization limit for drinking water of 50 µg of Cr(VI) per liter . Chromium is widely used in numerous industrial processes and as a result, is a contaminant of many environmental systems. Commercially chromium compounds are used in industrial welding, chrome plating, dyes and pigments, leather tanning and wood preservation. Chromium is also used as anticorrosive in cooking systems and boilers(64,35,19) .

1-4-1-5 -2 Potential for Human Exposure:

It is estimated that more than 300,000 workers are exposed annually to chromium and chromium-containing compounds in the workplace. In humans and animals, [Cr (III)] is an essential nutrient that plays a role in glucose, fat and protein metabolism by potentiating the action of insulin. However, occupational exposure has been a major concern because of the high risk of Cr-induced diseases in industrial workers occupationally exposed to Cr (VI) . Also, the general human population and some wildlife may also be at risk. It is estimated that 33 tons of total Cr are released annually into the environment. The U.S. Occupational Safety and Health Administration (OSHA) recently set a "safe" level of 5µg/m3, for an 8-hr time-weighted average, even though this revised level may still pose a carcinogenic risk. For the general human population, atmospheric levels range from 1 to 100 ng/cm3. but can exceed this range in areas that are close to Cr manufacturing.

Non-occupational exposure occurs via ingestion of chromium containing food and water whereas occupational exposure occurs via inhalation. Chromium concentrations range between 1 and 3000 mg/kg in soil, 5 to 800 µg/L in sea water, and 26 µg/L to 5.2 mg/L in rivers and lakes . Chromium content in foods varies greatly and depends on the processing and preparation. In general, most fresh foods typically contain chromium levels ranging from <10 to 1,300 µg/kg. Present day workers in chromium-related industries can be exposed to chromium concentrations two orders of magnitude higher than the general population]. Even though the principal route of human exposure to chromium is through inhalation, and the lung is the primary target organ, significant human exposure to chromium has also been reported to take place through the skin For example, the widespread incidence of dermatitis noticed among construction workers is attributed to their exposure to chromium present in cement .Occupational and environmental exposure to Cr(VI)-containing compounds is known to cause multiorgan toxicity such as renal damage, allergy and asthma, and cancer of the respiratory tract in humans (64,14,19) .

Breathing high levels of chromium (VI) can cause irritation to the lining of the nose, and nose ulcers. The main health problems seen in animals following ingestion of chromium (VI) compounds are irritation and ulcers in the stomach and small intestine, anemia, sperm damage and male reproductive system damage. Chromium (III) compounds are much less toxic and do not appear to cause these problems. Some individuals are extremely sensitive to chromium (VI) or chromium (III), allergic reactions consisting of severe redness and swelling of the skin have been noted. An increase in stomach tumors was observed in humans and animals exposed to chromium (VI) in drinking water. Accidental or intentional ingestion of extremely high doses of chromium (VI) compounds by humans has resulted in severe respiratory, cardiovascular, gastrointestinal, hematological, hepatic, renal, and neurological effects as part of the sequelae leading to death or in patients who survived because of medical treatment (14). Although the evidence of carcinogenicity of chromium in humans and terrestrial mammals seems strong, the mechanism by which it causes cancer is not completely understood.

1-4-1-5 -3 Mechanisms of Toxicity and Carcinogenicity:

Major factors governing the toxicity of chromium compounds are oxidation state and solubility. Cr (VI) compounds, which are powerful oxidizing agents and thus tend to be irritating and corrosive, appear to be much more toxic systemically than Cr (III) compounds, given similar amount and solubility. Although the mechanisms of biological interaction are uncertain, the variation in toxicity may be related to the ease with which Cr(VI) can pass through cell membranes and its subsequent intracellular reduction to reactive intermediates. Since Cr (III) is poorly absorbed by any route, the toxicity of chromium is mainly attributable to the Cr (VI) form. It can be absorbed by the lung and gastrointestinal tract, and even to a certain extent by intact skin. The reduction of Cr (VI) is considered as being a detoxification process when it occurs at a distance from the target site for toxic or genotoxic effect while reduction of Cr (VI) may serve to activate chromium toxicity if it takes place in or near the cell nucleus of target organs. If Cr (VI) is reduced to Cr(III) extracellularly, this form of the metal is not readily transported into cells and so toxicity is not observed. The balance that exists between extracellular Cr (VI) and intracellular Cr (III) is what ultimately dictates the amount and rate at which Cr (VI) can enter cells and impart its toxic effects (64, 6) .

Cr (VI) enters many types of cells and under physiological conditions can be reduced by hydrogen peroxide (H2O2), glutathione (GSH) reductase, ascorbic acid, and GSH to produce reactive intermediates, including Cr (V), Cr (IV), thiylradicals, hydroxyl radicals, and ultimately, Cr (III). Any of these species could attack DNA, proteins, and membrane lipids, thereby disrupting cellular integrity and functions. Studies with animal models have also reported many harmful effects of Cr (VI) on mammals. Subcutaneous administration of Cr (VI) to rats caused severe progressive proteinuria, urea nitrogen and creatinine, as well as elevation in serum alanine aminotransferase activity and hepatic lipid peroxide formation .Similar studies reported by Gumbleton and Nicholls that Cr (VI) induced renal damage in rats when administered by single sub-cutaneous injections. Bagchi et al. demonstrated that rats received Cr (VI) orally in water induced hepatic mitochondrial and microsomal lipid peroxidation, as well as enhanced excretion of urinary lipid metabolites including malondialdehyde (19,64).

Adverse health effects induced by Cr (VI) have also been reported in humans. Epidemiological investigations have reported respiratory cancers in workers occupationally exposed to Cr (VI)-containing compounds .DNA strand breaks in peripheral lymphocytes and lipid peroxidation products in urine observed in chromium-exposed workers also support the evidence of Cr (VI)-induced toxicity to human. Oxidative damage is considered to be the underlying cause of these genotoxic effects including chromosomal abnormalities and DNA strand breaks .Nevertheless, recent studies indicate a biological relevance of non-oxidative mechanisms in Cr(VI) carcinogenesis. Carcinogenicity appears to be associated with the inhalation of the less soluble/insoluble Cr (VI) compounds. The toxicology of Cr(VI) does not reside with the elemental form. It varies greatly among a wide variety of very different Cr(VI) compound. Epidemiological evidence strongly points to Cr (VI) as the agent in carcinogenesis. Solubility and other characteristics of chromium, such as size, crystal modification, surface charge, and the ability to be phagocytized might be important in determining cancer risk(64).

Studies in our laboratory have indicated that chromium (VI) is cytotoxic and able to induce DNA damaging effects such as chromosomal abnormalities [162], DNA strand breaks, DNA fragmentation and oxidative stress in Sprague-Dawley rats and human liver carcinoma cells .Recently, our laboratory has also demonstrated that chromium (VI) induces biochemical, genotoxic and histopathologic effects in liver and kidney of goldfish, carassius auratus].

Various hypotheses have been proposed to explain the carcinogenicity of chromium and its salts, however some inherent difficulties exist when discussing metal carcinogenesis. A metal cannot be classified as carcinogenic per se since its

different compounds may have different potencies. Because of the multiple chemical exposure in industrial establishments, it is difficult from an epidemiological standpoint to relate the carcinogenic effect to a single compound. Thus, the carcinogenic risk must often be related to a process or to a group of metal compounds rather than to a single substance. Differences in carcinogenic potential are related not only to different chemical forms of the same metal but also to the particle size of the inhaled aerosol and to physical characteristics of the particle such as surface charge and crystal modification (19,14,64).

1-4-1-6 Copper:

Copper is an essential trace element that is vital to the health of all living things (humans, plants, animals, and microorganisms). In humans, copper is essential to the proper functioning of organs and metabolic processes. The human body has complex homeostatic mechanisms which attempt to ensure a constant supply of available copper, while eliminating excess copper whenever this occurs. However, like all essential elements and nutrients, too much or too little nutritional ingestion of copper can result in a corresponding condition of copper excess or deficiency in the body, each of which has its own unique set of adverse health effects.

Daily dietary standards for copper have been set by various health agencies around the world. Standards adopted by some nations recommend different copper intake levels for adults, pregnant women, infants, and children, corresponding to the varying need for copper during different stages of life (3,4546,49).

1-4-1-6-1 Copper deficiency and excess health conditions:

If insufficient quantities of copper are ingested, copper reserves in the liver will become depleted and a copper deficiency leading to disease or tissue injury (and in extreme cases, death). Toxicity from copper deficiency can be treated with a balanced diet or supplementation under the supervision of a doctor. On the contrary, like all substances, excess copper intake at levels far above World Health Organization limits can become toxic. Acute copper toxicity is generally associated with accidental ingestion. These symptoms abate when the high copper food source is no longer ingested.

In 1996, the International Program on Chemical Safety, a World Health Organization-associated agency, stated "there is greater risk of health effects from deficiency of copper intake than from excess copper intake." This conclusion was confirmed in recent multi-route exposure surveys. A number of nutrition surveys have indicated that the diets of approximately 25% of adolescents, adults, and people over 65, do not meet the recommended daily nutrient intake for copper. These studies also suggest that long-term acquired copper deficiency is under-diagnosed and is much more common than suspected. Acquired copper deficiency has recently been implicated in adult-onset progressive myeloneuropathy and in the development of severe blood disorders including myelodysplastic syndrome. Fortunately, copper deficiency can be confirmed by very low serum metal and ceruloplasmin concentrations in the blood (72.6).

Other conditions previously linked to copper deficiency include osteoporosis, osteoarthritis, rheumatoid arthritis, cardiovascular disease, colon cancer, and chronic conditions involving bone, connective tissue, heart, and blood vessels. Copper deficiency alters the role of other cellular constituents involved in antioxidant activities, such as iron, selenium, and glutathione, and therefore plays an important role in diseases in which oxidant stress is elevated. In both humans and animals, the major target organs for copper deficiency are the blood and hematopoietic system, the cardiovascular system, connective tissue and bone, the nervous system, and the immune system. A marginal (i.e., 'mild') copper deficiency, believed to be more widespread than previously thought, can impair human health in subtle ways Those affected suffer from lowered resistance to infection, general fatigue, impaired neurological function, and elevated risk for coronary heart disease and osteoporosis (21,72).

1-4-1-6-2 Copper toxicity and exposures:

Copper excess is a subject of much current research. Distinctions have emerged from studies that copper excess factors are different in normal populations versus those with increased susceptibility to adverse effects and those with rare genetic diseases this has led to statements from health organizations that could be confusing to the uninformed. For example, according to a U.S. Institute of Medicine report, the intake levels of copper for a significant percentage of the population are lower than recommended levels. On the other hand, the U.S. National Research Council concluded in its report Copper in Drinking Water that there is concern for copper toxicity in susceptible populations and recommended that additional research be conducted to identify and characterize copper-sensitive populations.

Excess copper intake causes stomach upset, nausea, and diarrhea and can lead to tissue injury and disease. The oxidation potential of copper may be responsible for some of its toxicity in excess ingestion cases. At high concentrations copper is known to produce oxidative damage to biological systems, including peroxidation of lipids or other macromolecules. While the cause and progression of Alzheimer's disease are not well understood research indicates that, among several other key observations, iron, aluminum, and copper accumulate in the brains of Alzheimer's patients. However, it is not yet known whether this accumulation is a cause or a consequence of the disease.

Research has been ongoing over the past two decades to determine whether copper is a causative or a preventive agent of Alzheimer's disease. For example, as a possible causative agent or an expression of a metal homeostasis disturbance, studies indicate that copper may play a role in increasing the growth of protein clumps in Alzheimer's disease brains, possibly by damaging a molecule that removes the toxic buildup of amyloid beta (Aβ) in the brain. There is an association between a diet rich in copper and iron together with saturated fat and Alzheimer's disease. On the other hand, studies also demonstrate potential beneficial roles of copper in treating rather than causing Alzheimer's disease. In humans, the liver is the primary organ of copper-induced toxicity. Other target organs include bone and the central nervous and immune systems. Excess copper intake also induces toxicity indirectly by interacting with other nutrients. For example, excess copper intake produces anemia by interfering with iron transport and/or metabolism.

The identification of genetic disorders of copper metabolism leading to severe copper toxicity (i.e., Wilson disease) has spurred research into the molecular genetics and biology of copper homeostasis (for further information, refer to the following section on copper genetic diseases). Much attention has focused on the potential consequences of copper toxicity in normal and potentially susceptible populations. Potentially susceptible subpopulations include hemodialysis patients and individuals with chronic liver disease. Recently, concern was expressed about the potential sensitivity to liver disease of individuals who are heterozygote carriers of Wilson disease genetic defects (i.e., those having one normal and one mutated Wilson copper ATPase gene) but who do not have the disease (which requires defects in both relevant genes However, to date, no data are available that either support or refute this hypothesis (3, 4,5).

1-4-1-6-3 Acute exposures:

In case reports of humans intentionally or accidentally ingesting high concentrations of copper salts (doses usually not known but reported to be 20–70 grams of copper), a progression of symptoms was observed including abdominal pain, headache, nausea, dizziness, vomiting and diarrhea, tachycardia, respiratory difficulty, hemolytic anemia, hematuria, massive gastrointestinal bleeding, liver and kidney failure, and death. Episodes of acute gastrointestinal upset following single or repeated ingestion of drinking water containing elevated levels of copper (generally above 3–6 mg/L) are characterized by nausea, vomiting, and stomach irritation. These symptoms resolve when copper in the drinking water source is reduced.

Three experimental studies were conducted that demonstrate a threshold for acute gastrointestinal upset of approximately 4–5 mg/L in healthy adults, although it is not clear from these findings whether symptoms are due to acutely irritant effects of copper and/or to metallic, bitter, salty taste. In an experimental study with healthy adults, the average taste threshold for copper sulfate and chloride in tap water, deionized water, or mineral water was 2.5–3.5 mg/L. This is just below the experimental threshold for acute gastrointestinal upset (72, 3).

1-4-1-6-4 chronic exposures:

The long-term toxicity of copper has not been well studied in humans, but it is infrequent in normal populations that do not have a hereditary defect in copper homeostasis. There is little evidence to indicate that chronic human exposure to copper results in systemic effects other than liver injury. Chronic copper poisoning leading to liver failure was reported in a young adult male with no known genetic susceptibility who consumed 30–60 mg/d of copper as a mineral supplement for 3 years. Individuals residing in U.S. households supplied with tap water containing >3 mg/L of copper exhibited no adverse health effects.

No effects of copper supplementation on serum liver enzymes, biomarkers of oxidative stress, and other biochemical endpoints have been observed in healthy young human volunteers given daily doses of 6 to 10 mg/d of copper for up to 12 weeks. Infants aged 3–12 months who consumed water containing 2 mg Cu/L for 9 months did not differ from a concurrent control group in gastrointestinal tract (GIT) symptoms, growth rate, morbidity, serum liver enzyme and bilirubin levels, and other biochemical endpoints. Serum ceruloplasmin was transiently elevated in the exposed infant group at 9 months and similar to controls at 12 months, suggesting homeostatic adaptation and/or maturation of the homeostatic response (4,6).

Dermal exposure has not been associated with systemic toxicity but anecdotal reports of allergic responses may be a sensitization to nickel and cross-reaction with copper or a skin irritation from copper. Workers exposed to high air levels of copper (resulting in an estimated intake of 200 mg Cu/d) developed signs suggesting copper toxicity (e.g., elevated serum copper levels, hepatomegaly). However, other co-occurring exposures to pesticide agents or in mining and smelting may contribute to these effects. Effects of copper inhalation are being thoroughly investigated by an industry-sponsored program on workplace air and worker safety. This multi-year research effort is expected to be finalized in 2011.

1-4-1-6-5 Copper metabolic diseases:

Several rare genetic diseases (Wilson disease, Menkes disease, idiopathic copper toxicosis, Indian childhood cirrhosis) are associated with the improper utilization of copper in the body. All of these diseases involve mutations of genes containing the genetic codes for the production of specific proteins involved in the absorption and distribution of copper. When these proteins are dysfunctional, copper either builds up in the liver or the body fails to absorb copper. These diseases are inherited and cannot be acquired. Adjusting copper levels in the diet or drinking water will not cure these conditions (although therapies are available to manage symptoms of genetic copper excess disease).

The study of genetic copper metabolism diseases and their associated proteins are enabling scientists to understand how human bodies use copper and why it is important as an essential micronutrient. The diseases arise from defects in two similar copper pumps, the Menkes and the Wilson Cu-ATPases The Menkes ATPase is expressed in tissues like skin-building fibroblasts, kidneys, placenta, brain, gut and vascular system, while the Wilson ATPase is expressed mainly in the liver, but also in mammary glands and possibly in other specialized tissues. This knowledge is leading scientists towards possible cures for genetic copper diseases (7, 4, 26).

1-4-1-6-6 Copper cause Cancer:

Cancer is a complicated disease that is not well understood. Some researchers are investigating the possible role of copper in angiogenesis associated with different types of cancers. A copper chelator, tetrathiomolybdate, which depletes copper stores in the body, is under investigation as an anti-angiogenic agent in pilot[113] and clinical trials. The drug may inhibit tumor angiogenesis in hepatocellular carcinoma, pleural mesothelioma, colorectal cancer, head and neck squamos cell carcinoma, breast cancer, and kidney cancer. The copper complex of a synthetic salicylaldehyde pyrazole hydrazone (SPH) derivative induced human umbilical endothelial cell (HUVEC) apoptosis and showed anti-angiogenesis effect in vitro. The trace element copper had been found promoting tumor growth. Several evidence from animal models indicates that tumors concentrate high levels of copper.

Meanwhile, extra copper has been found in some human cancers., therapeutic strategies targeting copper in the tumor have been proposed. Upon administration with a specific copper chelator, copper complexes would be formed at a relatively high level in tumors. Copper complexes are often toxic to cells; therefore tumor cells were killed, while normal cells in the whole body remained alive for the lower level of copper. Some copper chelators get more effective or novel bioactivity after forming copper-chelator complexes. It was found that Cu2+ was critically needed for PDTC induced apoptosis in HL-60 cells The copper complex of salicylaldehyde benzoylhydrazone (SBH) derivatives showed increased efficacy of growth inhibition in several cancer cell lines, when compared with the metal-free SBHs SBHs can react with many kinds of transition metal cations and thereby forming a number of complexes. Copper-SBH complexes were more cytotoxic than complexes of other transitional metals (Cu > Ni > Zn = Mn > Fe = Cr > Co) in MOLT-4 cells, an established human T-cell leukemia cell line. SBHs, especially their copper complexes appeared to be potent inhibitors of DNA synthesis and cell growth in several human cancer cell lines, and rodent cancer cell lines. Salicylaldehyde pyrazole hydrazone (SPH) derivatives were found to inhibit the growth of A549 lung carcinoma cells. SPH has identical ligands for Cu2+ as SBH. The Cu-SPH complex was found to induce apoptosis in A549, H322 and H1299 lung cancer cells (3,4,7,23,36).

1-4-1-7 Cobalt:

Cobalt, $_{27}$Co

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Cobalt is a chemical element with symbol **Co** and atomic number 27. Like nickel, cobalt is found in the Earth's crust only in chemically combined form, save for small deposits found in alloys of natural meteoric iron. The free element, produced by reductive smelting, is a hard, lustrous, silver-gray metal.

Occurrence:-

The stable form of cobalt is produced in supernovas through the r-process(38) It comprises 0.0029% of the Earth's crust and is one of the first transition metals. Free cobalt (the native metal) is not found on Earth because of oxygen in the atmosphere and chlorine in the ocean. Oxygen and chlorine are abundant enough in the upper layers of the Earth's crust to prevent the formation of native metal cobalt. Except as recently delivered in meteoric iron, pure cobalt in native metal form is unknown on Earth (see below). Though the element is of medium abundance, natural compounds of cobalt are numerous. Small amounts of cobalt compounds are found in most rocks, soil, plants, and animals.

In nature, cobalt is frequently associated with nickel, and both are characteristic components of meteoric iron, though cobalt is much less abundant in iron meteorites than nickel. As with nickel, cobalt in meteoric iron alloys may have been well enough protected from oxygen and moisture to remain as the free (but alloyed) metal though neither element is seen in that form in the ancient terrestrial crust. Cobalt in compound form occurs as a minor component of copper and nickel minerals. It is the major metallic component in combination with sulfur and arsenic in the sulfidic cobaltite (CoAsS), safflorite ($CoAs_2$), glaucodot ((Co,Fe)AsS), and skutterudite ($CoAs_3$) minerals. The mineral cattierite is similar to pyrite and occurs together with vaesite in the copper deposits of the Katanga Province. Upon contact with the atmosphere, weathering occurs and the sulfide minerals oxidize to form pink erythrite ("cobalt glance": $Co_3(AsO_4)_2 \cdot 8H_2O$) and spherocobaltite ($CoCO_3$) (14,41).

1-4-1-7-1 Cobalt poisoning:

Cobalt is an essential element for life in minute amounts. The LD_{50} value for soluble cobalt salts has been estimated to be between 150 and 500 mg/kg. the US, the Occupational Safety and Health Administration (OSHA) has designated a permissible exposure limit (PEL) in the workplace as a time-weighted average (TWA) of 0.1 mg/m^3. The National Institute for Occupational Safety and Health (NIOSH) has set a recommended exposure limit (REL) of 0.05 mg/m^3, time-weighted average. The IDLH (immediately dangerous to life and health) value is 20 mg/m^3.

However, chronic cobalt ingestion has caused serious health problems at doses far less than the lethal dose. In 1966, the addition of cobalt compounds to stabilize beer foam in Canada led to a peculiar form of toxin-induced cardiomyopathy, which came to be known as *beer drinkers cardiomyopathy*. After nickel and chromium, cobalt is a major cause of contact dermatitis. Cobalt can be effectively absorbed by charred pigs' bones; however, this process is inhibited by copper and zinc, which have greater affinities to bone char (41,6,5,14).

1-4-1-8 Manganese

Manganese is a chemical element with symbol **Mn** and atomic number 25. It is not found as a free element in nature; it is often found in minerals in combination with iron. Manganese is a metal with important industrial metal alloy uses, particularly in stainless steels.

Manganese, $_{25}$Mn

General properties:	
Name, symbol	manganese, Mn
Pronunciation	/ˈmæŋgəniːz/ ***MANG-gə-neez***
Appearance	silvery metallic

No conclusive studies have been located that show inhalation exposure of humans to manganese resulting in death. Hobbesland et al. (1997a) investigated nonmalignant respiratory diseases as a cause of death in male ferromanganese and

silicomanganese workers. The authors found a slight excess in the numbers of deaths caused by pneumonia for manganese furnace workers, but could not discount other work-related exposures as potential causes of the pneumonia.

A protein called DMT1 is the major transporter in manganese absorption from the intestine, and may be the major transporter of manganese across the blood–brain barrier. DMT1 also transports inhaled manganese across the nasal epithelium. The proposed mechanism for manganese toxicity is that dysregulation leads to oxidative stress, mitochondrial dysfunction, glutamate-mediated excitoxicity, and aggregation of proteins(41,20,4).

1-4-1-9 Nickel :-

Nickel, $_{28}$Ni

General properties

Name, symbol	nickel, Ni
Pronunciation	/ˈnɪkəl/ *NIK-əl*
Appearance	lustrous, metallic, and silver with a gold tinge

Nickel is a chemical element with symbol **Ni** and atomic number 28. It is a silvery-white lustrous metal with a slight golden tinge. Nickel belongs to the transition metals and is hard and ductile. Pure nickel, powdered to maximize the reactive surface area, shows a significant chemical activity, but larger pieces are slow to react with air under standard conditions because an oxide layer forms on the surface and prevents further corrosion (passivation). Even so, pure native nickel is found in Earth's crust only in tiny amounts, usually in ultramafic rocks, and in the interiors of larger nickel–iron meteorites that were not exposed to oxygen when outside Earth's atmosphere (41).

Meteoric nickel is found in combination with iron, a reflection of the origin of those elements as major end products of supernova nucleosynthesis. An iron–nickel mixture is thought to compose Earth's inner core (41). Use of nickel (as a natural meteoric nickel–iron alloy) has been traced as far back as 3500 BCE. Nickel was first isolated and classified as a chemical element in 1751 by Axel Fredrik Cronstedt, who initially mistook the ore for a copper mineral. The element's name comes from a mischievous sprite of German miner mythology, Nickel (similar to Old Nick), that personified the fact that copper-nickel ores resisted refinement into copper. An economically important source of nickel is the iron ore limonite, which often contains 1–2% nickel. Nickel's other important ore minerals include garnierite, and pentlandite. Major production sites include the Sudbury region in Canada (which is thought to be of meteoric origin), New Caledonia in the Pacific, and Norilsk in Russia.

1-4-1-9-1 Occurrence: Ore genesis and Category: Nickel minerals:

Because the ores of nickel are easily mistaken for ores of silver, understanding of this metal and its use dates to relatively recent times. However, the unintentional use of nickel is ancient, and can be traced back as far as 3500 BCE.

Widmanstätten pattern showing the two forms of nickel-iron, kamacite and taenite, in an octahedrite meteorite On Earth, nickel occurs most often in combination with sulfur and iron in pentlandite, with sulfur in millerite, with arsenic in the mineral neckline, and with arsenic and sulfur in nickel galena.[21] Nickel is commonly found in iron meteorites as the alloys Kama cite and taenite.

The bulk of the nickel is mined from two types of ore deposits. The first is laterite, where the principal ore minerals are nickeliferous limonite: (Fe, Ni) O (OH) and garnierite (a hydrous nickel silicate): (Ni, Mg) $3Si_2O_5(OH)$ 4. The second is magmatic sulfide deposits, where the principal ore mineral is pentlandite: (Ni, Fe)9S .Identified land-based resources throughout the world averaging 1% nickel or greater comprise at least 130 million tons of nickel (about the double of known reserves). About 60% is in laterites and 40% in sulfide deposits. On geophysical evidence, most of the nickel on Earth is believed to be in the Earth's outer and inner cores. Kamacite and taenite are naturally occurring alloys of iron and

nickel. For kamacite, the alloy is usually in the proportion of 90:10 to 95:5, although impurities (such as cobalt or carbon) may be present, while for taenite the nickel content is between 20% and 65%. Kamacite and taenite are also found in nickel iron meteorites.

1-4-1-9-2 Biological role:

Although not recognized until the 1970s, nickel plays important roles in the biology of some microorganisms and plants. The plant enzyme urease (an enzyme that assists in the hydrolysis of urea) contains nickel. The NiFe-hydrogenases contain nickel in addition to iron-sulfur clusters. Such [Ni Fe]-hydrogenases characteristically oxidize H 2. A nickel-tetrapyrrole coenzyme, Cofactor F430, is present in the methyl coenzyme M reductase, which powers methanogenic archaea. One of the carbon monoxide dehydrogenase enzymes consists of an Fe-Ni-S cluster. Other nickel-bearing enzymes include a rare bacterial class of superoxide dismutase and glyoxalase I enzymes in bacteria and several parasitic eukaryotic trypanosomal parasites (this enzyme in higher organisms, including yeast and mammals, contains divalent zinc, Zn^{2+}).

Nickel is implicated in the catalytic formation of the hard calcium carbonate plates of the spiny tests on larval sea urchins. Nickel can affect human health through infections by nickel-dependent bacteria. Nickel released from Siberian Traps volcanic eruptions (site of the modern city of Norilsk) is suspected of assisting the growth of *Methanosarcina*, a genus of euryarchaeote archaea that produced methane during the biggest extinction event on record.

1-4-1-9-3 Toxicity:

The major source of nickel exposure is oral consumption. Nickel is found naturally in both food and water, and may be increased by human pollution. For example, nickel-plated faucets may contaminate water and soil; mining and smelting may dump nickel into waste-water; nickel–steel alloy cookware and nickel-pigmented dishes may release nickel into food. The atmosphere may be polluted by nickel metal refining and fossil fuel combustion. Humans may absorb nickel directly from tobacco smoke and skin contact with jewelry, shampoos, detergents, and coins. A less-common form of chronic exposure is through hemodialysis as traces of nickel ions may be absorbed into the plasma from the chelating action of albumin.

The average daily exposure does not pose a threat to human health. Most of the nickel absorbed every day by humans is removed by the kidneys and passed out of the body through urine or is eliminated through the gastrointestinal tract without being absorbed. Nickel is not a cumulative poison, but larger doses or chronic exposure may be toxic, even carcinogenic, and constitute an occupational hazard. In the US, the minimal risk level of nickel and its compounds is set to 0.2 µg/m^3 for inhalation during 15–364 days. Nickel sulfide fume and dust are believed carcinogenic, and various other nickel compounds may be as well , Nickel carbonyl [Ni(CO) 4] is an extremely toxic gas. The toxicity of metal carbonyls is a function of both the toxicity of the metal and the off-gassing of carbon monoxide from the carbonyl functional groups; nickel carbonyl is also explosive in air (54, 23).

People can be exposed to nickel in the workplace by inhalation, ingestion, and contact with skin or eye. The Occupational Safety and Health Administration (OSHA) has set the legal limit (permissible exposure limit) for the workplace at 1 mg/m^3 per 8-hour workday, excluding nickel carbonyl. The National Institute for Occupational Safety and Health (NIOSH) specifies the recommended exposure limit (REL) of 0.015 mg/m^3 per 8-hour workday. At 10 mg/m^3, nickel is immediately dangerous to life and health. In the US, the Tolerable Upper Limit of dietary nickel is 1000 µg/day, while estimated average ingestion is 69–162 µg/day. Large amounts of nickel (and chromium) – comparable to the estimated average ingestion above – leach into food cooked in stainless steel. For example, the amount of nickel leached after 10 cooking cycles into one serving of tomato sauce averages 88 µg.

Sensitized individuals may show a skin contact allergy to nickel known as a contact dermatitis. Highly sensitized individuals may also react to foods with high nickel content. Sensitivity to nickel may also be present in patients with pompholyx. Nickel is the top confirmed contact allergen worldwide, partly due to its use in jewelry for pierced ears. Nickel allergies affecting pierced ears are often marked by itchy, red skin. Many earrings are now made without nickel or low-release nickel to address this problem. The amount allowed in products that contact human skin is now regulated by the European Union. In 2002, researchers found that the nickel released by 1 and 2 Euro coins was far in excess of those standards. This is believed to be the result of a galvanic reaction. Nickel was voted Allergen of the Year in 2008 by the American Contact Dermatitis Society. In August 2015, the American Academy of Dermatology adopted a position statement on the safety of nickel: "Estimates suggest that contact dermatitis, which includes nickel sensitization, accounts for approximately $1.918 billion and affects nearly 72.29 million people.

Reports show that both the nickel-induced activation of hypoxia-inducible factor (HIF-1) and the up-regulation of hypoxia-inducible genes are caused by depletion of intracellular ascorbate. The addition of ascorbate to the culture medium increased the intracellular ascorbate level and reversed both the metal-induced stabilization of HIF-1- and HIF-1α-dependent gene expression(41,32,7) .

1-4-1-9-3 NICKEL EXPOSURE:

Exposures by inhalation, ingestion or skin contact occur in nickel an nickel alloy production plants as well as in welding, electroplating, grinding and cutting operations. Airborne nickel levels in excess of 1 mg·m-3 have been found in nickel refining, in the production of nickel alloys and nickel salts, and in grinding and cutting of stainless-steel. Although in these industries, modern control technologies have markedly reduced exposures in recent years, several million workers worldwide are exposed to airborne nickel and its compounds. Occupational exposure has been shown to give rise to elevated levels of nickel in blood, urine and body tissues, with inhalation as the main route of uptake. Nonoccupational sources of nickel exposure include food, air and water, but the levels found are usually several orders of magnitude lower than those typically found in occ.

1-4-1-9-4 NICKEL EFFECT ON HEALTH:

Human exposure to highly nickel-polluted environments causes a variety of pathologic effects. The toxic effects of nickel on the lung were recognized first by Agricola in the 16th century. Some fatal cases were noted following exposure to nickel carbonyl, and by the early 1930s, nickel was a recognized cause of contact dermatitis. Elevated incidences of lung and nasal cancer in workers exposed to nickel were also observed .In 2008, nickel received the shameful name of "Allergen of the Year" (GILLETTE 2008). According to the dermatologist the frequency of nickel allergy is still growing, and it can't be explained only by fashionable piercing and nickel devices used in medicine (like coronary stents and end prostheses). All those observations caused that the interest in the nickel impact on human health increased .

Like many environmental agents, the toxic effect of nickel is related to the way it gets into an organism. Nickel can enter body *via* inhalation, ingestion and dermal absorption, but the route by which nickel enters cells is determined by its chemical form. For example, fat soluble nickel carbonyl can cross cell membranes by diffusion or through calcium channels), while insoluble nickel particles enter the vertebrate cells by phagocytosis . The main transport protein of nickel in blood is albumin, but nickel can bind also to histidine and α2-macroglobulin , and in this form is distributed throughout the tissues. A number of nickel-binding proteins including α1-antitrypsin, α1-lipoprotein and prealbumin were also described. The highest nickel concentrations are found in the bone, lung, kidney, liver, brain and endocrine glands. Nickel is also found in breast milk, saliva, nails and hair. Transplacental transfer of nickel has been demonstrated in rodents. Nickel does not accumulate in the body; it is excreted in the urine, feces, bile and sweat.

Contact with nickel compounds can cause a variety of adverse effects on human health, such as nickel allergy in the form of contact dermatitis, lung fibrosis, cardiovascular and kidney diseases and cancer of the respiratory tract .. Chronic noncancer health effects may result from long-term exposure to relatively low concentrations of pollutants. Acute health effects generally result from short-term exposure to high concentrations of pollutants and they manifest as a variety of clinical symptoms (nausea, vomiting, abdominal discomfort, diarrhea, visual disturbance, headache, giddiness, and cough). The most common type of reaction to nickel exposure is a skin rash at the site of contact. Skin contact with metallic or soluble nickel compounds can produce allergic dermatitis. This health problem caused by exposure to nickel affects people both at and away from work. Data indicate that women have greater risk for dermatitis, possibly due to a more frequent contact with nickel-containing items: jewelry, buttons, watches, zippers, coins, certain shampoos and detergents, pigments etc. About 10% of women and 2% of men in the population are highly sensitive to nickel. Sensitization to the metal is generally caused by direct and prolonged skin contact with items that release nickel ions.

In large doses (>0.5 g), some forms of nickel may be acutely toxic to humans when taken orally The acute lethality of nickel following oral exposure is dependent on the chemical form of nickel. A fatal case of nickel poisoning was reported for a 21/2- -year-old girl who had ingested 15 g of NiSO4 (3.3 g elemental Ni) and died of a cardiac arrest). Death due to nickel-induced Adult Respiratory Distress Syndrome was reported for a worker spraying nickel using a thermal arc process.

Death occurred after 690 13 days, and a total nickel intake was estimated at nearly 1 g. Nausea, vomiting, abdominal, headache, cough, shortness of breath, and giddiness were reported for 32 workers of an electroplating plant who drank water contaminated with nickel chloride and nickel sulfate (1.63 g·dm-3) . Some studies have also provided information

indicating the deterioration of nickel-induced dermatitis for women following exposure to dietary nickel . Only a small portion of nickel ingested is absorbed by the body. From nickel balance experiments, HORAK and SUNDERMAN (1972) have estimated that about 10% of the nickel in a normal diet is absorbed. Alternatively, other studies have shown that an average nickel resorption from a normal diet is between 20 and 25% .Adverse health effects after oral exposure occurred only when nickel levels exceed many times levels of the metal normally occurred in food or drinking water and are decidedly rare cases.

The most hazardous route of exposure to nickel is by inhalation.. The chemical form of the metal and its solubility is a key determining factor in the toxicity mechanisms. Water-soluble nickel compounds can be absorbed by the lungs into the bloodstream and removed by the kidneys. Insoluble nickel compounds, however, can build up and remain in the lungs for a longer time. Inhalation of soluble nickel causes irritation of the nose and sinuses and can also lead to loss of the sense of smell or perforation of the nasal septum. Long-term exposure may lead to asthma, bronchitis or other respiratory diseases. The most acute nickel poisoning is caused by Ni $(CO)_4$. Exposure to nickel carbonyl can cause headaches, nausea, vomiting, chest pain and breathing problems, in the case of high exposure it may even lead to pneumonia and death. Inhalation of nickel can also cause cancer of the lungs, nose and sinuses.

Cancers of the throat and stomach have also been attributed to inhalation of nickel. Nickel carbonyl and insoluble nickel compounds (Ni_3S_2, NiO) are the forms of nickel responsible for cancer. Epidemiological studies have demonstrated increased mortality from cancers of the lung and nasal cavities in nickel refinery workers who were chronically exposed by inhalation of nickel- containing dusts and fumes. Nickel subsulphide (Ni_3S_2) is a well-known respiratory carcinogen. When it is inhaled, particles of Ni3S2 lodge themselves deep in the lungs, where they reside in contact as a solid with epithelial cells. These particles are cleared by macrophage cells, which remove them through the digestive tract.

Under a condition of high exposure, the macrophage capacity for removal could be perturbed and Ni_3S_2 particles may be taken into epithelial cells by endocytosis. In this way nickel is delivered to the nucleus of lung epithelial cells and can cause a heritable change in chromosomes. It was also demonstrated that Ni_3S_2 induced lesions of both double- and single-stranded DNA in human cells; Ni_3S_2 treatment of cultured HeLa cells induced a 1.5-fold 691 increase in 8-hydroxy-2'-deoxyguanosine compared with a control (10,11). When mice were orally administered acute doses of $NiCl_2$ (from 3.4 to 108.8 mg·kg-1 body weight), a significant dose-dependent increase in DNA damage was observed in comparison with controls.

The results of research by CAVALLO et al. (2003) confirm involvement of nickel ($NiSO_4$) in production of reactive oxygen metabolites and in inhibition of DNA repair at doses comparable to environmental exposures such as concentrations found in biological fluids. It was demonstrated that some nickel complexes such as $[NiCR]_2$+ and [Ni(CR-2H)]2+ bind to the minor groove of double-stranded. Moreover, macro cyclic nickel complex [Ni (CR-2H)]2+ can damage DNA *in vivo* and *in vitro* even in the absence of oxidizing agents. This activity leads to DNA strand breaks and *in vivo* cytotoxicity. Nuclear nickel may be also involved in production of oxygen radicals (•OH, H_2O_2) which could damage DNA.

showed that the level of hydroxyl radical in the Ni-treated group was much higher than in control. Moreover, nickel has been also shown to inhibit DNA repair in a way that may play a role in its toxicity. It has been proposed that nickel may bind to DNA-repair enzymes and generate oxygenfree radicals which cause *in situ* protein degradation. This irreversible damage to the proteins involved in DNA repair, replication, recombination, and transcription could be important for the toxic effects of nickel.

It happens especially when such DNA is associated with tumor suppression genes; under this condition, cancer cells could replicate at a high rate, thus reducing the time available for repair of the DNA damages Often co-exposure to a second carcinogen caused a synergistic cancer increase. For example, intramuscular injection of nickel sulfide with 3,4-benzopyrene in rats produced more sarcomas in shorter time than with nickel sulfide alone .When the transforming potential of soluble nickel(II) was compared with such potential of other carcinogens, the efficiency of immortalization by nickel(II) was found to be higher than that by other carcinogens, including benzo[a]pyrene, diol epoxide, N-methyl- N-nitrosourea or, g or X-rays .

It was also found that nickel(II) chloride with a classical carcinogen, such as UV radiation (UVR) had synergistic effect on skin cancer induction in Skh1 hairless mice). Mice drinking water containing Ni had significantly higher skin concentration of nickel compared with mice having no nickel in water. It was shown that co-carcinogenic effect of oral

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nickel with UVR as a matter of cancer yield and incidence was directly correlated with nickel concentration in the skin. Since humans are exposed to both UVR from sunlight and to nickel *via* environmental exposure, there is a potential co-carcinogenic hazard posed by environmental metals (arsenic, chromium, nickel) with UVR, which may be more serious than the hazard of the metals alone.

Some studies have also revealed that compounds of the essential metals: Mn (II), Mg(II) and Zn(II) given to rats with Ni_3S_2, significantly reduced local tumor incidence in a dose dependent manner. Mg(II) was the strongest and Zn(II) was the weakest inhibitor (9,41,7,,23,34,53,45,10,11) .

2. MATERIALS AND METHODS

2-1 Materials and Methods:

The sample collection from Shagra area in Darfur region (western of Sudan). Samples were collected from different parts of the plants as shown in table (2.1) blew. Take up three weight from sample (2 g)and ached all of them in oven at 500 ^{o}C temperature to overnight to volatile basic element after that analyzed with gas chromatograph to indicate the percentage of nicotine. Weight 0.5 g from sample and solved to prepared to heavy metals determined used Optics parameter (type QA / QC parameters) . The table blow illustrated the results of metals and nicotine .

Table (2.1): show sample types and location

Sample Type	Location	Number of Sample
Tobacco leaves	Farms	2

2.2. Reagents and Equipments:

- Oven for drying the samples.
- Ceramic mortar to grind dry samples.
- Siever to Sieving the grinder.
- Sensitive balance to weight the grinder.
- Toflen beakers 100ml for digestion.
- Buchner funnels with glass wool, and separating funnel.
- Sand bath for heating.
- Glassware (beakers, measuring cylinders, volumetric flasks, conical flasks)
- Polyethylene bottles to keep the solutions.

2.3. Instrumentation:

There were three different instruments used in this study applied for different analysis as follow:

2.3.1. Atomic Absorption Spectroscopy:

Absorption of light is used for measuring the concentration of gases of atoms. Since samples are usually liquids or solids, the analyze atoms or ions must be vaporized in flame or graphite furnace. The atoms absorb ultraviolet or visible light to exited for higher electronic energy levels. The analyze concentration is determine from the amount of light absorbance. Applying Beer- Lambert law directly in atomic absorption spectroscopy is difficult due to variations in the atomization efficiency form the sample matrix ,and non-inform of concentrations, and path length of analyze atoms (in graphite furnace atomic absorption). Concentration measurements are usually determined from a working curve after calibrating the instrument with towards of known concentration.

Methods for the determination of aluminum, calcium, copper, iron, magnesium, manganese, and zinc etc are associated with techniques to concentrate trace metals, involving complexion, digestion and solvent extraction. In this study Atomic Absorption Spectroscopy(Vrian AA 220, Australia 2000) was used for measuring of concentrations of the trace elements (Cu , , Ni, Cr ,Co ,Pb , Mn and Cd) under the following setting :-

2.3.2. High performance liquid chromatography:

High performance liquid chromatography (HPLC) is a quantitative and qualitative method developed in recent years from traditional column chromatography. It becomes as important as gas chromatography for separation of mixtures of organic

components. The main advantage compared with gas chromatography, is that it isn't necessary first to prepare volatile derivatives.

In HPLC, the liquid mobile phase (solvent) is pumped through a column filled with a solid stationary phase. A liquid sample is injected manually into the solvent and washed through the column, individual components being separated on the basis of their relative affinities between the mobile and stationary phases. The time for a particular component to reach the detector is used in identification. In this study the HPLC instrument was used for measuring nicotine concentration in the sample. It has following characterization:-

1. COLUMN: CARBON COLUMN, VP-ODS length 15cm, diameter 4.6 µm.

2. PUMP MODEL: LC-10 AD VP VOLUID CHROMATOGRAPH.

3. SHIMADZU DEGASSER: DGU. 14A

4. SHIMADZU DEGASSER: SOL. 10A

5. SYSTEM CONTROLLER: SCL-10A VP

6. REFRACTIVE INDEX DETECTION: RID-10A

7. DIODE ARRAY DETCTOR: SPD-M-10AVP

8. ALITO INUECTOR: SIL-10AVP

9. COLUMN OVEN: CTO- 10A SVP

10. SOFTE WERE CLASS P.P.

2.4. Preparation of samples:

All samples were treated chemically to allow measuring of concentrations of Cu ,Fe, Zn, Pb, Cd, Ni, Cr and Nicotine content in the parts of plant using different instruments. The parts of tobacco plant were dried and grinded softly in a ceramic mortar and sieved. The powdered kept in a bottles to use in next steps.

2.4.1. Sample preparation for AAS:

The parts of tobacco plant were dried and grinded softly in a ceramic mortar and sieved. 0.5g of the sample was placed into 100 ml Teflon beaker, 6 ml of (1:5) perchloric acid and nitric acid were added and allowed to stand at room temperature overnight for initial the reaction , and subsequently 10 ml of concentration $HClO_4$ were added to the mixture .The Teflon beaker was tightly stopping (to reflux the vapours of the acid) and heated on sand bath at200-250 c for at least 6 hours until complete digestion was achieved , which is indicated by anon – turbid and/or a white solution . Then the solution was evaporated to dryness or semi dryness. The residue was diluted with distilled water into 50 ml volumetric flask. The prepared solution was placed in to 50 ml of polyethylene bottle and stored at room temperature to be ready to used for AAS within 30 days.

2.4-2 Sample preparation of HPLC:-

The dried sample leave was grinded and sieved with 180mm 380mm. mesh and the meal was oven dried at 60^{o}C for 24 hour to a constant dry weight. The milled samples were weighed into 0.5 g lots and extracted with 10 ml 25 Mm sodium phosphate buffer (pH7.7) at 30 ^{o}C for 24 hour with constant agitation . the aqueous extract was filtered under reduced pressure through a What man No.2 filter paper and diluted ten – fold with water . Each extract was filtered through a 0.45Mm Millipore filter and sealed in a screw- capped septum vial to permit automatic injection of a 20-ml a liquor.

2.4.3 Sample preparation of precipitation of alkaloid (nicotine):

Weighed10 gm. from grinded leaves and placed into beaker 250 ml100 gm. of NaOH (%5) solution was added and stirred very well for 15 min .The solution was filtered by using Buchner funnel and glass wool then tobacco leaves were pressed very well by using other beaker. Tobacco was transferred again to beaker 250 ml ,30ml of distilled water was added and stirred and filtered. The filtrated was collected together. The filtrate was transferred to the separation funnel and extracted by 25 ml of ether. The extraction was repeated 3 times .The four filtrated were gathered in conical flask, and

dried by using 1 teaspoon anhydrous potassium carbonate, then filtered .Ether was evaporated on water bath .4ml methanol was added to dissolved the extracted oil . 10ml of saturated picric acid solution was added ,the nicotine depurate crystals was precipitated in ice bath, and then filtered. The product was dried and weighed

2-5 Methods of nicotine analysis used Gas Chromatography:

Analytical line 1 (AOC-20i+s)

Of Rinses with presolvent	1
Of Rinses with solvent (post)	1
Of rinses with sample	2
Plunger speed (suction)	high
Syringe Insertion Speed	high
Injection Mode	normal
Pumping times	5
Injection port Dwell time	0.3 sec
Terminal Air Gap	No
Plunger Washing Speed	High
Washing Volume	8 uL
Syringe suction position	0.0
Syringe Injection position	0.0
Solvent Selection	All A, B, C

Used GC- 2010 (GC program MS- TQ8040)

Column Oven Temp	80.0 ^{o}C
Injection Temp .	250.00 ^{o}C
Injection Mode	Split
Flow Control Mode	Pressure
Pressure	122.0 Kpa
Total flow	50.0 ml/ min
Control flow	1.80 ml/ min
Linear Velocity	49.4 cm/sec
Purge g Flow	6.0 ml/ min
Split Ratio	-1.0
High Pressure Injection	OFF
Carrier Gas Saver	OFF
Splitter Hold	OFF
Solvent Selection	All A, B, C

Oven Temp. Program:

Rate	**Temperature (^{o}C)**	**Hold Time (min)**
-	80.0	1.00
15.00	200.0	1.00
10.00	260.0	1.00
10.00	280.0	2.00

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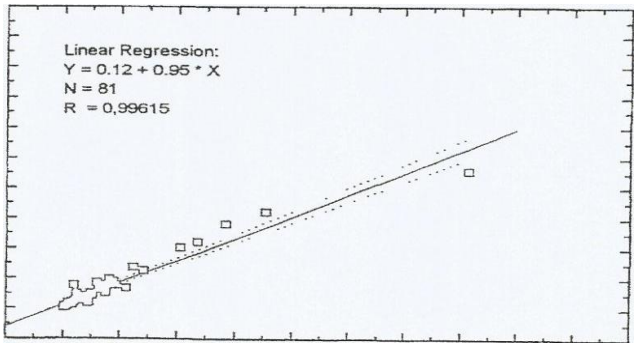
3. RESULTS AND DISCUSSION

Figure (1) show the calibration curves of nicotine were linear across the range of 0-20 ng (r =0.99615) which represented lower concentration levels, and 25 to l000ng *(r* = 0.990) representing higher levels. The intra-day precision value, estimated from relative standard deviation percentages (RSD%) was 4.4% *(N* = 5) and between-run precision was 6.3% (A' =11). In result of nicotine analysis figure 2 show the peak report the height height % percentage of nicotine figure 3show the formula of C10H14N2O CAS 2820 -55-5 Mole Weight 178 , comp name pyridine,3 – (1- methyl-2-pymolidimyl,- 1- oxide (S) –SS Nicotine, 1- oxide SS Nicotine N- oxides SS nicotine 1- N oxide SS Nicotine.

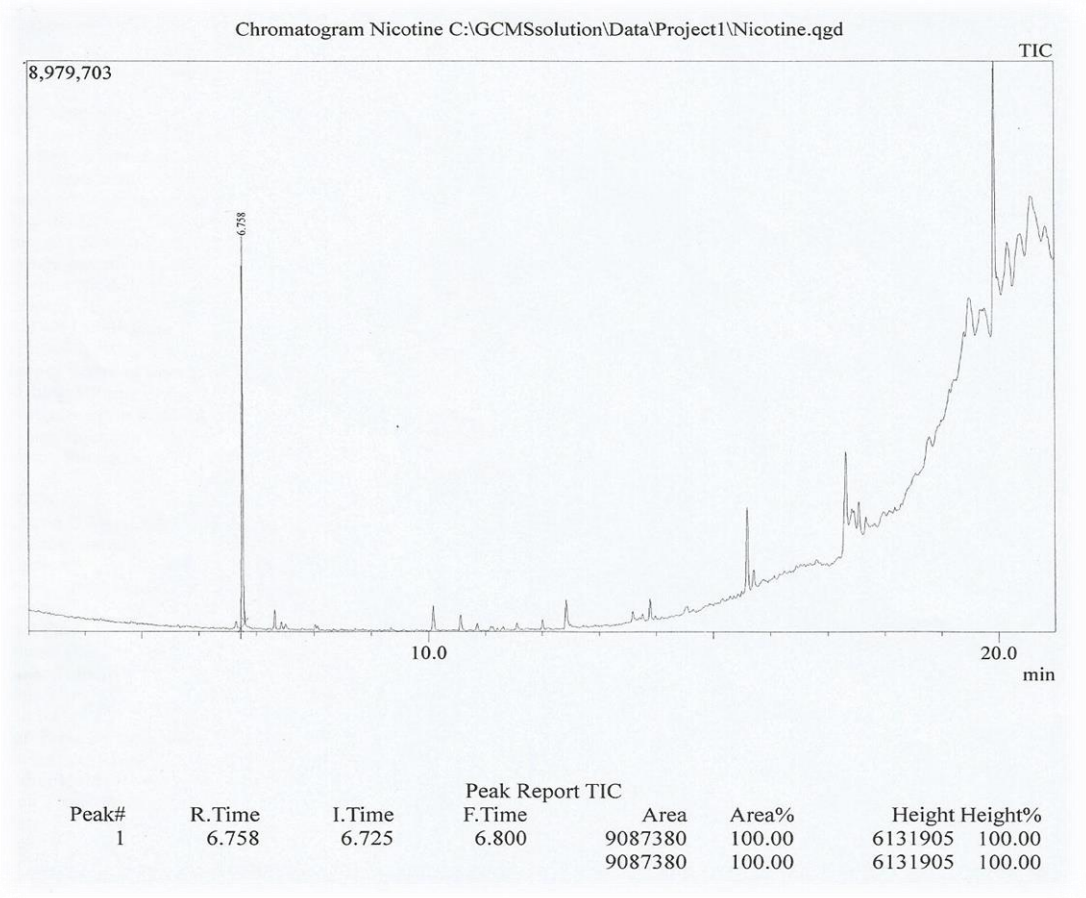
And fig 4 , 5 , illustrated that the raw mode single is 6.758 (452) base peak 40.00 (3069) and spectrum entry 22055 formula C_{10} $H_{14}N_2$ CAS 54 – 11-5 Mol Weight 162 mass peak (101) ,base peak 84.15 (1000).

Nicotine structures:



SIM,concentration of nicotine , µ/m^3

Fig (1) concentration of nicotine at work plase analysis with SIM and SCAN methods



Peak Report TIC

Peak#	R.Time	I.Time	F.Time	Area	Area%	Height	Height%
1	6.758	6.725	6.800	9087380	100.00	6131905	100.00
				9087380	100.00	6131905	100.00

Figure (2) nicotine analysis with GC

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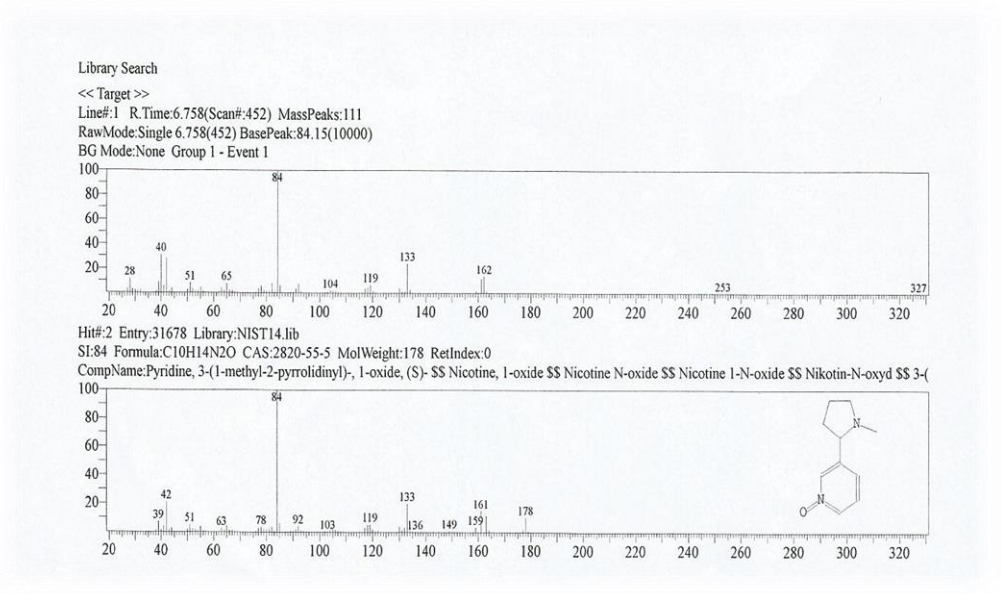

Figure (3) nicotine structure

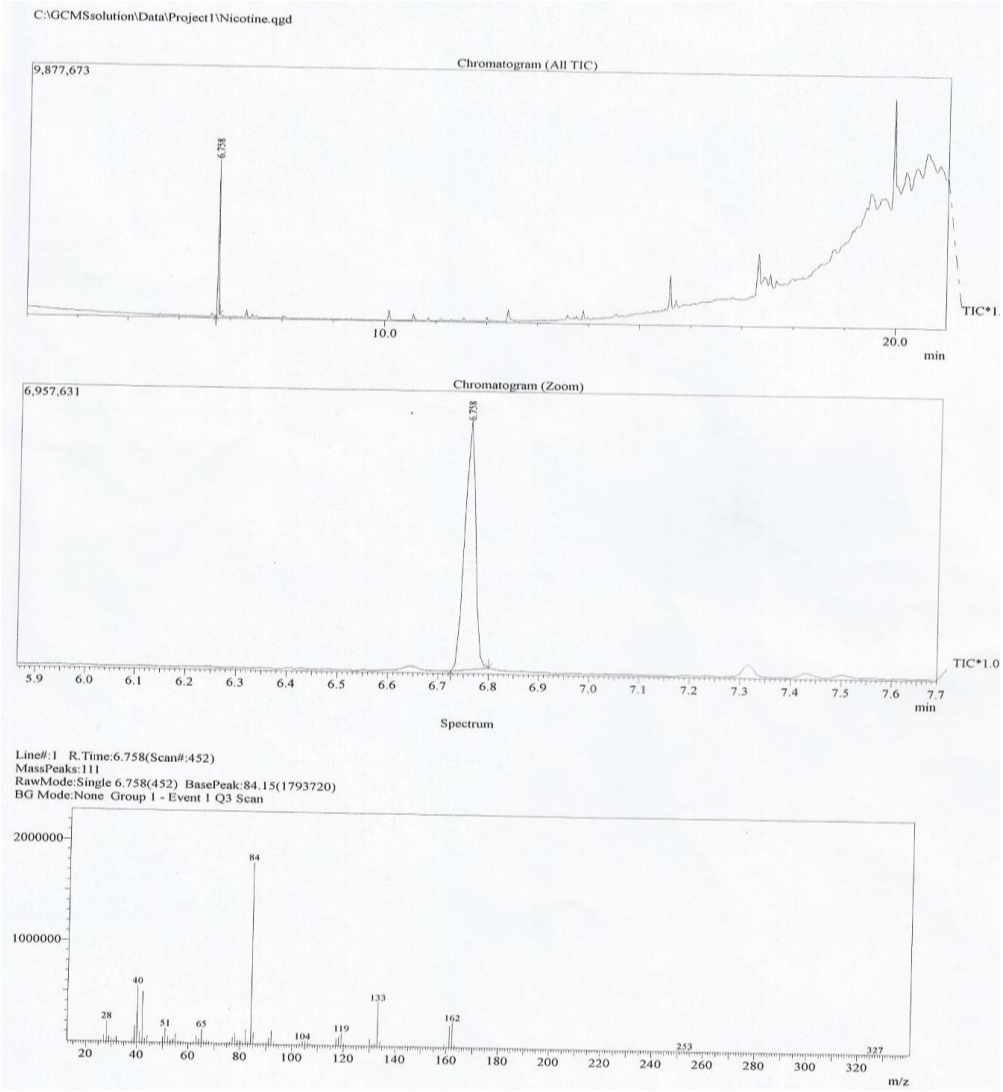

Fig (4) of nicotine analysis with SCAN methods

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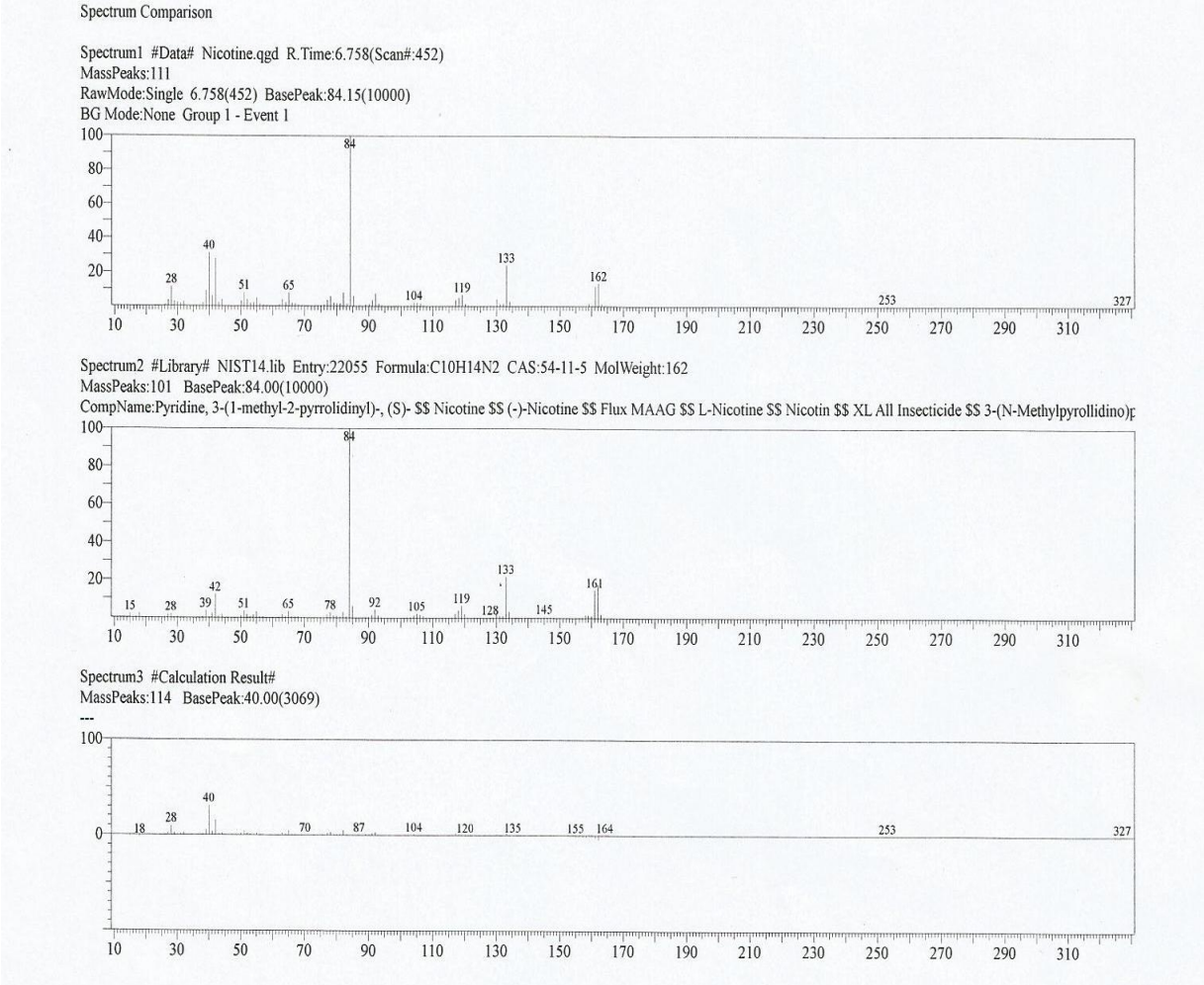

Fig (5) nicotine scan, comp name and calculation result

3-2 Heavy metals results:

Metal content in tobacco depends on soil properties, atmospheric conditions, and requirements for tobacco farming (use of pesticide and fertilizer). Tobacco plants take up lead and arsenic from soil and concentrate these metals in leaves. For this reason, there are large variations in the content of metals in tobacco between countries.

In this study content of Pb , Cr, Cd ,Cu. Ni ,Co and Mn in tobacco leave, the sample observed that maximum permitted levels is Cr higher concentration one and other metal flow respectively Cu , Mn ,Co , Ni , Cd and Pb leave samples of tobacco from Shagra area in Darfur region but all of them are found higher concentration in tobacco. Metal concentrations found in tobacco leaves are shown in Table 2 and Table 3 The study showed significant positive correlation metal content in tobacco contain including heavy metals .

A significant positive correlation was observed between metals content in tobacco. These results suggest the possibility that the higher concentration of metals in tobacco refer to the origin from source.

Table (2-1) concentration of heavy metals

Element	Element Symbol	Wavelength(nm)	Lamp Current Low (mA)	Slit Width (nm)
Cobalt	Co	240.7	12	0.2
Copper	Cu	324.8	6	0.5
Manganese	Mn	279.5	10	0.5
Chromium	Cr	357.9	10	0.5
Cadmium	Cd	228.8	8	I.0
Lead	Pb	217.0	10	0.5
Nickle	Ni	232.0	12	0.2

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Table (2-2) Atomizer / Gas Flow Rate Setup

Element	Element Symbol	Fuel gas flow rate(L/min)	Flam type	Burner Height(mm)	Burner lateral pos.(pulse)	Burner angle (degree)
Cobalt	Co	1.6	Air- C_2H_2	7	0	0
Copper	Cu	1.8	Air- C_2H_2	7	0	0
Manganese	Mn	2	Air- C_2H_2	7	0	0
Chromium	Cr	2,8	Air- C_2H_2	9	0	0
Cadmium	Cd	1.8	Air- C_2H_2	7	0	0
Lead	Pb	2.0	Air- C_2H_2	7	0	0
Nickle	Ni	1.6	Air- C_2H_2	7	0	0

Table (2-3) Measurement Parameters:

Element	Element Symbol	Zero Intercept	Conc . Unit	Repetition Sequence	Pre-spray time(sec)	Integration time(sec)
Cobalt	Co	No	Mg/L	SM-M-M	3	5
Copper	Cu	No	Mg/L	SM-SM	3	5
Manganese	Mn	No	Mg/L	SM-SM	3	5
Chromium	Cr	No	Mg/L	SM- SM	3	5
Cadmium	Cd	No	Mg/L	SM-SM	3	5
Lead	Pb	No	None	SM- SM-	3	5
Nickel	Ni	No	None	SM-M-M	3	5

Table (2-4) Tobacoo : UNK

- 0.2 - 100. 0.000 0.100 0.200 0.300 0.400 0.500 0.600 0.700 0.800

Element	Conc	Abs	BG	WF	VF	DF	CF	Actual conc mL/g
Cd	-0.0611	-0.0049	-0.0286	1.0000000	1.00	1.00	1.000000	-0.0611
Cu	0.0787	0.0000	0.0013	1.000000	1.00	1.00	1.000000	0.0787
Co	-0,0947	-0.0020	-0,0047	1.000000	1.00	1.00	1.000000	-0.0947
Cr	0.0155	0.0045	-0.0259	1.0000000	1.00	1.00	1.000000	0.0155
Mn	0.0156	0.0006	-0.0056	1.000000	1.00	1.00	1.000000	0.0156
Pb	0.1267	0.0010	0.0007	1.000000	1.00	1.00	1.000000	0.1267
Ni	0.0867	0.0017	0.0004	1.000000	1.00	1.00	1.000000	0.0867

3. CONCLUSION

Heavy metal-induced toxicity and carcinogenicity involves many mechanistic aspects, some of which are not clearly elucidated or understood. However, each metal is known to have unique features and physic-chemical properties that confer to its specific toxicological mechanisms of action. This review provides an analysis of the environmental occurrence, production and use, potential for human exposure, and molecular mechanisms of toxicity, genotoxicity, and carcinogenicity of arsenic, cadmium, chromium, lead, and mercury. A comprehensive analysis of published data indicates that heavy metals such as cadmium, chromium, lead, and mercury, occur naturally. However, anthropogenic activities contribute significantly to environmental contamination. These metals are systemic toxicants known to induce adverse health effects in humans, including cardiovascular diseases, developmental abnormalities, neurologic and neurobehavioral disorders, diabetes, hearing loss, hematologic and immunologic disorders, and various types of cancer. The main pathways of exposure include ingestion, inhalation, and dermal contact.

The severity of adverse health effects is related to the type of heavy metal and its chemical form, and is also time- and dose-dependent. Among many other factors, speciation plays a key role in metal toxicokinetics and toxicodynamics, and is highly influenced by factors such as valence state, particle size, solubility, biotransformation, and chemical form. Several studies have shown that toxic metals exposure causes long term health problems in human populations. Although

the acute and chronic effects are known for some metals, little is known about the health impact of mixtures of toxic elements. Recent reports have pointed out that these toxic elements may interfere metabolically with nutritionally essential metals such as iron, calcium, copper, and zinc . However, the literature is scarce regarding the combined toxicity of heavy metals. Simultaneous exposure to multiple heavy metals may produce a toxic effect that is either additive, antagonistic or synergistic.

A recent review of a number of individual studies that addressed metals interactions reported that co-exposure to metal/metalloid mixtures of arsenic, lead and cadmium produced more severe effects at both relatively high dose and low dose levels in a biomarker-specific manner .These effects were found to be mediated by dose, duration of exposure and genetic factors. Also, human co-exposure to cadmium and inorganic arsenic resulted in a more pronounced renal damage than exposure to each of the elements alone [248]. In many areas of metal pollution, chronic low dose exposure to multiple elements is a major public health concern. Elucidating the mechanistic basis of heavy metal interactions is essential for health risk assessment and management of chemical mixtures. Hence, research is needed to further elucidate the molecular mechanisms and public health impact associated with human exposure to mixtures of toxic metals. Future : They are works in progress and should be considered drafts. Any additional information on smokeless tobacco products would be greatly appreciated for the development of future editions.

It is also important to note that in the existing literature on mechanisms of tobacco-induced disease, there is an overbearing focus on nicotine. While this approach is valid, it must be remembered that tobacco smoke contains more than 4000 chemicals and there is an urgent need for studies that examine other components of cigarette smoke as well as whole mainstream and side stream smoke preparations. The research recommended that the tobacco leaves from Shagra area which most of Sudanese preferably used. The result showed that it has a profound impact on the health indicate to high concentration of heavy metals and Nicotine in it.

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