HEAVY METAL CONTAMINATION OF PHARMACEUTICAL PRODUCTS COMMONLY USED IN NIGERIA

BY

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CERTIFICATION

This project has been supervised and approved for submission to the Department of Chemistry, Delta State University, Abraka.

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Dr. Iwegbue, C.M.A **Date**
(Project Supervision)

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DEDICATION

This project work is dedicated to my late grandmother, Madam Onyemali Ossai.

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ABSTRACT

The study evaluates the contamination by heavy metals of pharmaceuticals commonly used in Nigeria. Pharmaceutical samples in sixteen pharmacological groups in different dosage forms were purchased from registered pharmacies and patent medicine shops from Abraka and Obiaruku in Delta State, Nigeria. The samples were digested using a bi acid mixture of HNO_3 and $HCIO_4$ in the ratio of 6:1 and analyzed using the Atomic Absorption spectrometer (AAS) for the presence of lead, chromium, cadmium, zinc, nickel, manganese, iron, copper and cobalt. The result reveals significant contamination by all the metals investigated with the exception of copper and cobalt. The contamination may be attributed to wear and tear of manufacturing machinery, contamination from water, packaging and raw materials. It is recommended that machinery used for the manufacture of pharmaceuticals should be well maintained and replaced were necessary and strict adherence to good manufacturing practice (GMP) as required by regulatory agencies.

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CHAPTER ONE

INTRODUCTION

1.1 Background to the Study

Twenty-four percent of global disease burden for adults and children under the age of five is caused by environmental exposures (WHO, 2008). In Nigeria, forty-four percent of deaths is traceable to poor environment (Babajide Alo, 2008).

A potent but often ignored environmental factor that affects all quality of life is the inevitable use of pharmaceutical products. Pharmaceuticals are products of medical and industrial advances used for the diagnosis, treatment and prevention of diseases and ailments, which have replaced to a large extent our reliance on crude herbal preparations.

Most pharmaceutical products are made by the synthesis of chemicals both organic and inorganic. Relatively few are derived from plants and animal sources. As a result, many of the most effective pharmaceuticals and diagnostic agent that have been introduced into medicine over the last few decades are metal based. Today drugs employing heavy metals have been extremely effective for cancer, treatment and other life threatening diseases (CHMR, 2008).

A majority of the population invariably use pharmaceutical products almost daily either as food supplements, analgesic, analgesic, antihypentensive etc. sustained exposure of our body to heavy metals will lead ultimately to the accumulation of toxins in our tissues and organs causing nutritional deficiencies, hormonal imbalances, neurological disorders, autoinimune reactions, cancer, and other chronic pathological conditions (Martin *et al,* 2008).

Infact heavy metal toxicity may be root of many health disorders today. Heavy metal ion produces large quantities of free radical compounds, which destroys lipids, proteins and DNA in the cellular system. Free radicals damage our cells, prevent cell stabilization and create an overly acidic terrain in the body (Choi *et al,* 1999). Also heavy metals cause the body to produce cholesterol and prevent the absorption of calcium. And, the more free heavy

metal ions in the body, the more build-up of acidic waste and hence the more calcium is deposited in the arteries (Alabaster and Lloyd, 1980).

Bryan (1976) reported that the threat heavy metal toxins pose to our health is beginning to gain attention. However, heavy metal toxicity is a condition that often goes overlooked in traditional medical diagnosis. While it is rare for an individual to experience a disease or health condition solely from a heavy metal toxin, it is reasonable to conclude that these toxins exert a dramatic effect on the health of an individual and contribute to the progression of many different debilitating conditions. Moreover, taking ill and our ability to over from one is almost always traceable to biochemical reactions in the body with heavy metals playing a significant role.

Moreover, heavy metals can interact with pharmaceuticals in the body to alter their pharmacological effects (Stargat *et al,* 1989). The interaction of aluminum ions with tetracycline to reduce the absorption of the latter is well known. Hence physical and pharmacological interactions between drugs and heavy metals may lead to altered biological actions, prolonged side effects tough delayed tubular excretion and biotransformation. Such interactions may also results in anaphylactic reactions and other untoward forms of drug effects leading to cumbersome management of diseases and hospital induced illness (Woods *et al*, 2002).

The term “heavy metal contaminants in pharmaceuticals” may seem a misnomer in some cases considering the fact that heavy metals are currently used in pharmaceuticals for therapeutic purposes. For example, aluminium as the hydroxide is used as an antacid for relieving the symptoms of peptic and other forms of hyperacidity. Arsenic, selenium, and copper are employed as nutritional supplements because of the belief that they have a functional role in haemoglobin formation. However, heavy metals found in pharmaceutical

products where they are not expected to play any therapeutic role and in excess of the desired quantity when used therapeutically may be regarded is a contaminant.

In tablets, contamination may occur from raw materials, active ingredients, excipients e.g. corn starch used as binders, magnesium stearate used as lubricants, disintegrants and lactose used as fillers. Contamination may also occur during granulation including sieving, granular flow from hopper to the die for compression. The sieve, hopper, die and punch in a tabletting machine are all made of stainless steel and therefore potential sources of contamination.

Liquid preparations, creams, ointments, liniments e.t.c may be contaminated by the raw materials,, active ingredients and excipients (sugar, suspending agents, ointment bases usually petroleum jelly, emulsiflers, water, preservatives, oil, surfactants e.t.c).

Contamination of pessaries, suppositories may occur from the raw materials, active ingredients, preservatives, moulders e.t.c. Injectables may be contaminated from the raw materials, active ingredients, preservatives, water and during ampoule sealing (Evans and Tom 2000).

Packaging materials like metal foils, glass bottles plastic containers, caps are also potential sources of heavy metal Contamination.

1.2 Statement of Research Problem

The manufacture of pharmaceutical products starts from the petrochemical industries where pharmaceutical raw materials like acetic anhydride used in the synthesis of aspirin, aniline, toluene e.t.c are synthesized. The next stage is ‘the synthesis of the active ingredient like chloroquine, paracetamol e.t.c and the manufacture of excipients like cornstarch. Lastly is the formulation and manufacture of pharmaceutical products and storage for patients and patrons. In these manufacturing plants, pharmaceutical comes in direct contact with steel,

aluminum and other metal products where contamination by heavy metals becomes highly probable.

1.3 Research Aims and Objectives

This research study is aimed at:

i. Determining the presence of some heavy metal contaminants in some commonly used pharmaceutical products.

ii. Establishing whether the contamination is within the acceptable limits established by relevant regulatory agency like National Agency for Food and Drug Administration and Control (NAFDAC).

iii. Providing a bird - eye view of the safety of pharmaceuticals commonly used in Nigeria.

1.4 Justification of the Study

From the uterus to birth until death, we consume pharmaceutical products, which are meant for the diagnosis, treatment and prevention of diseases and ailments.

Routinely, quality control measures in the manufacture of pharmaceuticals include qualitative and quantitative analysis of raw materials and finished products, water analysis (usually microbiological) weight variation, disintegration/dissolution and friability rates in tablets (Peters and Juelin, 2001). Analysis of heavy metals is completely ruled out.

Considering its significance to health, analysis of heavy metals in pharmaceuticals will further ensure good manufacturing practice (GMP), safety and quality of pharmaceutical products used in Nigeria.

1.5 Scope and Delimitation of Study

The contamination of pharmaceutical products by heavy metals undermines its safety and quality. This study intends to assess the presence of heavy metals in some commonly used pharmaceuticals spread in diverse therapeutic classes.

Dearth of reagents and analytical tools, paucity of funds constitute serious impediment in the study and ultimately influence the choice of analytical procedures used in carrying out this research.`

CHAPTER TWO

LITERATURE REVIEW

2.1 Sources of Heavy Metal Contamination of Pharmaceuticals

Despite stringent quality control standards regulated by the National Agency for Food, Drug Administration and Control, and highly trained quality control officers, microscopic metal contaminant have continued to go unnoticed in pharmaceuticals. The most common source of contamination is processing equipment that generates wear particles, but metal particles can also originate from contaminated raw materials (Mary and Kent, 2010). Manufacturing equipment for pharmaceuticals are mainly made up of stainless steel which contains at least 10% chromium as well as varying amount of various alloying elements. (Anselisca *et al,* 2009).

Water used in granulation for tableting and liquid, and semi- solid preparations are veritable sources of contamination of pharmaceuticals by heavy metals (Koller, 1995).

Additives such as preservatives, sweeteners, colourants, fillers, lubricants, binders, disintegrants have also been identified as potential sources of metal contaminants of drugs. (Obi *et al,* 2006).

Packaging materials, especially poorly washed glass bottles and plastic bottles, aluminum foils may serve as sources of contaminant (Alu, 2004).

2.2 Toxicology of Heavy Metals

The adverse environment effects of heavy metals have been of grave concern to researchers. However, heavy metal contamination of pharmaceutical products come to the fore recently probably because of the embarrassing paradoxical effect such contamination evokes. Thus routine testing of raw and auxiliary materials, active ingredients used in the manufacture of pharmaceuticals, as well as intermediate and end products for heavy metals from a wide range of contamination sources is mandatory (Fullman *et al,* 2003). This

becomes imperative as new metal - based pharmaceutical products for the treatment of a wide range of human and animal diseases and conditions, including cancer, arthritis, microbial infections, diabetes and heart and circulatory diseases are been developed (CHMR, 2000).

Exposure to low level of toxic metals such as mercury, lead, arsenic, aluminum, copper, iron can effect human health regardless of whether they are present in substances we ingest or apply (Dalas, 1972). These effects ranges from simple gastrointestinal disturbances like nausea and vomiting to severe emotional and cognitive dysfunction. Metal toxins have the ability to impair not just a single cell or tissue, but many of the body systems that are responsible for our behavior, mental health and proper physiological functioning that we depend on for sustained life. If undetected these metal toxins can cause immeasurable suffering for any afflicted individual. Fortunately there are avenues that an affected person can pursue to detoxify heavy metal already in the body usually through chalation method with EDTA (Adams et al, 1983).

Lead

Lead is number two on the ATSDR'S 'TOP 20 LIST' Lead accounts for most of the cases of paediatric heavy metal poisoning like autism (Roberts 1999). Lead has been known to accelerates ageing process, mental decline years 'after exposure. Researchers have demonstrated the exact mechanism by which lead ions (Pb^{2+}) impair brain functions. Exposure to lead during early childhood at even later in life affects the release of critical neurotransmitters by affecting the levels of several key proteins involved in the formation of synapses (Tomos Guilarie, 2011).

High level of lead in women and higher level in men delays pregnancy in couples seeking to have children (Germaine Bade, 2011).

At the concentration of 30 - 50mcg/dL in the blood, lead can induce anaemia by interference with the heme synthesis and increasing erythecyte membrane fragility and decreases red cell severely (Michael, 2010).

In the kidney, high lead exposure (concentration if up to 80 mcg/dL) may result in renal intestitial fibrosis lead nephropathy and may ulter uric acid excretion resulting in gouty arthritis (Micheal, 2010).

High - dose lead exposure is a recognized risk factor for still birth or spontaneous abortion. In males, blood lead concentration higher than 40 mcg/dl have been associated with aberrant sperm production (Kadzing, 2010).

In the gastrointestinal system, lead poisoning may cause loss of appetite, constipation and less commonly diarrhea. It may also affect the teeth leading to 'gingival red lines' (Kadzing *et al*, 2010).

Epidemiological studies indicate that lead exposure elevates blood pressure in susceptible individuals. Also low or moderate lead exposure is risk factors in cardiovascular mortality.

Cadmium

Cadmium causes severe kidney damage including renal failure with continuous exposure. Cadmium is a human carcinogen and is listed as a group 1 carcinogen by 1 A R C. 2 -7% of ingested cadmium is absorbed through the gastrointestinal tract. Target organs are the liver, placenta, kidneys, lungs, brains and bones (Roberts, 1999).

Chromium

The toxicity and carcinogenicity of chromium (iv) have been known for a long time. Because of specific transport mechanisms only limited amount of chromium (III) enter the cells. Several invitro studies indicated that high concentration of chromium (III) in the cell can lead to DNA damage (Ellenhom *et al* 1997). Acute oral toxicity ranges between 1900 and

3300mg/kg (Godfrank *et al*, 2002). The proposed beneficial effects of chromium (III) and the use of dietary supplements yielded some controversial results but recent reviews suggest that moderate uptake of chromium (III) through dietary supplements has no risk (Godfrank *et al*, 2002).

World Health Organization recommended maximum allowance concentration in drinking water for chromium (VI) is 0.005 mg/kg (WHO, 2001).

Hexavalent chromium is one of those substances whose use is restricted by the European Restriction of Hazardous Substances Directive. The LD_{50} for chromium (VI) ranges between 50 and 150 mg/kg (Ball *et al*, 2007). The acute toxicity of chromium (VI) is due to its strong oxidative properties. After it reaches the blood stream, it damage the kidneys, the liver and blood cells through oxidative reactions. Haemolysis, kidney and liver failure are the result of these damages.

Its genotoxicity may be due to the highly reactive hydroxyl radicals and the reactive radicals which are by-products of the reduction of chromium (VI) to chromium (IV). The second process may be due to direct building of chromium (V) produced by reduction in the cell and chromium (IV) compounds to the DNA.

Chromate salts (chromate) also causes allergic skin reactions in some people (Kaye *et al*, 2003).

Nickel

Nickel is a metal of widespread distribution in the environment with many commercial and industrial uses. Nickel and nickel compounds belong to the classic noxious agents encountered in industrial but are also known to affect non- occupationally exposed individuals. Although, it has limited absorption in the intestinal track, dietary intake and ingested nickel is said to be the most important route of exposure (Campbell *et al*, 2007). The

ingestion of nickel is dependent on its physicochemical form with water soluble forms (chloride, nitrate, sulphate) being most readily absorbed.

Nickel is an ubiquitous metal frequently responsible for allergic skin reaction and has been reported to be one of the most common of allergic contact dermatitis (Cavani *et al,* 2005). In clinical cases, allergic contact hypersensitivity to nickel develops much more readily in inflamed skin than normal skin. Approximately 8 - 10% of women and 1 -2% of men demonstrate a sensitivity to nickel (Kitaurel et al, 2005). Several studies have shown that oral exposure to nickel may invoke an eruption or worsening of eczema in nickel sensitive individuals.

Epidemiological investigations and experimental studies have demonstrated that nickel is carcinogenic. The bioavailability of nickel and the presence of constituents that promote oxygen free-radicals reaction evidently influence the carcinogenicity of nickel oxides and related compounds with ‘vi soluble, nickel compounds being the most potent (Costa et al, 1999). A dietary intake of 187 - 302 mg/day may be considered safe (Lreszezynskar *et al*, 2000).

Manganese

Manganese is located largely in the mitochondria, the highest concentration are found in the liver, thyroid, pituitary, pancreas, kidneys and bone. The total manganese content of a 70kg man is approximately 12 - 20mg. A daily intake of 2.5 to 7mg meets human needs (Hegsted, 2006).

Manganese activates numerous enzymes in the body and is infact a constituents of some enzymes. Manganese is involved in fatty acid metabolism, protein synthesis and in neurological functions. Manganese is also involved in normal thyroid function (Preiffer, 1999).

Mild manganese toxicity produces manganese psychosis and includes the following symptoms: asthenia, anorexia, insomnia, muscular pains, mental excitement, hallucination, unaccountable laughter, impaired memory and compulsive actions. Moderate toxicity symptoms include speech disorder, clumsy movements, abnormal gait, poor balance, hyper reflexia in the lower limbs and fine tremor, severe toxicity include rigidity, spasmodic laughter, (Chandra, 1983).

Iron

The only clinical use of iron preparation is in the prevention and treatment of iron deficiency, anaemia and is the leading cause of childhood poisoning deaths (Kent, 2001). Iron poisoning result from necrolizing gastro - entiretics with vomiting, abdominal pain and blood diarrhea followed by severe metabolic acidosis and death. Chronic iron intake can result in a condition known as haemochromatosis with excess iron deposited in the liver, heart, pancreas and open organs. Daily iron requirement varies from 6 — 18 mg/day, other high doses in adults posses no serious risk (FNB, 2000).

Zinc

Zinc is one of the most common elements and is available in all foods. It is an essential element needed by the body in small quantities. Long term exposure to zinc can be toxic especially when ingested at a much higher dose than the recommended dietary allowance (RDA) of 11mg/day for men and 8mg/day for women. If larger doses are taken (10 -l5times) higher than the RDA) by mouth, even at short time, stomach cramps, nausea and vomiting may occur. Ingesting high levels of zinc for several months may cause anaemia, damage to the pancreas and decrease levels of high density lipoprotein (HDL) cholesterol (Hailton et al, 2000). effect includes congestion of the liver, kidneys, and conjunctiva, cardiac enlargement and immunological effects.

Gastrointestinal effects include nausea, vomiting and diarrhea, and exposure may also result in injury to the liver, kidneys and allergic dermatitis.

2.3 Analytical Approaches

The wet chemical heavy metal test as an analytical method is prescribed by the United States pharmacopoeia (USP), the British Pharmacopoeia (BP), the Japanese Pharmacopoeia (JP) and European Pharmacopoeia (EP) (Allison, 2000).

The described methods provides specific detection and quantitation for each of the elements expected to give rise to a positive response in the compendia methods; arsenic (As), palladium (Pd), selenium (Se), cadmium (Cd), indium (In), tin (Sn), antimony (Sb), lead (Pb), bismuth (bi), silver (Ag), platinum (Pt), mercury (Hg), molybdenum (Mo) and rubidium (Rb). One disadvantage of this compendial visual semi-quantitative comparism method is that it is subjective (Lewen et al, 2001). The subjectiveness of the compendial method is eliminated by the use of Inductively Coupled Plasma- Mass Snectromery (ICP-MS) method (Peters *et al*, 2001). This method has been in use for several years and its versatility has been demonstrated by successfully applying it to a wide variety of sample matrices. Analysis of the scientific elemental data from the numerous sample matrices investigated indicates that there is no dependence of the various chemical functionalities contained in the sample matrices on the individual element recoveries. The average recovery for each element from the various sample matrices investigated ranged from 89 to 102% (Raglione *et al*, 2004).

Another analytical tool used for the identification of heavy metal contamination in pharmaceuticals is the use of energy- dispersive x - ray fluorescence (x R f). This method also conforms to procedures described in pharmacopoeia e.g. the third edition of the European pharmacopoeia (Lewen *et al*, 2001).

This method provides a time saving, cost effective solution to a considerable problem in quality assurance during the production of pharmaceutical products. The analysis

procedure describe in the pharmacopoeia for the determination of heavy metal contaminants in some cases require extensive sample preparation and often exhibit an unsatisfactory reproducibility of results. In addition, numerous wet chemical methods are proposed, each of which require the test setup to be adapted to the matrix of the sample.

As a universal instrument, the energy - dispersive x-ray fluorescence analysis delivers an overview analyses from sodium to uranium in 100 seconds. The polarized excitation radiation that delivers an almost complete suppression of the spectral background coupled with the high luminous intensity of the optical system, permits quantitative analysis of individual elements in the ngfkg range (Schenkenberger *et al*, 2002).

The application -specific optimization of the excitation system provides the analytical performance of a wavelength - dispersive spectrometer at the typical instrument price of an energy dispersive instrument. In addition to the standardization and accelerations of the process for the determination of essential trace elements (e.g Fe, Cu, Zn, Cr, Se, Ca, Mg, CO, Sc, and Mn) as well as toxic elements (Cd, Mo, Pb, Hg, As, and Sn), The XRF offers the advantage of minimal sample preparation (Mathew *et al*, 2000).

Usually, the sample is already provided as a ground powder. For analysis, this powder only has to be filled into a measurement cuvette. The sample is analysed non-destructively and thus can be used for further tests in contrast to wet chemical methods.

In a validation study, Gary et al (1998) found the atomic emission and optical emission spectrometry a suitable method for the analysis of heavy metals in pharmaceutical products. This method of determining the analyte concentration through a quantitative measurement of the optical emission from excited atoms. Analyte atoms in solution is aspirated into the excitation region where they are dissolvated, vapourized and atomized by a flame, discharge or plasma.

Analysis of pharmaceuticals for heavy metal contaminants may begin with physical examination. The trained eye of a quality control officer can detect contaminants and detects as small as 5 and hazy appearance in liquid preparations can be observed. However, microscopic metal contaminants, as well as other defects and particulates are often in the sub-visible range and may also go unnoticed thus requiring specialized technical skills and analytical instrumentation for analysis (Mary et al, 2009).

If visible particles are present in a vial of liquid sample, a magnet can be drawn along the vial wall to collect susceptible particles. If the particles, follow the movement of the magnet, the liquid sample likely contain metal particles. The absence of a response to the movement of the magnet does not eliminate the possibility of metal contamination, however. The liquid can be filtered on a polycarbonate membrane filter - typically 0.2pm or 0.4p.m pore size in a vacuum filtration apparatus. The smooth shiny surface of these filters allows the analyst to see the microscopic metal particles and remove them from the filter surface for analysis with a bit of adhesive on a tungsten needle.

Metal particles in solid tablets may appear as discrete chunks that can be easily removed. Particles as small as several hundred micrometers if lodged at the tablet surface can often be removed with forceps for analysis. Smaller discreet particles may need to be freed from their surrounding by applying a few micro- drops of water or other suitable solvent to the tablet surface. They softens and dissolves the surrounding tablet material, freeing the metal particle which can then be lifted with a tungsten needle (Mary *et al*, 2009).

In some cases, solid tablets exhibit gray or brown stains that on further examination provide evidence of metal contamination. These stained areas commonly contain sub-visible metal corrosion particles that are 10pm and smaller, mixed with normal tablet ingredients and sometimes machine oil. A tungsten needle is used to remove and transfer a portion of the stained material to a glass slide. A micro drop of hexane or other suitable solvent is applied to

the stained materials and any oils present are extracted and identified using infrared spectroscopy. The remaining insoluble materials which include metal particles and tablet materials are divided into two portions. One portion is analyzed with infrared spectroscopy to verif' the presence of the normal tablet ingredients and expedients and the other portion is submitted for energy dispersive. X-ray spectrometer (EDS) analysis to confirm the presence of metal or metal corrosion particles.

The development of analytical instruments over the past years have made possible not only for heavy metal to be detected in parts per quadrillion (PPQ) level but also to know its valency state, bimolecular form, elemental species and isotopic structure. Lead was the most commonly studied of all the trace elements and the techniques that developed early in time are mostly described on the basis of their lead estimation capacities. In the early 1960s, trace elemental determination were predominately carried out by traditional wet chemical methods such as volumetric, qravimetric, colourimetry assays. But it was the development of atomic spectroscopy (AS) in the early to mid 1960 that the clinical community realized that they had a highly sensitive and diverse trace element determination technique that could be automated (Ananth *et al,* 2007). Improvement in AS had made it possible for multi-elemental analysis and made it possible to understand how trace elements interacts with the body.

The Scanning Election Microscopy (SEM) offers the added advantage of detection and analyzing heavy metals in pharmaceutical samples. The SEM uses electrons instead of light to form an image. The sample is bombarded with electrons and atom in the sample interacts with the electron to produce secondary electrons and backscattered electrons. The electrons are collected by a detector and used to produce a high - quality morphological image showing the physical features of a sample. Metal particles, can be easily distinguished form organic materials by their backscattered electrons signal. The electron beam of the SEM also generates x-rays from the sample. Each element has a unique x-ray pattern, and the EDS

defector is used to collect the x-ray and analyze their energies. For a pure metal particle such as iron, the EDS spectrum will display a composition showing close to 100% iron. If the particle is oxidized or corroded, the EDS spectrum will display the presence of oxygen and some amount of and a proportionately increase amount of the metal (Mary Stellmack, 2010).

2.4 Chemistry of Heavy Metals

A heavy metal is a member of a loosely defined subset of elements that exhibit metallic properties. It mainly include the transition metals, some metalloids, lanthanides and actinides. Many different definitions have been proposed -some based on density, others on atomic number or atomic weight and some on chemical properties or toxicity (Tervon, 2007). The term heavy metal have been term ‘misinterpretation; in an 10PAC technical report due to the contradictory definitions and its lack of a coherent scientific basis (Tervan, 2007). There is an alternative term, toxic medal for which no consensus of exact definition exists either. Depending on context heavy metal can include elements higher than carbon and can exclude some of the heaviest metals. Heavy metal occur naturally in the ecosystem with large variations in concentrations.

Living organisms require varying amounts of ‘heavy metals, iron, cobalt, manganese, copper, zinc etc. are required by humans. Excessive levels can be hazardous to health. Other heavy metals, such as mercury, lead, platinium, are toxic metals that have no vital or beneficial effects on organisms and their accumulation in the body over times can cause serious illness (Cupper, 2010).

CHAPTER THREE

MATERIALS AND METHODS

3.1 Sampling

One Hundred (100) samples of various brands of pharmaceuticals from sixteen pharmacological classes in different dosage farms were purchased from pharmaceutical shops and patent medicine stores in Abraka and Obiaruku in Delta State, Nigeria. The samples were manufactured in Nigeria, India and China. None of the sample have expired and are all registered with the National Agency for Food and Drug Administration and Control (NAFDAC) in Nigeria.

The pharmacological/therapeutic classes of pharmaceutical products purchased include the following:

I. Analgesics
II. Antiniierobials
III. Antimalarials
IV. Antihypertensives
V. Antidiabetics
VI. Anthelmintics
VII. Antituberculosis
VIII. Anticonvulsants
IX. Antidiarrhoeas
X. Antipsychosis
XI. Antiasthmatics
XII. Haematinics
XIII. Antiulcers
XIV. Antihistamines

XV. Corticorsteroids

XVI. Contraceptives

3.2 Chemicals and Reagents

The perchioric acid and concentrated nutric acid used were of analytical grade. They were manufactured by Merch Kga A of Germany and BDH Limited Poole, England respectively. The distilled water used was double distilled (DD).

3.3 Sample Preparation

Two grams (2g) of sample was accurately weighed on electronic balance into an Elenmeyer Flask. 2m1 of perchloric acid and 12m1 of concentrated nitric acid are added into the flask. The bi-acid digested mixture was heated on a hot plate in a fume cupboard and the temperature maintained at 122°C until dense white fumes appear. The flask was then allowed to cool to room temperature. 50m1 of distilled water was then added and digestion continued until a clear solution was formed. The solution was cooled and made up to 50 ml with distilled water (Musa & Homza, 2009).

3.4 Chemical Analysis

The levels of metals (Cd, Pb, Ni, Cr, Cu, Co, Fe, Mn and Zn) contaminants in the sample solutions were analyzed using atomic absorption spectrometry (Analyst 200, Norwalk CA, USA).

3.5 Quality Control/Assurance

The laboratory table and glasswares were thoroughly cleared to avoid cross contamination. Blank was used to correct instrument readings and spike recovery method was used to check the analytical procedure. The spike recovery achieved for the metals were greater than 89.4%.

3.6 Statistical Analysis

Analysis of variance (ANOVA) was used to test for the difference within the same pharmacological groups studied and lukeep test was used to compare differences in the mean concentrations.

CHAPTER FOUR

RESULTS AND DISCUSSION

4.1 Result

The study of heavy metal contamination in pharmaceutical samples purchased are presented below in Table 4.1 to 4.16.

Table 4.1: Levels of heavy metal contamination (µg/g) in some brands of analgesics

S/N	ANALGESICS (A)	Brand Code	Pb	Cd	Cr	NI	Mn	Fe	Zn	Cu	Co
1	Teb, Ibuprofen 200mg/Tab Paracetamol 500mg Caffme 50mg	A_1	Nd	Nd	1.9	0.5	1	224.03	10.53	1.55	**3.45**
2	Cap Indomethacin 25mg	A_2	11.00	0.2	2.7	3.1	22.9	224.78	7.18	2.75	2.58
3	Cap Piroxicam 20mg	A_3	3.00	Nd	8.8	1.7	3	170.11	Nd	0.125	Nd
4	Cap Piroxicam 20mg	A_4	Nd	04	Nd	1	2.6	190.21	6.12	03	Nd
5	Cap Piroxicam 20mg	A_5	Nd	Nd	0.6	Nd	Nd	50.3	2.11	0.55	0.73
6	Tab Aspirin 300mg	A_6	17.1	Nd	9.4	0.6	27.7	6.7	23.1	8.32	2.58
7	Cap Tramadol 50mg	A_7	Nd	0.2	Nd	Nd	Nd	24.81	Nd	0.1	Nd
8	Inj Diclofenac 75mg	A_8	Nd	2.4	0.2	5	1.7	27.73	38.42	1.4	8.93
9	Pu/v Aspirin 760mg/Caffeine 60mg	A_9	Nd	Nd	Nd	1.7	3	36.28	14.43	2.75	Nd
10	Tab Diclofenac 100mg	A_{10}	2.5	Nd	3.63	1.8	0.8	31.93	7.35	40	0.05
11	Tab Ibuprofen 400mg	A_{11}	3.6	Nd	3.4	2.1	4.23	162.05	7.35	1.18	2.93
12	Tab Ibuprofen 400mg	A_{12}	6.1	Nd	Nd	3.7	11.1	67.05	5.93		1.95
13	Tab Ibuprofen 400mg	A_{13}	43.5	1.6	1.8	14.4	4.93	34.13	8.13	2.3	0.45
14	Cap Ibuprofen 200mg! Paracetamol 500mg? Caffeine 50mg	A_{14}	Nd	1	24.4	44	28.7	29.3	2.85	Nd	Nd
15	Tab Paracetamol 500mg	A_{15}	Nd	Nd	7.9	0.7	1.5	81.2	9.12	2.06	Nd
16	Tab Paracetamol 500mg	A_{16}	1.1	Nd	3.88	1	1.33	34.13	7.73	2.3	0.45
17	Tab Paracetamol 500mg	A_{17}	Nd	Nd	Nd	Nd	1.2	109.56	4.6	3.6	Nd
18	Tab Paracetamol 500mg	A_{18}	Nd	1.1	Nd	1	2.1	19.56	0.83	0.18	Nd

19	Tab Paracetamol 500mg! Aspirin 300mg	A_{19}	Nd	Nd	1.4	0.5	2	52.83	3.21	13.3	Nd
		Mean	4.62	0.78	3.68	2.27	6.3	82.98	8.37	4.39	1.27
		S.D	9.84	0.67	5.84	3.6	9.08	72.57	9.08	9.25	2.02

Table 4.2: Levels of heavy metal contamination (µg/g) in some brands of antimicrobials

S/N	ANTIMICROBIALS (AM)	Brand Code	Pb	Cd	Cr	NI	Mn	Fe	Zn	Cu	Co
20	Cap Ampicillin 250mg/Cloxacillin 250mg	A_1	1.4	Nd	5.5	0.2	18.6	Nd	11.7		Nd
21	Syl Ampicillin 125mg	AM_2	Nd	Nd	Nd	1.2	2.9	60.78	5.28	2.58	Nd
22	Syl Ampicillin 125mg/Cloxacillin	AM_3	Nd	Nd	2.5	1.4	8.1	4223	2.63	0.48	Nd
23	Cap Amoxicillln 500mg	$AM._4$	Nd	0.5	Nd	1.1	3.5	25.39	3.33	0.28	Nd
24	Syl Ampicillin 125mg/5m1	AM_5	Nd	Nd	Nd	2.3	4.4	57.85	2.23	0.23	Nd
25	Cap Chloramphenicol 250mg	AM_6	Nd	Nd	3	1.7	8.2	69.58	3.23	0.22	Nd
26	Clotrimazole Pessaries 100mg	AM_7	5.6	1	Nd	1.5	2.4	48.18	5.03	0.88	0.68
27	Clotrimazole Pessaries 100mg	AM_8	4.3	0.5	Nd	1.9	16.1	13.9	2	2.1	Nd
28	Tab Cotrimoxazole 480mg	AM_9	Nd	Nd	16.1	1.7	4	36.06	2.23	0.08	Nd
29	Cap Chioramphenicol 250mg	AM_{10}	Nd	Nd	Nd	1.6	1.3	63.6	3.43	3.45	Nd
30	Tab Cotrimoxazole 480mg	AM_{11}	Nd	Nd	Nd	2.3	5.3	44.48	4.2	10	0.58
31	Tab Erythromycia 250mg	AM_{12}	Nd	Nd	Nd	Nd	1.3	50.13	6.12	3.11	Nd
32	lnj Genticia280mg	AM_{13}	4.2	Nd	1.2	46	6.5	49.3	6.63	4.5	Nd
33	Tab Griseoflulvin 500mg	AM_{14}	3.3	0.02	0.6	1.7	22.9	11.48	3.23	1.3	0.3
34	Cap Lincomycin 500mg	AM_{15}	0.5	0.05	1.7	2.4	2.7	30.1	7.5	1.58	0.48
35	Tab Metronidazole 200mg	AM_{16}	4.9	0.03	3.6	5.5	3.1	99.33	8.93	1	2.73
36	Tab Meironidazole 400mg	AM_{17}	Nd	Nd	Nd	1.8	8.3	48.05	1.63	0.05	Nd
37	Tab Metronidazole 400mg	AM_{18}	0.02	Nd	2.7	1.3	1.8	36.4	15.1	2.43	Nd
38	Nystati n Pessaries 100,000iu	AM_{19}	1.6	Nd	Nd	1.4	3.2	358	7.18	13.28	Nd
39	Penicillin Skin Ointment 10,000iu	AM_{20}	6.90	0.6	Nd	1.2	0.9	29.48	8.65	0.23	Nd
40	Cap Tetracycline 250mg	AM_{21}	4.9	Nd	3.5	5.5	7.8	48.2	3.88	1.08	0.88
		Mean	1.85	0.13	1.92	2.01	5.93	59.21	5.46	2.33	0.27
		S.D	2.34	0.26	3.45	1.21	31.93	72.06	3.49	3.39	0.62.

Table 4.3: Levels of heavy metal contamination (µg/g) in some brands of antimicrobials

S/N	ANTIMALARIALS (AL)	Brand Code	Pb	Cd	Cr	NI	Mn	Fe	Zn	Cu	Co
41	lnj. Chioroquine 40mgIml	A_1	1.1	Nd	0.8	250	2.6	80.83	14.58	3.13	nd
42	Cap Chicroquine Phosphate 400mg	A_2	1.1	Nd	0.8	4.1	4.1	8.83	4.34	8.83	nd
43	SyrAitermether/ Lumefantrine 260mmg I 80m1	A_3	Nd	Nd	6.0	Nd	6.1	305.25	11.7	11.2	Nd
44	Tab Amodaquine 200mg	A_4	1.1	0.6	2.1	0.9	5.2	78.25	9.14	5.13	Nd
45	Tab Artesunate 50mg	A_5	7.6	0.3	Nd	2.3	11.5	50.25	4.58	3.855	1.2
46	Tab Quinine 300mg	A_6	9.6	0.88	4.3	6.1	3.5	31.17	262	5.23	5.3
47	Tab Sulphadoxine 500mg/Pyrimethamlue 75mg	A_7	Nd	Nd	4.1	4.4	3.7	112.3	12.13	2.15	Nd
48	Tab Artemether/lumefeñtine 20mg/Lufemantrine 120mg	A_8	1.6	0.05	Nd	1.4	3.2	51.11	6..3	1.19	0.9
		Mean	2.76	0.22	2.26	2.68	4.98	59.11	8.17	5.09	0.93
		S.D	3.49	0.32	2.27	1.99	2.36	19.32	0.06	1.1	2.67

Table 4.4: Levels of heavy metal contamination (µg/g) in some brands of antihypertensives

S/N	ANTIHYPERTENSIVES (AH)	Brand Code	Pb	Cd	Cr	NI	Mn	Fe	Zn	Cu	Co
49	Tab Apresolin 25mg	A_1	Nd	Nd	Nd	1.3	3.4	20.50	2.60	4.15	Nd
50	Tap Captopril 25mg	AM_2	0.6	08	0.5	3.7	3.8	60.93	3.9	5.13	Nd
51	Tab Hydrochiorothiazide 50mg/Ameloride 75mg	AM_3	6.2	0.4	0,55	3.9	12.1	41.25	1.24	0.025	2.35
52	Tab Hydrochiorothiazide 50mg/Amoloride 75mg	$AM._4$	4.3	Nd	0.7	3.1	14.6	51.15	3.12	1.5	Nd
53	Tab Methyldopa 250mg	AM_5	1.3	0.1	Nd	0.8	1.1	6.2	6.53	5.43	Nd
54	Tab Methyldopa 250mg	AM_6	0.2	Nd	0.1	1.4	1.7	37.45	6.88	2.45	Nd
55	Tab Methyldopa 250mg	AM_7	1.2	Nd	1	1.4	1	28.83	5.28	4,14	Nd
56	Tab Methyldopa 250mg	AM_8	15.3	0.4	5.8	6.8	37.5	252	7.08	6.96	4.9
57	Tab Hydrochiorothiazide 50mg	AM_9	Nd	0.4	Nd	06	0.7	8.8	4.1	5.15	Nd
58	Tab Nifedipine 20mg	AM_{10}	3.9	Nd	29.7	15.7	1.8	27.8	4.78	9.88	1.95
59	Tab Nifedipine 20mg	AM_{11}	1.7	Nd	Nd	1.7	12	37.45	17.4	15.78	Nd
60	Tab Methyldopa 250mg	AM_{12}	22.2	Nd	1.6	09	2.9	46.33	3.95	3,44	Nd

61	Tab Captopril 25mg	AM_{13}	Nd	Nd	2.8	2	20	144.13	6.45	0.53	0.68
62	Tab Methyldopa 250mg	AM_{14}	4.3	0.5	Nd	1.6	1.3	24.8	8.63.	0.55	Nd
		Mean	4.34	0.19	3.05	3.2	6.86	58.9	5.33	4.69	0.76
		S.D	6.56	0.26	7.83	3.96	9.99	67.3	2.05	4.37	1.48

Table 4.5: Levels of heavy metal contamination (µg/g) in some brands of antihypertensives

S/N	ANALGESICS (AD)	Brand Code	Pb	Cd	Cr	NI	Mn	Fe	Zn	Cu	Co
63	Tab Chiorpromide 250mg	A_1	3.9	Nd	Nd	1.1	8.5	30.13	8.23	6.23	0.55
64	Tab Glipizide 5mg	A_2	Nd	0.1	Nd	1.3	4.6	31.48	3.63	0.53	Nd
65	Tab glucophape 250mg	A_3	11	0.8	0.9	1.5	1.3	24.78	3.43	7.63	Nd
66	Tab glipizide 5mg	A_4	30.2	0.2	9.5	8.2	8.0	329.8	25.23	1.73	2.8
67	Metformin 250mg	A_5	Nd	0.3	Nd	1.,5	1.0	49.9	4.83	2.4	Nd
		Mean	9.02	0.28	2.08	2.72	4.68	43.22	9.07	3.7	0.67
		S.D	11.83	0.31	4.03	3.07	3.56	134.10	2.04	0.65	2.17

Table 4.6: Levels of heavy metal contamination (µg/g) in some brands of anthelmentics

S/N	ANTHELMENTICS (AT)	Brand **Code**	Pb	Cd	Cr	NI	Mn	**Fe**	Zn	Cu	Co
68	Tab levamisole 40mg	AT_1	0.03	Nd	1.6	Nd	4.2	60.9	16.2	23.73	Nd
69	Tab Mbendazole 100mg	AT_2	9.8	0.2	5.6	4.9	39.8	408.25	0.48	0.18	4.55
70	Tab pyrantel pamoate 100mg	AT_3	15.7	1.2	12.6	37.4	6.4	53.93	8.11	1.53	2.75
		Mean	**10.51**	**0.47**	**6.4**	**14.1**	**16.8**	**174.36**	**8.36**	**8.48**	**2.43**
		S.D	**4.87**	**0.64**	**5.63**	**20.23**	**19.95**	**121.17**	**3.72**	**3.87**	**0.4**

Table 4.7: Levels of heavy metal contamination (igIg) in some brands of antituberculosis

S/N	**antituberculosis** (AC)	Brand **Code**	Pb	Cd	Cr	NI	Mn	**Fe**	Zn	Cu	Co
71	Tab Ethambutol 500mg pyrazinamid 150mg Isonizide 150mg/ Rifampicin 300mg	AT_1	Nd	0.2	1.9	1.9	2.6	114.3	2,28	Nd	Nd
72	Tab Isonizide 150mg	AT_2	8.3	Nd	2.4	3.9	15.9	104.2	1.19	0.03	1.1
73	Tab comb Dot	AT_3	Nd	Nd	1.4	0.5	2	52.83	0.36	41.2	Nd
74	Cap Rifampicin	AT_4	0.09	Nd	0.1	1.5	2.6	41.20	1.66	12.10	Nd
		Mean	2.11	0.05	1.45	1.9	5.78	90.44	1.28	13.74	0.37
		S.D	4.16	0.1	0.18	14	6.76	32.96	0.96	23.78	0.64

Table 4.8: Levels of heavy metal contamination (µg/g) in some brands of anticonvulsants

S/N	**ANTICONVULSANTS**	**Pb**	**Cd**	**Cr**	**NI**	**Mn**	**Fe**	**Zn**	**Cu**	**Co**
75	Tab Carbamazepine 200mg	1.8	0.7	6.5	2.7	6.1	98.16	17.82	1.7	Nd
76	Tab phenobarbitone 30mg	9.9	0.3	1.8	7.7	4,4	133.77	‘33.25	1.38	3.85
77	Cap phenytoin 100mg	3.8	Nd	1.8	2.7	23.2	204.85	16.63	1.55	0.83
	Mean	**5.17**	**0.33**	**4.34**	**4.2**	**11.23**	**145.59**	**22,57**	**1.54**	**156**
	S.D	**4.22**	**0.35**	**2,37**	**2.6**	**10.4**	**54.33**	**9.32**	**0.17**	**2.03**

Table 4.9: Levels of heavy metal contamination (µg/g) in some brands of antidiarrhoea

S/N	ANTIDIARRHOEA (AR)	Brand code	Pb	Cd	Cr	Ni	Mn	Fe	Zn	Cu	Co
78	Tab Loperamide 4mg	AR_1	6.7	Nd	5.3	3.3	26.6	261.14	11.22	0.03	2.23
79	Oral Rehydration Salt	AR_2	Nd	1	4.4	2.4	28.7	224.03	10.53	1.56	3.45
		Mean	**3.35**	**0.05**	**4.85**	**3.85**	**27.65**	**242.59**	**10.88**	**0.78**	**2.84**
		S.D	**4.73**	**0.71**	**0.63**	**0.77**	**1.48**	**26.21**	**0.68**	**1.08**	**0.86**

Table 4.10: Levels of heavy metal contamination (µg/g) in some brands of antipsychosis

S/N	ANTIPSYCHOSIS (AC)	Brand code	Pb	Cd	Cr	Ni	Mn	Fe	Zn	Cu	Co
80	Tab chiorpromazine 50mg	AC_1	10.6	0.3	6.6	4.8	36.2	97.23	24.19	0.83	1.45
81	Tab triflourperazine 5mg	AC_2	7.2	0.1	3.9	5	11.2	67.33	20	1.18	1.78
		Mean	**8.9**	**0.2**	**5.25**	**4.9**	**23.7**	**82.28**	**22.09**	**1.01**	**1.62**
		S.D	**2.4**	**0.14**	**1.91**	**0.14**	**17.68**	**21.14**	**2.93**	**0.25**	**0.23**

Table 4.11: Levels of heavy metal contamination (µg/g) in some brands of antiastmatics

S/N	ANTIASTMATICS (AA)	Brand code	Pb	Cd	Cr	Ni	Mn	Fe	Zn	Cu	Co
82	Tab Aminophylilne 100mg	AA_1	10.6	0.3	0.3	4.5	12	53.93	8.4	15.73	2.75
83	Tab Salbutamol 4mg	AA_2	6.8	Nd	0.4	3	53.6	200.73	7.83	13.21	243
84	Tab Salbutamol 2mg	AA_3	1	2.3	1.1	10	1.5	29.78	3.5	1.53	Nd
		Mean	6.13	0.87	0.6	2.87	22.37	98.15	10.16	10.16	1.73
		S.D	4.83	1.25	0.44	1.7	27.55	89.12	2.68	7.58	1.5

Table 4.12: Levels of heavy metal contamination (µg/g) in some brands of haematinics

S/N	IIAEMATINICS (H)	Brand code	Pb	Cd	Cr	Ni	Mn	Fe	Zn	Cu	Co
85	Tab Ferrous Sulphate 300 mg	H_1	0.7	0.04	4.7	2.8	15.7	305.19	10.5	16.63	0.3
86	Cap IronfMultivitamin/Minerals	H_2	Nd	Nd	1.7	2.6	Nd	224.9	3.48	1.63	1.16
87	Cap Iron/Multivitamin/ Minerals	H_3	Nd	Nd	Nd	Nd	30.5	154.08	5.53	2.81	Nd
88	Tab Vitamin B complex	H_4	Nd	21	Nd	1.5	12.2	160.12	7.11	3.2	Nd
89	Tab Multivite	H_5	0.5	Nd	3	2.2	9.1	89.62	1.1	2.06	1.01
		Mean	0.24	0.43	1.88	1.82	13.5	186.78	5.54	5.27	0.49
		S.D	0.34	0.93	2.02	1.14	11.15	82.6	3.57	6.39	0.56

Table 4.13: Levels of heavy metal contamination (µg/g) in some brands of antiulcers

S/N	ANTIULCERS (AV)	Brand code	Pb	Cd	Cr	Ni	Mn	Fe	Zn	Cu	Co
90	Tab Cimetidine 400mg	AV_1	2	Nd	Nd	2	7.6	109.55	4.60	3.60	Nd
91	Cap Omeprazole 20mg	AV_2	Nd	0.4	Nd	0.8	1.2	33.83	4.16	16.5	Nd
92	Tab Ranitidine 150mg	AV_3	Nd	0.1	Nd	0.5	3.8	178.6	9.68	11.23	Nd
		Mean	0.67	0.17	0	1.1	4.2	107.3	6.15	10.44	0
		S.D	1.15	0.21	0	0.79	3.22	72.4	3.07	6.49	0

Table 4.14: Levels of heavy metal contamination (µg/g) in some brands of anthistamines

S/N	ANTHISTAMINES (AM)	Brand code	Pb	Cd	Cr	Ni	Mn	Fe	Zn	Cu	Co
93	Tab Chlorpheniramine 4mg	AM_1	6.6	6.4	14.1	1.7	3.9	77.63	18.23	2.22	3.89
94	Tab Chlorpheniraine 4mg	AM_2	Nd	Nd	Nd	1	2.6	63.6	3.43	2.58	Nd
95	Tab Cyproheptadine 4mg	AM_3	9.1	1	4.40	5.40	25.4	81.22	38.43	1.4	8.93
96	Tab Cyproheptadine 4mg	AM_4	25.9	3.1	13.9	13.2	24.4	113.68	8.63	2.85	4.45
		Mean	10.4	2.63	8.1	5.33	14.08	84.03	17.18	2.26	4.34
		S.D	11.022	2.83	7.05	5.59	12.52	21.18	16.55	0.65	3.45

Table 4.15: Levels of heavy metal contamination (ig/g) in some brands of corticorsteroids

S/N	CORTICORSTEROIDS (C)	Brand code	Pb	Cd	Cr	Ni	Mn	Fe	Zn	Cu	Co
97	Tab Prednisolone 5mg	C_1	Nd	Nd	Nd	Nd	1.1	39.9	6.88	3.95	Nd
98	Tab Dexamethazone 1mg	C_2	Nd	Nd	6	Nd	Nd	56.13	7.11	Nd	Nd
99	Tab Bethainetrazone 5mg	C_3	1.2	0.91	5.2	3.1	7.1	43.89	6.83	5.82	Nd
		Mean	0.4	0.3	3.73	1.03	2.73	46.64	6.94	3.26	
		S.D	0.69	0.52	3.26	1.79	3.82	8.46	0.15	2.97	

Table 4.16: Levels of heavy metal contamination (pg/g) in some brands of contraceptives

S/N	CONTRACEPTWES (CT)	Pb	Cd	Cr	Ni	Mn	Fe	Zn	Cu	Co
100	Tab Ethinyestradiol 0.03/ Norgesterone 0.3mg Fenocs Fumerate 75mg	2,7	Nd	2.9	1.8	9.1	141.2	2.83	4.11	3.22
		Mean	1.45	0	0.01	0.04	1	19.92	0.3	0.48
		S.D	1.06	0	0.002	0.029	0.65	4.04	0.53	0.74

4.2 Discussion

4:2.1 Lead

From the study, 61% of all the samples studied shows significant contamination by lead. The level of lead contaminant ranges from 10.1 5mgfL among anthelmintics to a mean value of 0.24mg/L in haematinics.

The value is higher than the level of 0.01 mgfL to 1.08 mg/L obtained by Ebere et al, 2010 in some paediatrics syrups commonly used in Nigeria. This may be due to the use of much lower quantity of pharmaceutical samples for analysis, in some cases, less than 500ng as against 2g used in the study. Moreover, tablets and capsules have higher contact with stainless steel materials in the course of their manufacture than the syrups.

However, thirty-nine percent (3 9%) of the samples were below detectable limits (BDL). The contamination levels in 61% are significantly above the National Agency for Food and Drug Administration and Control (NAFDAC) tolerable limit of 0.001 mg/dL.

Consequently, these observed values may increase the blood levels of patients with continuous use. Undoubtably one of the oldest occupational toxins as evidence of lead poisoning can be found dating back to Roman times. Some pharmaceuticals such as antidiabetics and some analgelsics used by arthritic patients are taken for life.

High levels of lead in the blood may lead to deleterious health consequences like autism, miscarriages and low birth weight of infants (Hordiestron et al, 1979). Lead also accelerates ageing process, mental decline, infertility in couples, as it is associated with reduction in sperm count and motility. (Apostolic Ct al, 2002). Other effects are anaemia and hypertension. (Kadzung, 2010).

4.2.2 Cadmium

Cadmium contamination level observed in this study ranges from BDL in commonly used oral contraceptive taken daily to a mean value of 2.63 mg/L in anthistamines used for cold and skin allergic reactions. The level is similar to the highest level of 2.45 mgfL obtained by Ebere et al, 2010. However only 46% of the samples shows Cd concentrations above the detectable limit. The level of cadmium contamination of pharmaceutical in this study is above the FAO/WHO tolerable daily intake, of cadmium of 70 tg to 97 ig for an average body weight of 70kg man (WHO, 1999). Cadmium is absorbed through the intestinal tract. Cadmium accumulation in the body may lead to clinical manifestation of kidney disorders like proximal tubular dysfunction. (Hayes, 1997). Other target organs include bones (Osteomalacia) liver, lung, testis (oligospermea) and haemopoietic systems (anaemia) (Kokik et al, 1997).

4.2.3 Chromium

Chromium is considered to be one of the most environmental toxic pollutant in the world. (Nurad et at, 2000). Pharmaceutical contamination of chromium in this study ranges from a mean value of 5.10 mgfL in antististamine to BDL among antiulcers. 68% of the samples shows detectable limits with the highest value of 29.9 mgfL in nifedipine, a commonly prescribed anhypertensive and 24.4 mg/L in ibuprofen/pracetamol/coffeine combination an over — the — counter (OTC) medicine used routinely as an analgesics. Persistence exposure to chromium may result in skin rashes, stomach upset, respiratory

disorders, weak immune system, kidney and liver damage, alteration of genetic material, lung and liver cancer and ultimately death. Tolerable limit for chromium is 0.005 mgfL (WHO, 2001).

4.2.4 Nickel

Nickel is considered a normal constituents of the diet and the dietary intake of nickel in most countries ranges from 100 -300 jig/day. (Cempel, 2001). In the pharmaceutical samples considered in this study, nickel level have been found to range form a mean value of 14.1 mg/L among anthelmintics to 1.03 mgfL in corticosteroids. Therefore, there is detectable level of nickel in all the classes of samples investigated. This may be expected as water generally contains nickel of at a concentration of about 100 mg/L (Solomons et a!, 1999). Although, nickel has a bioavailability of 1% - 10% when ingested, high level of nickel is known to cause allergic determatitis known as nickel itch (Pendiues et al, 1998). Other toxicological effects of nickel exposure include kidney damage, cardiovascular and immune systems and blood disorders (Coogan et al, 1989) These effects may occur when nickel is taken above the dietary limit of 0.187 — 302 mg/day.

4.2.5 Manganese

Manganese as its sulphate is commonly used in pharmaceuticals as food supplements for bone development and is a constituent of enzymes (Watt, 2011) This study shows high level of manganese with 96% of the sample having various level of manganese contamination. The highest mean value of 27 65 mg/l, was observed in antidiarrheoa. The least mean value of 2.73 mg/l was recorded among corticosteroids. Despite its human requirement however, high level of manganese may result in health problems Mild manganese toxicity may lead to manganese psychosis with symptoms of asthema, anolexia, insonmca, muscular pains, mental excitement hallucinations, unaccountable laughter impaired memory and compulsive actions. Moderate toxicity include speech disorder clumsy

movement, abnormal gait, poor balance, hyperplexia in the lower limbs, and fine tremor severe signs include rigidity, spa - laughtei and Parkinson type syndrome (Aschna, 2000). With a daily requirement of 2.5 mg to 7.0 mg, the level of manganese contamination in this study is above the tolerable limit.

4.2.6 Iron

Iron has the highest level of contamination of all the metals considered in the study. The highest mean values of 242.58 mgfL was seen among the corticosteroids. All .100 % of the samples studied shows high level of iron contamination This may be the result of wear and tear of the manufacturing equipment which are stainless steel composed predominantly of iron The food and nutrition board (FNB) of the institile of medicine (IM) USA recommended dietary allowance of 7-10 mg/day for children, 8 mg/day for adult and 27 mg/day during pregnancy for mothers (Edebi et a!, 201 1). Iron is used for the treatment of iron deficiency anaemia and is stored in the spleen and bone marrow injection of large quality of iron salt may lead to several necrolizing gastritis with vomiting and haemorrage. (Buwat, 2010). Chronic iron toxicity also known as haemochromatoses results when excess iron is deposited in the heart, liver, pancreas and other organs, which may lead to organ failure and death. The level of iron contamination among pharmaceuticals in this study may be deleterious to health.

4.2.7 Zinc

Varying level of zinc was found in 98% of the samples studied. The highest mean concentration of 22.57 mg/L was found among anticulvusants with the least

mean level of 1.28 mgfL among antituberculosis. A trace level of Zn is an essential

element in man. The catalytic activities of about one hundred (100) enzymes are zinc dependent in the human body and also participate in cell signaling, release of hormones and apoptosis (Mohammed, 2010) The recommended dietary allowances are 4 mg —5 mg/day

mg — 13 mg/ day, 13 mg — 19 mg/day for children, women and men respectively (Brown et al, 2004). Although human body can tolerate high level of zinc, acute zinc toxicity (oral dose of 225 mg — 450 mg) can causes health problems like stomach cramps, skin irritation, vomiting, nausea and aneamia. Chronic zinc expose may lead to copper deficiency in man and very high level of zinc can damage the pancreas, distort protein metabolizing enzymes and arthero sclerosis. It can be a danger to unborn foetus and breastfeeding mothers as the foetus and children can get exposed through blood and breast milk respectively. The National Research Council (NRC) recommended daily zinc intake between 10 mg to 20 mg /day (MRC, 1980). It is therefore unlikely that the use of pharmaceuticals considered in this study will result in zinc toxicity.

4.2.8 Cobalt

Among the metals investigated, cobalt have the least level of contamination of only 46%. Cobalt have BDL among antiulcers and corticosteroids and the highest mean value of 4.34 mg/i among antihistamines. At low concentration, cobalt plays a prominent role in the formation of cyanocobalamine viz B 12. Exposure to high concentration of cobalt may lead to symptoms of cobalt poison characterized by visual impairment, hypothyrodism, peripheral neuropathy, rashes, cardiomyopathy, auditory and cognitive impairment (Karovic et a!, 2007). Since 50% of ingested cobalt is absolved through the intestine (Angelisco, 2005), long term use of pharmaceutical contaminated by cobalt may be hazardous However, cobalt contamination level among pharmaceuticals considered in this study is relatively safe,

4.2.9 Copper

Copper is present in 97% of the samples studied with the lowest mean value of 0.76 mg/L in antidiarrhea. Antituberculosis has the highest level of contamination with a mean value of 13.74 mgfL. The blood level of copper is about 100 .tg / 100 ml in adult (Fraga, 2000). In humans, copper is necessary for the development of connective tissue, nerve

endings and bone. It also participates in iron metabolism. There is about 80 mg of copper in the adult body with the highest concentration in the head and brain Medium intake of Cu ranges between 1.0 to 1.6 mg/day (Herpa, 1999). Chronic copper toxicity is rare in humans and is mostly associated with liver damage. Acute Cu intoxication leads to gastrointestinal effect such as abdominal pain, nausea, diarrhea, vomiting. From the study, Cu contamination level is relatively safe as the risk of acute or chronic toxicity is most improbable.

CHAPTER FIVE

SUMMARY, CONCLUSIONS / RECOMMENDATION

The study of one hundred (100) pharmaceutical samples in sixteen pharmacological and therapeutic classes commonly used in Nigeria shows a significant contamination by heavy metals with the exception of copper and cobalt. Iron has the highest contamination level of 100 % with cobalt of 46% as the least. Therefore repeated use can lead to adverse health effects ranging from minor stomach upset to metal poisoning with lead and chromium being the most dangerous. In addition, untoward drug reactions and drug hypersensitivity reactions may occur.

To protect consumers and patients from metal contamination that can undermine the safety and quality of pharmaceutical, drug manufacturing companies must follow strictly Good Manufacturing Practice (GMP) by abiding by the strict quality control (QC) standards required by the National Agency for Food and Drug Administration and Control (NAFDAC). In addition, in-house quality control officer must examine solid and liquid pharmaceuticals with the naked eyes and then with stereomicroscope. This will help detect signs of metal contamination like hazy liquid appearances of shinky metal slakes or dark, brittle particles ranging in colour from red or orange to brown or black in tablets. This is with a view measures in the manufacturing process.

Moreover, pharmaceutical companies should engage the services of independent analytical laboratories with requisite skill, experience and instrumentation to identify' contamination and their source(s) before the drugs get to the shelves of pharmacy stores or patient medicine shops.

Also, processing machinery and equipment that generates wear particles must be thoroughly cleaned and data bases of commonly used stainless steel composition should be known to easily identify sources of contamination.

Although, the natural wear and tear of manufacturing machinery cannot be avoided, pharmaceutical companies must strive continually to diligently monitor not only the quality of the product but also condition of the manufacturing machinery to actually safeguard the health of Nigerians.

Pregnant women and lactating mothers should be given high doses of calcium of at least 200mg daily. This will reduce lead absorption by 31% as there is no safe threshold for lead exposure in developing nervous system (Schwartz, 2000).

Children should be regularly screened for lead, as high consumption of pharmaceuticals gives sufficient concern for lead exposure.

National Agency for Food and Drug Administration and Control (NAFDAC) should demand for data on bean metal level of pharmaceutical as a prerequisite for drug registration with the exception of Zinc, copper and cobalt, all other heavy metals considered in this study has levels of contamination of pharmaceutical that may be unsafe if taken repeatedly.

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