Journal of Chemistry and Chemical Sciences, *Vol.6(5), 458-475, May 2016* *ISSN 2229-760X (Print)*
(An International Research Journal), *www.chemistry-journal.org* *ISSN 2319-7625 (Online)*

Effluences of Heavy Metals, Way of Exposure and Bio-toxic Impacts: An Update

Rajesh Pandey[1], Manish K Dwivedi[1], P.K. Singh[2], Babbulal Patel[2], Sunil Pandey[1], Balendra Patel[3], Anita Patel[2] and Bhavna Singh[4]

Department of Chemistry,
A.P.S. University, Rewa, M.P., INDIA.
Department of Chemistry,
Govt. SGS Autonomous P.G. College, Sidhi, M.P., INDIA.
Department of Chemistry, SIT College, Sidhi, M.P., INDIA.
Department of Chemistry,
Govt. P.G. College Devsar, Sidhi, M.P., INDIA.
Department of Science,
Govt. P.G. College BHEL, Bhopal, M.P., INDIA.
rajeshrdu29@gmail.com

(Received on: May 6, 2016)

ABSTRACT

Heavy metals have importance as trace elements, but they show various direct and indirect bio-toxic impacts concerned with human or its biochemistry. Consequently, there is the need for appropriate thoughtful of the situation, such as their series, concentrations and states of oxidation, which promote and make to them destructive and lethal for human. It is also decisive to distinguish sources, discharge processes, element conversions and their manners of authentication to pollute the environment, which essentially supports lives. Investigated information point to piece of confirmation that these metals are released addicted to the environment by accepted and anthropogenic causes, especially mining and industrialized performance, and automobile exhausts etc. Poisoning and toxicity in human occur through exchange and co-ordination mechanism process of metals. During the dietary mechanism, they come together with the body's biomolecules to produce bio-toxic compounds, thereby newly produced compound change their structures and execute multiple reaction.

Present review represents the heavy metals and their bio-toxic impacts on human biochemistry and the mechanisms of their biochemical action.

Keywords: Heavy metals, environment, exposure pattern, human biochemistry.

INTRODUCTION

Heavy metals are elements, have a relatively high density and are toxic in nature at low concentration. Its comprise group of metals and metalloids having atomic density greater than $4g/cm^3$ or greater than water[1]. Environment is defined as the totality of circumstances surrounding an organism especially, the combination of external physical conditions which affect and influence the growth, development and survival of organisms[2]. It consists of the flora, fauna and the abiotic, and includes the aquatic, terrestrial and atmospheric habitats. Environment is considered as the most tangible aspects like air, water and food, and the less tangible, though no less important, the communities we live in Contaminants are substances of environment, which created or causes objectionable responses, impairing the interests of environment, decline the specificity of life and may eventually cause death[3]. Such a substance has to be attending in environment beyond tolerance limit, which could be moreover a desirable or satisfactory limit. Hence, pollution is presence of a pollutant in environment; (air, water and soil), which may be toxic and will cause harm to living things in polluted environment.

Mostly heavy metals include lead (Pb), cadmium (Cd), zinc (Zn), mercury (Hg), arsenic (As), silver (Ag) chromium (Cr), copper (Cu) iron (Fe) etc. these are recovered from their ores by optimized processing operations[4-6]. Ore minerals have a tendency to occur in families whereby they exist naturally as sulphides would mostly occur together, likewise for oxides. Therefore, sulphides of Pb, Cd, As and Hg would naturally be found occurring together with sulphides of iron (pyrite, FeS_2) and copper (chalcopyrite, $CuFeS_2$) as minors, which are obtained as by-products of hydrometallurgical processes and other processes which pursue subsequent to mining to recover them. During conduction of mining processes, some metals are left behind as tailings scattered or dispersed in open or partially covered pits; some are transported via wind or flood, creating various ecological problems[7].

Metal contamination concern metal toxicity shown by mining industries, smelters, coal-burning, hydro power plants and agriculture system etc. Heavy metals occur as natural constituents of earth crust, and are persistent as contaminants since they cannot be degraded or destroyed. Rocks, metals are existing as ores in diverse compound forms, which they are recovered as minerals. Some exist and can be recovered as both sulphide and oxide ores such as iron, copper and cobalt[6]. Both sulphide and oxide form possess various aspects of chemistry along with benefits and toxicity response. A small extent of heavy metals, enter internally the body system via dietary consumption, surrounding and breathing air and water which additional bio-accumulate more than a period of time[8].

Bio-importance of heavy metals

Some heavy metals known for bio-importance in human biochemistry, physiology and consumption even at very low range (Fe, Zn, Ca and Mg) have been reported to be of bio-importance to man and their daily medicinal and dietary allowances had been recommended. Their tolerance limits in drinking and potable waters have also been reported, and are indicated. Magnesium is an important electrolytic constituent of blood, found in blood plasma, body fluids, viz; interstitial and cell fluids. Its daily dietary requirement increases from infants to adults and from males to females, with highest daily requirements for pregnant and lactating women 8. Even for those that have bio-importance, dietary intakes have to be maintained at regulatory limits, as excesses will result in poisoning/toxicity, which is evident by certain reported medical symptoms that are clinically diagnosable [9].

Calcium is a very vital element in human metabolism. It is chief element in production of very strong bones, teeth in mammals. Its tolerance limit is high relative to other bio-useful metals, that is, at 50 mg/l of drinking water. Daily dietary requirement of calcium soars at the highest across both sexes and all ages of humans. Similarly Zinc is a 'masculine' element that balances copper in the body, and is essential for male reproductive activity [10,11]. It serves as a co-factor for dehydrogenating enzymes and in carbonic anhydrase 8. Zinc deficiency causes anaemia and retardation of growth and development [12]. It can be accommodated at higher doses in the body because its concentration in the blood is well regulated by thyrocalcitonin and parathormone hormones[8].

Heavy Metals and Ecological alteration

Heavy metal contaminations of land resources also affected the ecosystem. Numerous environmental studies suggested and attract a great deal of attention worldwide. This is attributed to no-biodegradability and persistence of heavy metals in soils. With the intention of identify spatial relationship of heavy metals in soil ecosystem. Some studied areas had potential contaminations by heavy metals, especially by Cd, Cu, Pb and Zn accumulation due to industrialization, agricultural hazardous chemicals and other human activities. Pb, Cd, Hg, and As are widely dispersed in environment. These elements have no beneficial effects in humans, and there is no known homeostasis mechanism[13,14]. They are generally considered the most toxic to humans and animals; the adverse human health effects associated with exposure, yet at low concentrations, are assorted and embrace, except are not limited to, neurotoxic and carcinogenic actions[15-17].

The sewage sludge of municipal solid waste had high content of organic waste and heavy metals, which easily transfused in higher ratio of exchangeable Na^+, K^+, Ca^{2+} and Mg^{2+} in plants. These processes promote the increases of beneficial utilization of sewage sludge for agriculture prospects. High contents of organic matter and nutrients make sewage sludge a perfect material for fertilization and recultivation of degraded soils. In case of all sludges, a stimulating influence on seed germination was observed and inhibiting influence of sludges on germination root growth and development [18]. Alternative aerobic and aerobic composting of sewage sludge including carbonic garbage efficient for improvements and concern features of sludge for reutilization in comparison with sewage sludge. Results of uptake of heavy metals by watercress show that the accumulation of Cu, Ni, Cd, Cr, Pb, and Zn in crops. In general, more than 98% of the heavy metals in the wastewater were removed by the soil and the rest of about 2% heavy metals were removed by the plant cell. Toxic levels of heavy metals in the soil are responsible for the reduced pigment like chlorophyll content of plants growing in the polluted areas. After composting of sewage sludges, positively influences on the growth and development of *plants*[19].

Municipal solid waste also comprised hazardous material which contains high amounts of heavy metals. Among various water cleaning and recycling technologies, adsorption is cheapest and universally accepted process. Spent grain is a maximum applicable brewing industrial waste generated in mashing process. Spent grain is a lignocellulosic biomass, consists hemicellulose, cellulose and lignin in variable range. Citric acid directly interact with hydroxyl groups of cellulose, hemicellulose and lignin in spent grain by esterification, which frequently produced adsorbent suitable for adsorption of heavy metal ions and its removal.

Heavy metals and human exposure

Heavy metal pollution of surface and underground water results in considerable soil pollution and pollution increases when mined ores are dumped on the ground surface for manual dressing[20]. Cement industries released various absorbing chemicals which affect the outer surface of soil and dumping exposes of metals also altered the air ecosystem. In the same consequences agricultural soils are polluted, metals are taken up by plants and accumulate in their tissues[21]. Animals that graze on such contaminated plants and drink from polluted waters, as well as marine lives that breed in heavy metal polluted waters also accumulate such metals in their tissues, and milk, if lactating[22,23]. Humans are in turn exposed to heavy metals by consuming contaminated plants and animals, and this has been known to result in various biochemical disorders. In summary, all living organisms within a given ecosystem are variously contaminated along their cycles of food chain.

Occupational exposure

Occupational exposure is also specific factors which affect to human health. Heavy metal exposure affected significantly by the occupational areas. Workers of the mining and production of cadmium, chromium, lead, mercury, gold and silver have been reported to be thus exposed; also inhabitants around industrial sites of heavy metal mining and processing, are exposed through air by suspended particulate matters[23,24]. Nature of effects could be 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[25,26].

Industrial products which are used in homes, and which have been produced with heavy metals are sources of human exposure to such heavy metals. Mercury exposure is through disinfectants (like mercurochrome), antifungal agents, toiletries, creams and organometallic[25]. Cadmium exposure is through nickel/cadmium batteries and artist paints; lead exposure is through wine bottle wraps, mirror coatings, batteries, old paints and tiles and linolein amongst others. Infants are more susceptible to the endangering effects of exposure to heavy metals. Routes of exposure include inhalation, skin, eye contact, and ingestion[27-29].

Heavy Metal 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. Some general signs associated with cadmium, lead, arsenic, mercury, zinc, copper and aluminium poisoning: gastrointestinal disorders, diarrhoea, stomatitis, hemoglobinuria causing a rust-red colour to stool, ataxia, paralysis, vomiting and convulsion, depression, and pneumonia when volatile vapours and fumes are inhaled[25]. Exposure to toxic heavy metals is generally classified as acute, 14 days or less; intermediate, 15-354 days; and chronic, more than 365 days. Additionally, acute toxicity is usually from a sudden or unexpected exposure of high level of heavy metal. Chronic toxicity results from repeated or continuous exposure, leading to an accumulation of toxic substance in body. Chronic exposure may result beginning of contaminated food, air, water, dust, living near a hazardous waste site, spending time in areas with deteriorating lead paint; maternal transfer in the womb; or from participating in hobbies that use lead paint. Chronic exposure may occur in either the home or workplace. Symptoms of chronic toxicity are often similar to many common conditions and may not be readily recognized [9]. High exposure can lead to obstructive lung disease, Cd pneumonitis, resulting from inhaled dusts and fumes. Symptoms are chest pain, cough with foamy and bloody sputum, and death of lining of lung tissues because of excessive accumulation of watery fluids[30].

Arsenic

Arsenic is a metalloid. Arsenic is quite widely distributed in natural waters and is often associated with geological sources, but in some locations anthropogenic inputs, such as the use of arsenical insecticides or metal arsenides. and the combustion of fossil fuels, can be extremely important sources. Arsenic occurs in natural waters in oxidation states III and V, in the form of arsenous acid (H_3AsO_3) and its salts, and arsenic acid (H_3AsO_5) and its salts, respectively[31]. Toxic effects of arsenic depend specially on oxidation state and chemical species, among others. Inorganic arsenic is considered carcinogenic and is related mainly to lung, kidney, bladder, and skin disorders[32]. The arsenic related health problems have led to a rethinking of the acceptable concentration in drinking water[30]. Following a thorough review and in order to maximize health risk reduction, the USEPA in 2001 decided to reduce the drinking water maximum contaminant limit to 0.010mg/L, which is now the same as the WHO guidelines[31]. Chronic arsenic ingestion from drinking water has been found to cause carcinogenic and non-carcinogenic health effects in humans 33,34. Inorganic form of arsenic and concern complexes is responsible for acute, subchronic, genetic, developmental and reproductive toxicity[35], immuno-toxicity[37], biochemical, cellular toxicity and chronic toxicity[34]. Drinking water is one of the primary routes of exposure of inorganic arsenic[38]. Ingestion of groundwater with elevated arsenic concentrations and the associated human health effects are prevalent in several regions across the world. Arsenic toxicity and chronic arsenicosis is of an alarming magnitude particularly in South Asia and is a major environmental health disaster[39-41].

Exposure to arsenic occurs mostly in the workplace, near hazardous sites, or in areas with high natural levels. Symptoms of acute arsenic poisoning are sore throat from breathing, red skin at contact point, or severe abdominal pain, vomiting, and diarrhea, often within a hour after ingestion. Other symptoms are anorexia, fever, mucosal irritation, and arrhythmia. Cardiovascular changes are often restrained in early stages but can progress to cardiovascular collapse. Chronic or lower levels of exposure can lead to progressive peripheral and central nervous changes, such as sensory changes, numbness, tingling and muscle tenderness. Symptom are typically described is a burning sensation in hands and feet[42]. Neuropathy occurs after several years of exposure. There may also be excessive darkening of skin in areas that are not exposed to sunlight, excessive formation of skin on the palms and soles or white bands of arsenic deposits across the bed of fingernails.

Birth defects, liver injury, and malignancy are also possible via arsenic toxicity. The adverse effects of arsenic in groundwater used for irrigation water on crops and aquatic ecosystems are also of major concern. The fate of arsenic in agricultural soils is less characterized compared to groundwater. However, the accumulation of arsenic in rice field soils and its introduction into the food chain through uptake by the rice plant is of major concern mainly in Asian countries[36, 43].

Lead

Acute exposure to lead is also more likely to occur in workplace, particularly in manufacturing processes that include the use of lead like printing ink, gasoline, and fertilizer contain lead. Symptoms include abdominal pain, convulsions, hypertension, renal dysfunction, loss of appetite, fatigue, sleeplessness hallucinations, headache, numbness, arthritis and vertigo. Chronic exposure to lead may result in birth defects, mental retardation, autism, psychosis, allergies, dyslexia, hyperactivity, weight loss, shaky hands, muscular weakness and paralysis etc. In humans, about 20-50% of inhaled, and 5 to 15% of ingested inorganic lead is absorbed. In contrast, about 80% of inhaled organic lead is absorbed, and ingested organic Pb is absorbed readily[44]. Once in the bloodstream, lead is primarily distributed among blood, soft tissue, and mineralizing tissue. Lead is most significant toxin of heavy metals, and the inorganic forms are absorbed through ingestion by food and water, and inhalation[9]. A notably serious effect of lead toxicity is its teratogenic effect. Lead poisoning also causes inhibition of synthesis of haemoglobin; dysfunctions in kidneys, joints and reproductive systems, cardiovascular system, acute and chronic damage to central nervous system and peripheral nervous system[45]. Other effects include damage to gastrointestinal tract and urinary tract resulting in bloody urine, neurological disorder and can cause severe and permanent brain damage. While inorganic forms of lead, typically affect organs and other biosystems, organic forms predominantly affect the nervous system.

Lead affects children by leading to poor development of grey matter of brain, thereby resulting in poor intelligence quotient[45]. Symptoms of acute and chronic lead exposure could be allergies, arthritis, autism, colic, hyperactivity, mood swings, nausea, lack of concentration, seizures and weight loss. Children are particularly sensitive to lead and are prone to ingesting lead because they chew on painted surfaces and eat products not intended for human consumption. Food, air and drinking water are major sources of lead exposure. Plant food may be contaminated with lead through its uptake from ambient air and soil; animals may then ingest the lead contaminated vegetation. In humans, lead ingestion may arise from eating lead contaminated vegetation or animal foods. Another source of ingestion is through the use of lead containing vessels or lead based pottery glazes[46].

Mercury

Mercury is most toxic heavy metals, exposure of high levels of metallic, inorganic, organic mercury can damage brain, kidneys, and developing fetus[47,48]. Man released mercury into environment by actions of agriculture industry (fungicides, seed preservatives), by pharmaceuticals, as pulp and paper preservatives, catalysts in organic syntheses, in thermometers and batteries, in amalgams and in chlorine and caustic soda production[49, 50]. The toxicity of mercury depends on its chemical form (ionic < metallic <organic)[51]. Up to 90% of organic mercury is absorbed from food [52]. Acute mercury exposure may occur in mining industry and in manufacturing of fungicides, thermometers, and thermostats. Liquid mercury is attractive to children because of its beautiful silver color and unique behaviour when spilled. Children are more likely to incur acute exposure in home from ingesting mercury from a broken thermometer or drinking medicine that contains mercury. Mercury vapours status at floor level; crawling children are subject to a significant hazard when mercury is sprinkled throughout environment during ceremonies[53]. Mercury spills are difficult to clean up, and mercury may remain undetected in carpeting for some time. Symptoms of acute exposure are cough, sore throat, and shortness of breath, metallic taste in mouth, abdominal pain, nausea, vomiting and diarrhea, headaches, weakness, visual disturbances, tachycardia, and hypertension.

Chronic exposure to mercury may result in damage to central nervous system and kidneys. Mercury can be detected in most foods and beverages, at levels of < 1 to 50μg/kg [52]. It can also cross the placenta from the mother's body to fetus, accumulate, resulting in mental retardation, brain damage, cerebral palsy, blindness, seizures, and inability to speak. Dental amalgam is also suspected as being a possible source of mercury toxicity from chronic exposure. Higher levels are often found in marine foods. Organic Hg compounds easily pass across biomembranes and are lipophilic. Therefore elevated Hg ranges are mainly found in liver of lean species and in fatty fish species. Methyl mercury accumulated with fish age increasing trophic level. This leads to higher mercury ranges in old fatty predatory species like tuna, halibut, redfish, shark and swordfish[54]. Interestingly, metallic mercury used by dentists to manufacture dental amalgam is shipped as a hazardous material to dental offices. Although the ADA does not advise removing existing amalgam fillings from teeth, it does support ongoing research to develop new materials that will prove to be as safe as dental amalgam[54,55].

Symptoms in adults and children could include tremors, anxiety, forgetfulness, emotional instability, insomnia, fatigue, weakness, anorexia, cognitive and motor dysfunction, and kidney damage. People who consume more than two fish meals a week are showing very high serum levels of mercury. Risk assessment was based on two major epidemiology studies which investigated the relationship between maternal exposure to mercury through high consumption of contaminated fish and seafood and impaired neurodevelopment in their children[56-58].

Cadmium

Cadmium is naturally present in environment: in air, soils sediments and in unpolluted seawater. It is emitted to air by mines, metal smelters and industries. Exposure to cadmium occurs in workplace, particularly in manufacturing processes of batteries and color pigments paint, plastics, electroplating and galvanizing work. Symptoms of acute cadmium exposure are nausea, vomiting, abdominal pain and breathing difficulty. Chronic exposure to cadmium can result in chronic obstructive lung, renal and fragile bones disease[59]. Symptoms include alopecia, anemia, arthritis, learning disorders, migraines, growth impairment, emphysema, loss of taste and smell, poor appetite and cardiovascular disease. It associated with bone defects, *viz;* osteomalacia, osteoporosis and spontaneous fractures, increased blood pressure and myocardic dysfunctions etc. Severe exposure may consequence in pulmonary odema and death. Pulmonary effects (emphysema, bronchiolitis, alveoliitis) and renal effects may occur following subchronic inhalation exposure to Cd[60-62]. Cadmium uses increased by human with increasing technology that is serious consideration as possible contaminant. Tobacco smoke is one of the largest single sources of cadmium exposure; all of its forms contain appreciable amounts of metal. Because absorption of cadmium from lungs is much greater than from gastrointestinal tract, smoking contributes significantly to total body burden[63,64].

In general, for non-smokers and non-occupationally exposed workers, food products account for most of the human exposure burden to cadmium[3]. In contrast to lead and mercury ions, cadmium ions are readily absorbed by plants. Cadmium is taken up through the roots of plants to edible leaves, fruits and seeds. During the growth of grains such as wheat and rice, cadmium taken from soil is concentrated in core of kernel. Cadmium also accumulates in animal milk and fatty tissues[62.] Therefore, people are exposed to cadmium when consuming plant and animal based and sea foods[54,55].

Aluminum

Aluminum is not a heavy metal; environmental exposure is frequent, leading to concerns about accumulative effects and a possible connection with Alzheimer's disease. Acute exposure is more likely in workplace (e.g., unintentional breathing of aluminum-laden dust from manufacturing or metal finishing processes). Chronic exposure may occur in workplace from accumulated exposures to low levels of airborne Al dust and handling Al parts during assembly processes. In home, constant contact with Al in foods and in water; from cookware and soft drink cans; from consuming items with high levels of Al (e.g., antacids, buffered aspirin, or treated drinking water; or even by using nasal sprays, toothpaste, and antiperspirants). Citric acid may increase Al levels by its leaching activity. Interestingly, aluminium based coagulants are used in purification of water. However, the beneficial effects of using Al in water treatment have been balanced against health. Water purification facilities follow a number of approaches to minimize the level in finished water [54]. Symptoms of Al toxicity include memory loss, learning difficulty, loss of coordination, disorientation, mental confusion, colic, heartburn, flatulence, and headaches. Its absorption in the body is enhanced by Ca and Zn deficiencies. Acute and chronic effects of lead result in psychosis.

Zinc

Zinc has been reported to cause the same signs of illness as does lead, and can easily be mistakenly diagnosed as lead poisoning [25]. 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 [10]. The clinical signs of zinc toxicosis have been reported as vomiting, diarrhea, bloody urine, icterus, liver failure, kidney failure and anemia[9]. 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 a 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[1,8]. Toxicity symptoms depend on the chemical form ingested[8]. It is possibly carcinogenic in com-pounds of all its oxidation states and high-level exposure can cause death[3].

Assessment of exposure to heavy metals

Human exposure is defined by WHO as the amount of a substance in contact, over time and space, with the outer boundary of the body[55]. The assessment of human exposure to contaminant chemicals in the environment can be measured by two major methods, each based on different data profiles, thus permitting the verification and validation of the information. One approach involves environmental monitoring i.e., determining the chemical concentration scenario. Second methodology is based on estimations of exposure through the use of biomarkers[65]. Biomarkers are relevant indices in human health studies and are defined by the National Institute of Health (NIH) as a characteristic that is objectively measured and evaluated as an indicator of normal biological processes, pathogenic processes, or pharmacologic responses to a therapeutic intervention[66]. Biomarkers may be used at any level within biological organization (eg. molecular, cellular, or organ levels). These tools may be used to identify exposed individuals or groups, quantify the exposure, assess the health risks, or assist in diagnosis of environmental or occupational disease[67].

Diagnosed by biological body fluids

A crucial measure for assessment of exposure to hazardous chemicals, such as those from waste sites is evaluation of potentially exposed populations. This step also includes the degree, incidence extent, and routes of potential exposure. A most significant direct approach to assess exposure to hazardous substances within potentially exposed populations is to determine chemicals or metabolic products on some biological fluids such as blood or urine, with certain defined levels being a reliable indicator of metal exposure[68]. However, long term storage of some toxic metals takes place in hard tissues such as teeth and bones. Additionally, samples of keratinous tissue components (hair, nails) are commonly used for routine clinical screening and diagnosis of long term exposure. The levels of lead in bones, hair, and teeth increase with age, suggesting a gradual accumulation of lead in the body. Therefore, contamination of food with lead and the possibility of chronic lead intoxication through diet need constant monitoring. In addition, during mineralization of teeth cadmium and lead may persist within the matrix[69]. Most of ingested arsenic is rapidly excreted via the kidney within a few days. However, high levels of arsenic are retained for longer periods of time in bone, skin, hair, and nails of exposed humans[69]. Studies of arsenic speciation in the urine of exposed humans indicate that the metabolites comprise 10-15% inorganic arsenic and monomethylarsonic acid and a major proportion (60-80%) of dimethylarsenic acid. Recent studies have found monomethylarsonous acid and dimethylarsinous acid in trace quantities in human urine[68].

Biomarker Indicators

The biomarkers and various other groups of indicators have become widely used and play a significant role in trend analysis of exposures and chemical management response strategies. For example, higher plants, fungi, lichens, mosses, molluscs, and fish are important biomonitors for heavy metals contamination within the ecosystem. More recently, some cellular functions have been used as biomarkers. For example, autophagy pathway was proposed as a biomarker for renal injury induced by cadmium[70]. Non-invasive or a minimally invasive monitoring techniques are nowadays preferred, although these assays may require further improvement and validation. For example, the use of buccal micronucleus assay as a biomarker of DNA damage is a contribution of epidemiological studies[71]. Children hand rinsing was used as a biomarker of short term exposure to As[72].

Potential biomarkers include DNA and protein adducts, mutations, chromosomal aberrations, genes that have undergone induction and a host of other early cellular or subcellular events thought to link exposure impacts Three classes of biomarkers (exposure, effect and susceptibility) include measurements of parent compound, metabolites or DNA or protein adducts, and reflect internal doses, the biologically effective dose or target dose [73]. Biomarkers of effects could be changes on a cellular level, such as altered expression of metabolic enzymes, and may also include markers for early pathological changes in complex disease developments, such as mutations and preneoplastic lesions. Biomarkers of susceptibility indicate an often constitutive ability of an individual to respond to specific exposures[74].

Genomics and Proteomics

Progress in the fields of heavy metal assessment, genomics and proteomics is also reported and more recent attention is focussed on proteomics technologies involved in finding new and relevant biomarkers for metal assessment. For example, preclinical changes in people exposed to heavy metals were recently monitored and analysed by proteomics biomarkers[75]. In addition to urine and blood analysis proteomic profiling of serum samples, one representing the metal-exposed group and the other a control group, revealed three potential protein markers of preclinical changes in humans chronically exposed to a mixture of heavy metal[76,77].

Symptoms associated with heavy metal exposure also evaluated by the study of effects on human skin damage, stress signals. For example, heavy metals down regulated the phosphorylation levels of HSP27, and the ratio of p-HSP27 and HSP27 may be a sensitive marker or additional endpoint for hazard assessment of potential skin irritation caused by chemicals and their products have critically reviewed early indicators of cadmium damage in kidneys, such as a low-molecular-weight protein reabsorbed by the proximal tubules. Glycosuria, aminoaciduria, and the reduced ability of the kidney to secrete PAH are also indicators of nephrons damage by cadmium. An increase in urinary excretion of low and high molecular weight proteins occurs as damage increases, reflecting the decline in glomerular filtration rate[78].

Health risk Ratio Analysis

The human health risk evaluation is to essential phenomena ensure by the mode of action analysis (MOA), as a sequence of key events and processes, starting with interaction of an agent with a cell, proceeding through operational and anatomical changes, and formation of disease78. Unfavourable reactions in animal and bioassays procedure may provide significant and relevant information for a better understanding of human health risk ratio. Moreover, the relevance of animal testing data to humans is well established. However, the differences (e.g. gender, nutritional status, age, genetic predisposition, and frequency of exposure) in metabolism between species, added to some intra-specific differences are some limitations. In order to overlap these differences, a safety margin must be considered and finalised. Finally, the complexity and number of available possible biomarkers for heavy metals exposure may be led to the expansion of improved prognostic and diagnostic tools.

Biochemistry of toxicity

Heavy metals and their derivates or its complexes disrupt the human metabolic functions especially via two ways: (1). Accumulate and disruption of performing functions in vital organs and glands such as heart, brain, kidneys, bone, liver[2]. They displace the vital nutritional minerals from their original place, thereby, hindering their biological function. It is, however, impossible to live in an environment free of heavy metals. Many ways by which these toxins can be introduced into the body such as consumption of foods, beverages, skin exposure, and the inhaled air. Poisoning directly and indirectly concern with structural modification of heavy metals which represent the interference with the normal body functions or biochemistry involved 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 structure of available body's biomolecules such as proteins and enzymes to produce strong and stable chemical bonds.

The most toxic forms of these metals in their ionic species are the most stable oxidation states. For example, Cd^{2+}, Pb^{2+}, Hg^{2+}, Ag^{+} and As^{3+}. In their most stable oxidation states, they form very stable bio-toxic compounds with the body's bio-molecules, which become difficult to be dissociated, due to their bio-stabilities, during extraction from the body by medical detoxification therapy.

The hydrogen atoms or the metal groups are replaced by poisoning metal and the enzyme is thus inhibited from functioning, whereas the protein metal compound acts as a substrate and reacts with a metabolic enzyme. In reaction (equation 1), enzymes (E) react with substrates (S) in either by the lock and key pattern or by the induced fit pattern, both cases a substrate fits into an enzyme in a highly specific fashion, due to enzyme chirality's, to produce an enzyme-substrate complex (E-S*) as follows 8.

E + S E-S E – S* E – P E + P (1)

[E = Enzyme; S = Substrate; P = Product; * = Activated Complex]

While at the E-S, E–S* and E-P states, an enzyme cannot accommodate any other substrate until it is freed. Sometimes, the enzymes for an entire sequence co-exist together in one multi-enzyme complex consisting of three or four enzymes. Product from one enzyme reacts with a second enzyme in a chain connecting process, with the last enzyme yielding the final product as follows: The final product (F) goes back to react with the first enzyme thereby inhibiting further reaction since it is not the starting material for the process. Hence, the enzyme E_1 becomes incapable of accommodating any other substrate until F leaves and F can only leave if the body utilizes it. If the body cannot utilize the product formed from the heavy metal protein substrate, there will be a permanent blockage of the enzyme E_1, which then cannot initiate any other bio-reaction of its function. Therefore, the metal remains embedded in the tissue, and will result in bio-dysfunctions of various gravities[8].

Furthermore, a metal ion in the body's metallo-enzyme can be conveniently replaced by another metal ion of similar size. Thus Cd^{2+} can replace Zn^{2+} in some dehydrogenating enzymes, leading to cadmium toxicity. In the process of inhibition, the structure of a protein particle can be mutilated to a bio-inactive pattern, and in the case of an enzyme can be completely destroyed. For example, toxic As^{3+} occurs in herbicide, fungicides and insecticides, and can interact with–SH groups in enzymes which further inhibit their possible bioactivities[13].

Research also indicates that Nitric Oxide (NO) is involved in the regulation of multiple plant responses to a variety of abiotic and biotic stresses[77]. Nitric Oxide NO helps plants resist heavy metal stress, by indirectly scavenging heavy metal induced Reactive Oxygen Species; It might be involved in increasing antioxidant content and anti-oxidative enzyme activity.

Second, by affecting root cell wall components it might increase heavy metal accumulation in root cell walls and decrease heavy metal accumulation in soluble fraction of leaves in plants. Finally, it could function as a signalling molecule in cascade of events leading to changes in gene expression under heavy metal stresses in the plant cell.

CONCLUSION

Metal toxicity concern with problem. However, certain groups of metal are at a higher risk, have been proved to be toxic for human and environmental health. Owing to their toxicity and their possible bioaccumulation, metals are in many ways indispensable, good precaution and adequate occupational hygiene. Workers of industries that manufacture batteries, pesticides, fertilizer, metal finishing industries and chemicals in scientific/ laboratory concern workers are easily exposed to the metal. Unrecognized toxicity will likely result in illness or reduced quality of life. Testing is essential if someone in our household might have concern toxicity. If diagnosed and the results are positive, initiation of appropriate conventional and natural medical procedures described earlier in protocol might be required. However, many proactive things you can do to provide yourself with natural chelating, detoxifying, anti-inflammatory, and antioxidant qualities and to assist your vital organs in performing at their best.

Although heavy metal poisoning could be clinically diagnosed and medically treated, the best option is to prevent heavy metal pollution and subsequent human poisoning. These compounds should be subject to compulsory monitoring. Some separation and detection methodology are available for laboratories engaged in routine investigation of biological samples. Developing molecular biological methods is bringing valuable advantages to the analytical field. Governments should encourage harmonized information collection, investigate, legislation, regulations, and believe on apply of indicators. Each of the two assessment methods outlined above provide useful data helping to set standards and guideline values designed to protect ecological balances from heavy hazard. Exposure measurements are essential for the protection of high risk populations.

REFERENCES

1. Lenntech R. Water Treatment and Air Purification, Published by Lenntech, Rotterdamseweg, Netherlands (2004).
2. Farlex Definition: Environment, The Free Dictionary, Farlex Inc. Publishing, U.S.A. (2005).
3. Gore A. Respect the land, Our Precious Plant, *Time Magazine*, 150, 17A: 8-9 (1997).
4. Peplow D. Environmental Impacts of Mining in Eastern Washington, Center for Water and Watershed Studies Fact Sheet, University of Washington, Seattle (1999).
5. United Nations Environmental Protection/Global Program of Action (2004). Why The Marine Environment Needs Protection From Heavy Metals, Heavy Metals, UNEP/GPA Coordination Office (2004).

6. United States Department of Labor. Occupational Safety and Health Administration (OSHA); Safety and Health Topics: Heavy metals, USDOL Publication, Washington, D.C (2004).
7. Habashi F. Environmental Issues in the Metallurgical Industry – Progress and Problems, Environmental Issues and Waste Management in Energy and Mineral Production. *Balkama, Rotherdam*, pp. 1143 -1153 (1992).
8. Holum J. R. Elements of General and Biological Chemistry, 6th Edition, John Wiley and Sons, *N.Y.* pp. 324, 326, 353, 469 (1983).
9. Ferner D.J. Toxicity, heavy metals. *eMed. J*. 2(5): 1 (2001).
10. Nolan K. Copper Toxicity Syndrome, *J. Orthomol. Psychiatry* 12(4): 270 -282 (2003).
11. Young R.A. Toxicity Profiles: Toxicity Summary for Cadmium, Risk Assessment Information System, RAIS, University of Tennessee (2005).
12. McCluggage D. Heavy Metal Poisoning, NCS Magazine, Published by The Bird Hospital, CO, U.S.A. (1991).
13. Draghici C., Coman G., Jelescu C., Dima C. and Chirila, E. Heavy metals determination in environmental and biological samples, In: Environmental Heavy Metal Pollution and Effects on Child Mental Development- Risk Assessment and Prevention Strategies, NATO Advanced Research Workshop, Sofia, Bulgaria, 28 April-1 May (2010).
14. Vieira C., Morais S., Ramos S., Delerue-Matos C. and Oliveira M.B.P.P. Mercury, cadmium, lead and arsenic levels in three pelagic fish species from the Atlantic Agency for Toxic Substance and Disease Registry (ATSDR). (2008). Draft Toxicological Profile for Cadmium U.S. Department of Health and Humans Services, Public Health Humans Services, Centers for Diseases Control. Atlanta (2011).
15. Castro-Gonzalez, M.I. and Mendez-Armenta M. (2008) Heavy metals: Implications associated to fish consumption. *Environmental Toxicology & Pharmacology*, 26, 263-271.
16. Jomova K. and Valko M. Advances in metal-induced oxidative stress and human disease. *Toxicology*, 283, 65-87 (2010).
17. Tokar E. J., Benbrahim-Tallaa L. and Waalkes M.P. Metal ions in human cancer development. *Metal Ions on Life Science*, 8, 375-401 (2011).
18. Pandey R., Singh P. K, Pandey S. K., Singh, B. Patel B.L. and Dwivedi M. K. Heavy metals Investigation in productivity parts of wheat crop during winter seasons in Singrauli district of Madhya Pradesh India: *A Case Study International Journal of Green and Herbal Chemistry Sec. A*; Vol.4, No.1, 208-220 (2015).
19. Pandey R. and Pandey S. K. Trace metal accumulation in vegetables grown in industrial and semi-urban areas of Singrauli district of Madhya Pradesh, India. *International Journal of Pharmaceutical Science and Research*. (12), 5518-5529 (2014).
20. Garbarino J. R., Hayes H., Roth D, Antweider R, Brinton T.I. and Taylor H. Contaminants in the Mississippi River, U. S. Geological Survey Circular 1133, Virginia, U.S.A. (1995).
21. Trueby P. Impact of Heavy Metals On Forest Trees From Mining Areas. In: International Conference On Mining And The Environment III, Sudbury, Ontario, Canada (2003).

22. Ogwuegbu M.O. and Ijioma M.A. Effects of Certain Heavy metals on the population due to mineral exploitation. In: International Conference on Scientific and Environmental Issues In The Population, Environment and Sustainable Development in Nigeria, University of Ado Ekiti, Ekiti State, Nigerian, pp. 8-10 (2003).
23. Horsfall M.N. and Spiff A.I. Speciation of Heavy Metals in Intertidal Sediments of the Okirika River System (Nigeria), *Bull. Chem. Soc. Ethiop*. 13, 1:1-9 (1999).
24. Heyer N. J. Neurological Disorder in Three Aluminium Smelter Workers, *Arch. Intern. Med*. 145(11): 1972-1975 (1985).
25. Ogwuegbu M. O. C. and Muhanga W. Investigation of Lead Concentration in the Blood of People in the Copperbelt Province of Zambia, *J. Environ*. (1): 66-75 (2005).
26. Apostoli P. and Catalani S. Metal ions affecting reproduction and development. *Metal Ions in Life Science*, 8, 263-303 (2011).
27. FAO/WHO Expert Committee on Food Additives, Arsenic. (2005). Available from http://www.inchem.org/documents/jecfa/jeceval/jec_159.htm
28. Michalski R. Trace level determination of Cr(III)/Cr(VI) in water samples using ion chromatography with UV detection. *Journal of Liquid Chromatography & Related Technologies*, 28, 2849-2862 (2005).
29. Costa M. Toxicity and carcinogenecity of Cr(VI) in animal models and humans. *Critical Review in Toxicology*, 27, 431-442 (1997).
30. Michalski R. Applications of ion chromatography for the determination of inorganic cations. *Critical Reviews in Analytical Chemistry*, 39, 230-250 (2009).
31. Sawyer C.N., McCarty P.L. and Parkin, G.F. Chemistry for environmental and Engineering and Science 5th ed, Mc Graw Hill, ISBN 0-07-248066-1, New York (2003).
32. Agency for Toxic Substance and Disease Registry (ATSDR). Toxicological Profile for Arsenic U.S. Department of Health and Humans Services, Public Health Humans Services, Centers for Diseases Control. Atlanta (2003a).
33. Pandey S. and Pandey R. Cadmium Monitoring among some plants and vegetables species in Singrauli Region of Madhya Pradesh. *International Journal of Pharmaceutical Science and Research* (11), 4482-4488 (2012).
34. Guney M., Zagurya G.J., Doganb N. and Onayb T.T. Exposure assessment and risk characterization from trace elements following soil ingestion by children exposed to playgrounds, parks and picnic areas. *Journal of Hazardous Materials*, 182, 656-664 (2010).
35. Agency for Toxic Substance and Disease Registry (ATSDR). Toxicological Profile for Mercury U.S. Department of Health and Humans Services, Public Health Humans Services, Centers for Diseases Control. Atlanta (2003b).
36. Mudhoo A., Sharma S.K., Garg V.K. and Tseng C-H. Arsenic: an overview of applications, health, and environmental concerns and removal processes. *Critical Reviews in Environmental Science & Technology*, 41, 435-519 (2011).

37. Chakraborti D., Sengupta M.K., Rahaman M.M., Ahamed S., Chowdhury U.K. and Hossain M.A. Groundwater arsenic contamination and its health effects in the United States Environmental Protection Agency (USEPA). (2010a) (2004).
38. Bhattacharya P., Welch A.H., Stollenwerk K.G., McLaughlin M.J., Bundschuh J. and Panaullah G. Arsenic in the environment: *Biology and Chemistry, Science of the Total Environment*, 379, 109-120 (2007).
39. Sakurai T., Kojima C., Ochiai M., Ohta T. and Fujiwara K. Evaluation of in vivo acute immunotoxicity of a major organic arsenic compound arsenobetaine in seafood. *International Immunopharmacology*, 4, 179-184 (2004).
40. Kapaj S., Peterson H., Liber K. and Bhattacharya P. Human health effects from chronic arsenic poisoning: a review. *Journal of Environmental Science Health Part A, Environmental Science Engineering Toxic Hazard Substance Control*, 41, 2399-2428 (2006).
41. National Research Council. Arsenic in drinking water-Update. Washington DC, National Academy Press (2001).
42. Duxbury J. M., Mayer A.B., Lauren J.G. and Hassan N. Food chain aspects of arsenic contamination in Bangladesh: effects on quality and productivity of rice. Journal of Environmental Science Health Part A, *Environmental Science Engineering & Toxic Hazard Substance Control*, 38, 61-69 (2003).
43. Ortega R. Analytical Methods for Heavy Metals in the Environment: Quantitative Determination, Speciation, and Microscopic Analysis, In: Heavy Metals in the Environment, Sarkar, B. (Ed), pp. 35-68, Marcel Dekker Inc., ISBN 0-8247-0630-7, New York (2002).
44. Udedi S.S. From Guinea Worm Scourge to Metal Toxicity in Ebonyi State, Chemistry in Nigeria as the New Millennium Unfolds, 2(2): 13-14 (2003).
45. Ming-Ho Y. Environmental Toxicology: Biological and Health Effects of Pollutants, Chap.12, CRC Press LLC, ISBN 1-56670-670-2, 2nd Edition, BocaRaton, USA (2005).
46. WHO. Evaluation of certain food additives contaminants. Sixty-first report of the joint FAO/WHO Expert Committee on Food Additives. WHO Technical Report Series, No. 922 (2004b).
47. Oehlenschläger J. Identifying heavy metals in fish In: Safety and Quality issues in fish processing, Bremner, H.A. (Ed), pp. 95-113, Woodhead Publishing Limited, 978-1-84569-019-9, Cambridge (2002).
48. Agency for Toxic Substances and Disease Registry (ATSDR). Toxicological Profile for Copper. U.S. Department of Health and Humans Services, Public Health Service, Centers for Diseases Control. Atlanta (2004).
49. Zhang I. and Wong M.H. Environmental mercury contamination in China: sources and impacts. *Environment International*, 33, 108-121 (2007).
50. Clarkson T. The toxicology of mercury and its chemical compounds. *Critical Reviewsin Toxicology*, 36, 609–662 (2006).
51. Reilly C. Pollutants in Food-Metals and Metalloids, In: Mineral Components in Foods, Szefer P. And Nriagu J.O. (Eds), pp. 363-388, Taylor & Francis Group, ISBN 978-0-8493-2234-1, Boca Raton, FL (2007).

52. Figueroa, E. Are more restrictive food cadmium standards justifiable health safety measures or opportunistic barriers to trade? An answer from economics and public health. *Science of the Total Environment*, 389, 1-9 (2008).
53. WHO. Guidelines for drinking-water quality. Sixty-first meeting, Rome, 10-19 June 2003. Joint FAO/WHO Expert Committee on Food Additives, Avaible from http://ftp.fao.org/es/esn/jecfa/jecfa61sc.pdf (2004a).
54. WHO. Evaluation of certain food contaminants. Sixty-fourth report of the Joint FAO/ WHO Expert Committee on Food Additives. WHO Technical Report Series, No. 930 (2006).
55. Grandjean P., Weihe P., White R.F., Debes F., Araki S., Yokoyama K., Murata K., Sorensen N. Dohl R. and Jorgensen, P.J. Cognitive deficit in 7-year-old children with prenatal exposure to methylmercury. *Neurotoxicology & Teratology*, 19,417-428 (1997).
56. WHO/IPCS. Human Exposure Assessment, Environmental Health Criteria 214, WHO, Geneva (2000).
57. Peterson P.J. Assessment of Exposure to Chemical Pollutants in Food and Water, In:Mineral Components in Foods, Szefer P. And Nriagu J.O. (Eds), pp. 413-431, Taylor & Francis Group, ISBN 978-0-8493-2234-1, Boca Raton, FL (2007).
58. National Institute of Health. Biomarkers Definitions Working Group. Biomarkers and Surrogate endpoints: preferred definitions and conceptual framework. *Clinical Pharmacology & Therapeutics*, 69, 89-95 (2001).
59. Cocker J., Morton J., Warren N., Wheeler J.P. and Garrod A.N. Biomonitoring for chromium and arsenic in timber treatment plant workers exposed to CCA wood preservatives. *Annals of Occupational Hygiene*, 5, 517-525 (2006).
60. European Commission. Regulation (EC) No 1881/2006. JO L364,20.12.06, pp.5-24 (2006).
61. ExtoxNet. Cadmium contamination of food, Available from http://ace.orst.edu/ info/extoxnet/faqs/foodcon/cadmium.htm (2003).
62. Joint FAO/WHO Expert Committee on Food Additives (JECFA). Safety evaluation of certain food additives and contaminants. WHO Food Additives Series No 52 (2004).
63. Aitio A., Bernard A., Fowler B.A. and Nordberg G.F. Biological monitoring and biomarkers. In: Handbook on the Toxicology of Metals, Nordberg, G.F., *et al*. (Eds.), pp. 65-78, Academic Press/Elsevier, 3rd ed., ISBN 0-123694132, USA (2007).
64. Fischer A., Wiechuła D., Postek-Stefańska L. and Kwapulinski J. Concentrations of metals in maxilla and mandible deciduous and permanent human teeth. *Biology of Trace Elements Research*, 132, 19-26 (2009).
65. Mandal B.K., Ogra Y. and Suzuki K.T. Speciation of arsenic in human nail and hair from arsenic-affected area by HPLC-inductively coupled argon plasma mass spectrometry. *Toxicology & Applied Pharmacology*, 189, 73–83 (2003).
66. Chargui A., Zekri S., Jacquillet G., Rubera I., Ilie M., Belaid A., Duranton C., Tauc M., Hofman P., 70 Poujeol, P., May, M.V. and Mograbi, B. Cadmium-induced autophagy in rat kidney: an early biomarker of subtoxic exposure. *Toxicology Science*, 121, 31-42 (2011).

67. Kot A. and Namiesnik J. The role of speciation in analytical chemistry. *Trends in Analytical Chemistry*, 19, 69-79 (2000).
68. Katz S.A. and Salem H. Chemistry and toxicology of building timbers pressure treated with chromate copper arsenate: a review. *J. of Applied Toxicology*, 25, 1-7 (2005).
69. Oehlenschläger, J. Identifying heavy metals in fish In: Safety and Quality issues in fish processing, Bremner, H.A. (Ed), pp. 95-113, Woodhead Publishing Limited, 978-1845 Cambridge (2002).
70. Ceppi M., Biasotti B., Fenech M. and Bonassi S. Human population studies with the exfoliated buccal micronucleus assay: statistical and epidemiological issues. *Mutation Research*, 705, 11-19 (2010).
71. Shalat S.L., Solo-Gabriele H.M., Fleming L.E., Buckley B.T., Black K., Jimenez M., Shibata T., Durbin M., Graygo J., Stephan W. and Van De Bogart G. A pilot study of children's exposure to CCA-treated wood from playground equipment. *Science of Total Environment*, 367, 80-88 (2006).
72. Silins I. and Johan Högberg J. Combined toxic exposures and human health: biomarkers of exposure and effect. *International Journal of Environmental Research & Public Health*, 8, 629-647 (2011).
73. Mattusch J. and Wennrich R. Novel analytical methodologies for the determination of arsenic and other metalloid species in solids, liquids and gases. *Mikrochimica Acta*, 51, 137-139 (2005).
74. Nordberg G.F. Biomarkers of exposure, effects and susceptibility in humans and their application in studies Harrison N. (2001). Inorganic contaminants in food, In: Food Chemical Safety Contaminants, Watson, D.H. (Ed.), pp. 148-168, Ltd, first Edition, Woodhead Publishing ISBN 1-85573-462-1, Cambridge (2010).
75. Vlaanderen J., Moore L. E., Smith M. T., Lan Q., Zhang L., Skibola C. F., Rothman N. and Vermeulen R. Application of OMICS technologies in occupational and environmental health research; current status and projections. *Occupational & Environmental Medicine*, 67, 136-43 (2010).
76. Middendorf, P.J. & Williams, P.L. Nephrotoxicity: Toxic Responses of the Kidney, In: Principles of Toxicology Environmental & Industrial Applications, Williams, P.L., James, (2000).
77. Institutes of Environmental Conservation and Research INECAR. Position Paper Against Mining in Rapu-Rapu, Published by INECAR, Ateneo de Naga University, Philippines (www.adnu.edu.ph/Institutes/ Inecar/pospaper1.asp) (2000).
78. Zhang X. and Zhang C. Atomic Absorption and Atomic Emission Spectrometry, In: Handbook of Elemental Speciation: Techniques and Methodology, Cornelis, R., Caruso, J.Crews, H. & Heumann, K. (Eds), pp. 241-257, John Wiley & Sons Ltd, ISBN: 0-471-49214-0, West Sussex, England (2003).