Arsenic induced diseases in human beings, their diagnosis & treatment

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ABSTRACT

In the modern age with the increased population, transportation and industrialization, our atmosphere is being constantly contaminated by huge number of toxic and harmful chemicals, gases and other substances. Human beings are freely exposed to them every day. These harmful chemicals reach inside the human body by the common ways which include air, water and food. Arsenic is one of the most harmful chemicals present in the environment. The arsenic toxicity in the body is called as arsenicosis. Continuous exposure to arsenic and arsenicals causes severe diseases in human beings like cancer. Arsenic induced diseases are difficult to recognize because the signs and symptoms are not seen in the early stage and they are non-specific. Moreover there are not sufficient medicines available to treat arsenic poisoning. A variety of skin diseases are caused by arsenic exposure. In the presented review authors have summarized various arsenic induced skin diseases, their signs and symptoms, diagnosis and treatment.

Keywords: Arsenicosis, cancer, skin diseases.

INTRODUCTION

Arsenic poisoning is a medical condition caused by elevated levels of arsenic in the body. The dominant basis of arsenic poisoning is from ground water that naturally contains high concentrations of arsenic. A 2007 study found that over 137 million people in more than 70 countries are probably affected by arsenic poisoning from drinking water [1]. Humans are exposed to arsenic (As) primarily from air, food and water [2]. However, elevated inorganic arsenic in drinking water is the major cause of arsenic toxicity. They can be contaminated by drinking water of natural sources which have origin in arsenic rich area [3]. They can eat the food which is grown through spray of arsenic rich pesticides or by irrigation with arsenic rich water. They may come in contact with arsenic contaminated dusts, fumes, or mists [4]. So arsenic enters inside the body in low doses through food and water, then its absorption takes place in stomach and intestine, then it enters to the systemic circulation. It is then metabolized by liver to less toxic form and excreted by kidney in urine. But if the exposure is to larger extent then it leads to accumulation of arsenic in body [5]. The clinical manifestations of arsenic toxicity are primarily on skin because the diagnosis is specific, although often arsenic affects many parts and organs of the body. Minor alternative pathways of entry are known through inhalation and dermal exposure. Arsenic is basically a protoplastic poison because it interferes with the sulphhydryl groups of cellular proteins, enzymes and thus interferes with cell respiration and mitosis [6]. Chronic arsenic poisoning is popular and well known from the ancient time. Its many medicinal uses are also well reported such as in the treatment of asthma, leukaemia [7], syphilis [8], topical eosinophilia [9], treponosomiasis [10], lichen planus, verruca planum and psoriasis [11]. Domestically it is used as pesticide, weedicide and rodenticide in agriculture [12].

Nowadays, it is well known that the various forms of an element have different toxic and pharmacological effects on animal and human beings [13]. This is same in compounds whose toxicity greatly varies. The inorganic forms of arsenic exhibit the highest toxicity level, while organoarsenicals are usually less toxic than the inorganic arsenic species. Indeed, some organic arsenic compounds, such as arsenobetaine (AsBet) and arsenocholine (AsChol) are
well tolerated by living organisms [14]. So, in the modern time it is most essential to determine the quantitative limits of arsenic in the inorganic compounds, biological fluids and specially in drugs obtained from the marine sources. The methods must be developed to reduce concentration of arsenic as well as to reduce its exposure to human beings so as to reduce the health related risks.

**SOURCES OF ARSENIC EXPOSURE**

Arsenic is widely distributed throughout Earth’s crust, generally as arsenic sulfide or as metal arsenates and arsenides. It can be released to the atmosphere, primarily as the trioxide, mainly by high-temperature processes. In the atmosphere, it is mainly adsorbed on particles, which are dispersed by winds and deposited on land and water [15]. Arsenic can be released into the atmosphere and water in the following ways:

- Natural activities, such as volcanic activity, dissolution of minerals (particularly into groundwater), exudates from vegetation and wind-blown dusts;
- Human activities, such as mining, metal smelting, combustion of fossil fuels, agricultural pesticide production and use, and timber treatment with preservatives;
- Remobilization of historic sources, such as mine drainage water;
- Mobilization into drinking-water from geological deposits by drilling of tube wells [16].

**Drinking-water**

Drinking-water poses the greatest threat to public health from arsenic. Inorganic arsenic is naturally present at high levels in the groundwater of a number of countries, such as Argentina, Chile, China, India (West Bengal), Mexico, the United States of America, and particularly Bangladesh where approximately half of the total population is at risk of drinking arsenic-contaminated water from tube wells. In one estimate, consumption of arsenic-contaminated drinking-water in Bangladesh resulted in about 9100 deaths and 125000 disability-adjusted life years (DALYs) in 2001 [17].

Since 1963, WHO has specified limits for arsenic in drinking water for public health safety. In 1963 it was fixed as 50µg/L of drinking water. But later considering the risk of cancer and other health related problems, in 1992 this limit was reduced to 10µg/L [18]. Elevated concentration of arsenic in drinking water have primarily resulted from natural sources such as erosion and leaching from geological formations or anthropogenic sources. Along with this arsenic used for industrial purposes, mining, metal processing and pesticides and fertilizers are other major sources of drinking water contamination.

**Industrial Processes**

Most arsenic in industrial processes is used to produce antifungal wood preservatives, which can lead to soil contamination. It is also used in the pharmaceutical and glass industries, in the manufacture of alloys, sheep dips, leather preservatives, arsenic-containing pigments, antifouling paints and poison baits and, to a diminishing extent, in the production of agrochemicals (especially for use in orchards and vineyards). Arsenic compounds are also employed in limited amounts in the microelectronics and optical industries. High arsenic levels in air can be found in the working environment as well as the general environment around non-ferrous metal smelters, where arsenic trioxide may be formed, and some coal-fired power plants (especially those using low-grade brown coal) [19]. Arsenic is also used in the pharmaceutical and glass industries, in the manufacture of alloy, sheep dips, leather preservatives, arsenic containing pigments, antifouling paints and poison bait.

**Food**

In areas where arsenic is not naturally present at high levels, food usually contributes most to the daily intake of arsenic. Fish, shellfish, meat, poultry, dairy products and cereals are the main sources of dietary intake. However, the arsenic content of fish and shellfish usually involves organic compounds (e.g. arsenobetaine) that are of low toxicity [15]. In areas where arsenic is naturally present at high levels, food (e.g. rice) prepared with high-arsenic water and food crops irrigated with contaminated water also contribute to total daily intake.

**Smoking**

Some reports have indicated that smoking is associated with a decreased ability to methylate ingested arsenic. Exposure of smokers to arsenic arises from the natural inorganic arsenic content of tobacco [20]. This content is increased where tobacco plants have been treated with lead arsenate insecticide. Smelter workers, who have an elevated risk of developing lung cancer due to arsenic exposure, further increase their risk by smoking [21].

**Cosmetics**

Cosmetics are another source of arsenic exposure. It includes the non-standardized cosmetics where limit tests have not been carried out for heavy metals. Here the exposure of arsenic mainly occurs on the dermis. The intensity of
exposure depends upon duration of cosmetics on the skin, nature of ingredients such as permeation enhancers etc [22].

Air
Arsenic is present in the air in the form of particulate matter. It generally exists as arsenite and arsensenate. The inorganic arsenic is present in negligible amounts. Places where spread of insecticides and pesticides is regular, in the surrounding of industries the air is rich in arsenic which is inhaled inside through breathing. Human exposure to arsenic through air occurs at very low concentrations ranging from 0.4-30ng/m³ [23].

CHEMISTRY AND TOXICITY OF ARSENIC
Arsenic exists in two oxidation states: Arsenite (AsO₂⁻, As III) which is trivalent and Arsenate (AsO₄³⁻, As V) which is pentavalent. Trivalent arsenic is 60 times more toxic than pentavalent arsenic. Organic arsenic is non-toxic whereas inorganic arsenic is very toxic.

From the toxicological and pharmacological studies it has been revealed that arsenic toxicity inactivates upto 200 enzymes which are involved in cellular energy pathways and DNA replication and repair. It is substituted in high energy rich compounds such as adenosine triphosphate. The unbound arsenic is also toxic and it shows its toxicity through generation of reactive oxygen intermediates which cause lipid peroxidation and cause severe damage to DNA [24]. The trivalent arsenic binds to sulphydryl or thiol groups of proteins of various organs like liver, kidney, lungs, spleen, GIT and keratin rich skin, hair and nails [25].

ABSORPTION AND METABOLISM
The absorption of ingested arsenic occurs majorily in the small intestine which involves an electrogenic process and proton (H⁺) gradient [26]. The optimal pH for arsenic absorption is 5.0 [27], though in the milieu of the small bowel the pH is approximately 7.0 due to pancreatic bicarbonate secretion [28]. The absorbed arsenic is metabolised by liver through biomethylation to form monomethylarsonic acid and dimethylarsinic acid. These metabolites are less toxic but not completely innocuous [29, 30]. About 50% of the ingested dose may be eliminated in the urine in three to five days. Dimethylarsinic acid is the dominant urinary metabolite (60%–70%) compared with monomethylarsenic acid [31]. A small amount of inorganic arsenic is also excreted unchanged. After acute poisoning electrothermal atomic absorption spectrometry studies show that the highest concentration of arsenic is in the kidneys and liver [32].

ARSENIC POISONING
Acute Poisoning: The symptoms of acute poisoning appear within 30 minutes after ingestion, but they appear late if arsenic is ingested through the food. The person feels a metallic taste and garlic like odour in breaths. Sometimes he feels difficulties in swallowing associated with dry mouth. Most cases of acute arsenic poisoning occur from accidental ingestion of insecticides or pesticides and less commonly from attempted suicide. Small amounts (<5 mg) result in vomiting and diarrhoea but resolve in 12 hours and treatment is reported not to be necessary [33]. The lethal dose of arsenic in acute poisoning ranges from 100 mg to 300 mg [34]. The early clinical symptoms which appear are severe nausea, vomiting, muscular pain, weakness, skin flushing etc. In some cases it may lead to capillary damage which results in vasodilation, transudation of plasma, and shock. The patients feel severe thirst, numbness, diarrhoea with watery stools, reddish rashes and drowsiness. Other clinical outcomes of acute arsenic poisoning include severe abdominal pain, haemaglobinuria [35], intravascular coagulation, bone marrow depression [36], severe pancytopenia, and normocytic normochromic anaemia and basophilic stippling and in some cases renal failure has been also reported. In nervous system it can cause severe peripheral neuropathy which may last for up to two years [37-38]. In extreme cases death may occur within the first 24 hours.

Chronic Poisoning: The long term exposure to arsenic is a serious matter and it involves complications in so many organs in which the most threatening is the malignancy. The consequences depend upon amount of exposure and duration of exposure. The clinical symptoms of chronic arsenic poisoning vary from person to person, geographic area and different population groups. Chronic arsenic poisoning is much more insidious in nature, often involving multiple hospital admissions before correct diagnosis is made. The symptoms are non specific such as abdominal pain, diarrhoea and sore throat [39].

AILMENTS CAUSED IN VARIOUS BODY ORGANS
Skin: So many changes occur in the skin when it is continuously exposed to arsenic for a long time [40]. The dermatological symptoms are considered for primary diagnosis such as hyper-pigmentation, keratosis of palm and sole [41]. The keratosis may appear in the form of uniform nodules. Arsenical hyperkeratosis appears predominantly on the palms and the plantar aspect of the feet, although involvement of the dorsum of the extremities and the trunk have also been described [42]. In the early stages, the involved skin might have an indurated, gritlike character that
can be best appreciated by palpation; however, the lesions usually advance to form raised, punctated, 2-4 mm wart like keratosis that are readily visible. Occasional lesions might be larger (0.5 to 1 cm) and have a nodular or horny appearance occurring in the palm or dorsum of the feet. In severe cases, the hands and soles present with diffuse verrucous lesions [43]. Arsenic associated skin cancer, Bowen’s disease, is an uncommon manifestation in Asians and may be due to the high skin melanin content and increased exposure to ultraviolet radiation. Arsenic may cause a basal cell carcinoma in a non-melanin pigmented skin. The latent period after exposure may be as long as 60 years and has been reported in patients treated with Fowler’s solution, in sheep dip workers, in vineyard workers using arsenical pesticides, and from drinking contaminated wine. Another manifestation due to arsenic deposition in keratin rich areas are prominent transverse white lines in the finger nails and toe nails called Mee’s lines [44].

Arsenic-induced Bowen’s disease (As-BD) is among the most common type of arsenic skin cancers. As-BD is characterized by acanthosis (increased proliferation) and dysplasia with moderate dermal inflammation. Studies have revealed that aberrant proliferation, aneuploidy, centrosome amplifications, Aurora A and Aurora B expression were significantly enhanced in As-BD. Epigenetic analysis revealed that arsenic induces SUV39 expression, which in turn activates E2F, leading to Aurora A expressions and centrosome abnormalities in arsenic-treated keratinocytes. In addition, arsenic activates NF-kB and enhances Aurora-B expression. Furthermore, arsenic induces expression of miRNA203, a keratinocyte specific miRNA, decreasing TAp63/ΔNp63 ratio, leading to aberrant cell proliferation. Inflammatory cells play an important role in facilitating arsenic carcinogenesis in the skin [45].

In the large scale population study in West Bangal region of India it was found that there was a relationship between concentration of arsenic which was consumed through drinking of tube well water and amount of hyperpigmentation and keratosis in people.

**Gastro-Intestinal Tract:** Diarrhoea is the primary symptom of acute arsenic poisoning in GIT [46]. In chronic arsenic poisoning diarrhoea occurs in recurrent pattern and is associated with vomiting. On the basis of diarrhoea arsenic poisoning is suspected if it is accompanied by other symptoms like skin pigmentation and neuropathy. In 248 patients with evidence of chronic arsenic toxicity from West Bengal, India who consumed arsenic contaminated drinking water for one to 15 years, hepatomegaly occurred in 76.6%, and of the 69 who were biopsied, 63 (91.3%) showed non-cirrhotic portal fibrosis [47].

**Cardio-vascular system:** It has been suggested by several epidemiological studies that chronic inhalation of arsenic trioxide can increase the risk of death in humans from cardiovascular disease. Long term inhalation of inorganic arsenic could injure the blood vessels or the heart [48-49]. There has been reported several cases of myocardial infarction and arterial thickening in children who consumed water containing about 0.6 mg/l arsenic. Arsenic ingestion through food or water may have serious effects on the human cardiovascular system. Both acute and chronic arsenic exposure cause altered myocardial depolarization and cardiac arrhythmias that may lead to heart failure [50-51]. Low level arsenic exposure by humans may also cause vascular system damage, a classical example of which is Blackfoot disease, which is endemic in an area of Taiwan where most drinking water contains 0.17 to 0.8 ppm arsenic, corresponding to doses of about 0.01 to 0.5 mg As/kg/day.32 In ground water arsenicosis of West Bengal this ischaemic gangrene from vasenlitis is not seen probably due to less arsenic concentration circulating in blood stream [52].

**Respiratory System:** Arsenic exposure has severe toxic effects on the respiratory system. This exposure may be occupational as well as from drinking water. The exposure through inhalation may cause laryngitis, bronchitis, rhinitis, tracheobronchitis, stuffy nose, sore throat, hoarseness and chronic cough [53]. Very high exposure to unprotected workers may manifest perforated nasal septum after 1-3 weeks of exposure, but such effects are minor or absent at exposure levels of 0.01-1 mg/m³ [54].

**Haematological System:** Arsenic exposure causes anaemia and leukopenia on both acute and chronic oral exposures [55]. These complications may be due to direct haemolysis of RBCs or due to suppression of erythropoiesis [56]. No such complications were observed in humans upon minor chronic exposure. But major exposure can result into bone marrow depression. Renal damage is secondary which may occur due to deposition of haemolytic debris in the nephrons [57]. The mechanism of hemolysis involved depletion of intracellular GSH, resulting in oxidation of sulfhydryl groups in the hemoglobin from ferrous to ferric in mice and rats. Haemocyanin combines with arsenic, which reduced oxygen uptake by cells and therapy prevents hatching.

**Neurological Effects:** It is reported in many studies that arsenic poisoning causes severe neural injury. In fact neurological system is the major target site for the action of heavy metals including Arsenic. Both the central nervous system and peripheral nervous system are affected by the arsenic poisoning [58]. In case of acute high exposures to arsenic the complications like headache, mental confusion, lethargy, hallucinations, coma and seizures
may appear. Neuropathy takes place after 1 to 5 weeks of acute arsenic poisoning and it causes the axonal damage. Encephalopathy is identified by the symptoms like persistent headache, recent memory loss, loss of libido, distractibility, restlessness, repeated urinary urgency and increased effects of alcohol in small amounts [59]. Inhalation of inorganic arsenic can cause neurological injury in humans they may include peripheral neuropathy of both sensory and motor neurons causing numbness loss of reflexes, and muscle weakness. An increased prevalence of cerebrovascular disease, especially cerebral infarction, was observed in a large study of 8102 men and women who experienced long term arsenic exposure from well water [60].

**Hepatic system:** Arsenic is very toxic to hepatic system and causes a lot of damage to liver and the whole hepatic system. The symptoms of initial exposure may include oesophageal bleeding, ascites, jaundice and enlarged tender liver [61-62]. The chronic exposure shows increased levels of hepatic enzymes in the systemic circulation [63]. Hepatic lesions appear after prolonged exposure. Arsenic also causes damage to mitochondria of liver cells and impairs porphyrin metabolism. Liver cirrhosis and hepatic failure may occur in extreme cases [64].

**Renal Effects:** Kidneys are the major sites for the arsenic excretion. The pentavalent arsenic gets converted to more toxic trivalent arsenic in kidney and causes damage to capillaries, glomeruli and tubules. Oliguria and accumulation of arsenic is very common. On the repeated exposure tubular damage occurs due to destruction of mitochondria of tubular cells which finally leads to renal failure [65-67].

**Genitourinary System:** From the world wide studies it has been reported that with chronic exposure to arsenic the carcinoma of prostate, bladder tumours and carcinoma of ureters and urethra were more prominent in both males and females. The published data reveals that a firm causal relationship between arsenic ingestion and adverse outcomes during pregnancy and on neonatal morbidity and mortality [68-70].

**Mutagenic effects:** Arsenic induces variety of mutations in genes and DNA sequence [71]. Some of such mutations are transferred to next generation and some of these mutations cause variety of cancers in the next generation [72]. Arsenic causes chromosomal damage and inhibits the DNA repair [73]. Comparisons of chromosome aberration frequencies induced by trivalent and pentavalent arsenic have indicated that the trivalent forms are far more potent and genotoxic than the pentavalent forms [74-75].

**Malignant diseases:** There is a linear relationship between chronic arsenic exposure and wide variety of cancerous diseases [76]. In Bangladesh and India arsenic toxicity is associated with skin, lung, liver, kidney and the bladder cancers. Studies have also reported that there are prominent cases of skin, lung, liver and kidney cancers in other countries also [77]. In Taiwan so many prominent cases of nasal, larynx, bone, liver, colon, skin, kidney and stomach cancers. The mechanisms of all type of cancers are not well established. But it is considerable that arsenic causes an adverse affect on DNA repair, methylation of DNA, and increased free radical formation and activation of the proto-oncogene c-myc. Arsenic may act as a co-carcinogen, tumour promoter, or tumour progressor under certain circumstances [78-79].

**DIAGNOSIS**

It is clear that with the exception of cutaneous manifestations other symptoms and signs of chronic arsenicosis are non specific and can occur with other unrelated medical conditions. Hence from the historic studies and case reports there has been selected a criteria for the diagnosis of chronic arsenic poisoning. It includes following points:

- At least 6 months exposure to arsenic levels of greater than 50 µg/L or exposure of high arsenic level from food and air.
- Dermatological features characteristic of chronic arsenicosis.
- **Non carcinomatous manifestations**: Weakness, chronic lung disease, non cirrhotic portal fibrosis of liver with/without portal hypertension, peripheral neuropathy, peripheral vascular disease, non pitting edema of feet/hand.
- **Cancers**: Bowens disease, Squamous cell carcinoma, Basal cell carcinoma at multiple sites, occurring in unexposed parts of the body.
- Arsenic level in hair and nail above 1 mg/kg and 1.08 mg/kg respectively and/or arsenic level in urine, above 50 µg/L (without any history of taking seafood) [80].

**BIOMARKERS FOR THE DIAGNOSIS OF ARSENIC POISONING**

Arsenic may be measured in blood or urine to monitor excessive environmental or occupational exposure, confirm a diagnosis of poisoning in hospitalized victims or to assist in the forensic investigation in a case of fatal over dosage. Some analytical techniques are capable of distinguishing organic from inorganic forms of the element. Organic arsenic compounds tend to be eliminated in the urine in unchanged form, while inorganic forms are largely
converted to organic arsenic compounds in the body prior to urinary excretion. Tests are available to diagnose poisoning by measuring arsenic in blood, urine, hair, and fingernails.

**Urine:** Urine test is the most reliable test to diagnose the arsenic poisoning [81]. The urine analysis must be done within 24-48 hours for an accurate analysis of acute poisoning. The concentration of arsenic in urine depends upon source of exposure, duration of exposure and type of arsenic.

**Hair & Nail:** Tests on hair and fingernails can measure exposure to high levels of arsenic over the past 6–12 months. These tests can determine if one has been exposed to above average levels of arsenic. They cannot predict, however, whether the arsenic levels in the body will affect health [82]. Chronic arsenic exposure can remain in the body systems for a longer period of time than a shorter term or more isolated exposure and can be detected in a longer time frame after the introduction of the arsenic, important in trying to determine the source of the exposure [83]. Hair is a potential bio-indicator for arsenic exposure due to its ability to store trace elements from blood. Incorporated elements maintain their position during growth of hair. Thus for a temporal estimation of exposure, an assay of hair composition needs to be carried out with a single hair which is not possible with older techniques requiring homogenization and dissolution of several strands of hair. This type of bio-monitoring has been achieved with newer micro-analytical techniques like Synchrotron radiation based X ray fluorescence (SXRF) spectroscopy and Micro-particle induced X ray emission (PIXE). Levels between 0.1 and 0.5 mg/kg on a hair sample indicate chronic poisoning while 1.0 to 3.0 mg/kg indicates acute poisoning [84].

**Blood:** Half life of inorganic as well as organic arsenic is very short in blood. It is readily cleared from the blood. But if the exposure to arsenic is steady and in large proportions the clearance of arsenic from blood stream becomes slow. However there is no direct relationship between in arsenic exposure and blood arsenic concentrations [85-86].

**Other Tissues:** The concentrations of arsenic in other organs is determined by neutron activation analysis. In a data by WHO, geometric mean values of arsenic mg/kg body weight were found to be 0.03 in adrenal, 0.04 in arota, 0.04 in whole blood, 0.01 in brain, 0.46 in hair, 0.02 in heart, 0.03 in kidney, 0.03 in liver, 0.08 in kidney, 0.06 in muscle, 0.28 in nails, 0.05 in ovary, 0.05 in pancreas, 0.04 in prostate, 0.08 in skin, 0.02 in spleen, 0.02 in stomach, 0.05 in teeth, 0.02 in thymus, 0.04 in thyroid and 0.04 in uterus [87-89].

**TREATMENT OF ARSENIC POISONING**

**Chelators:** A chelating agent forms ring structure with a metal or metalloid. When used for treating heavy metal poisoning, the administration of the chelating agent results in the formation of a chelate structure which has water solubility greater than that of the offending metal and thus increases its excretion by the kidney. The chelating agent usually has a greater affinity for the metal ion than do endogenous legends to which the offending metal is bound. A number of chelating agents are considered for use against Arsenic poisoning.

- Dimercaprol analogues DMSA (meso–2,3-dimercaptosuccinic acid, Succimer, Chemet) and DMPS (sodium 2,3 – dimercapto-1-propane sulfonic acid, Dimaval) [90]
- BAL (British antilewsite)
- D-Penicillamine [91]
- Retinoids [92]
- Calcium sodium edentate

**Supportive and symptomatic treatment:** The use of chelating agents in the treatment of arsenic poisoning is prominent but along with this supportive and nutritional treatment is of most importance. The arsenic contaminated water should not be used for drinking. Hospitalization with good nutritional diet reduces the primary symptoms. A high protein diet in food helps in clearance of inorganic arsenic by the process of methylation. Supplemental potassium decreases the risk of experiencing a life threatening heart rhythm problem from arsenic trioxide. The patients should be treated clinically based upon the symptoms. Bronchial irritation must be stopped to prevent arsenic induced bronchitis. Hence the smokers must be motivated to quit smoking. Purulent sputum may be treated with oral oxytetracycline or ampicillin in a dose of 250-500 mg 4 times a day or Co-trimoxazole 960 mg twice daily. A 5-10 day course of treatment is usually effective and sputum becomes mucoid. Bronchodilators are less effective in case of chronic bronchitis. Hence beta-2 adrenoreceptor agonists must be given to the patients. Excision of early skin cancer and bladder cancer due to chronic arsenicosis can be curative [93-95].

**Removal:** Various techniques have been evolved for arsenic removal, most frequently using absorbents such as activated carbon, aluminium oxide, cooperative with iron oxide to form sludges, adsorption onto iron-oxidecoated polymeric materials, and electrocoagulation by nanoparticle. Bacteria, yeast, fungi, and algae can also be used for remediation processes [96].
WHO GUIDELINES FOR ARSENIC

Tolerable intake level
In a review of the latest scientific evidence conducted in 2010, the Joint Food and Agriculture Organization of the United Nations (FAO)/WHO Expert Committee on Food Additives (JECFA) determined the lower limit on the benchmark dose for a 0.5% increased incidence of lung cancer (BMDL) from epidemiological data to be 3.0 µg/kg body weight per day (2–7 µg/kg body weight per day based on the range of estimated total dietary exposure). The Committee noted that the previously established provisional tolerable weekly intake (PTWI) of 15 µg/kg body weight (equivalent to 2.1 µg/kg body weight per day) for inorganic arsenic was in the region of the BMDL and therefore was no longer appropriate.

Drinking-water
10 µg/L (provisional guideline value, in view of scientific uncertainties surrounding the risk assessment for arsenic carcinogenicity).

Air
A safe level of arsenic in air cannot be established.

CASES OF ARSENIC POISONING FROM THE HISTORY

Francesco I de' Medici, Grand Duke of Tuscany
Recent forensic evidence uncovered by Italian scientists suggests that Francesco (1541-1587) and his wife were poisoned, possibly by his brother and successor Ferdinando [97].

George III of Great Britain
George III's (1738–1820) personal health was a concern throughout his long reign. He suffered from periodic episodes of physical and mental illness, five of them disabling enough to require the King to withdraw from his duties. In 1969, researchers asserted that the episodes of madness and other physical symptoms were characteristic of the disease porphyria, which was also identified in members of his immediate and extended family. In addition, a 2004 study of samples of the King's hair revealed extremely high levels of arsenic, which is a possible trigger of disease symptoms [98].

Theodor Ursinus
Theodor Gottlieb Ursinus (1749–1800), a high ranking Prussian civil servant and justice official, was poisoned by his wife Charlotte Ursinus (1760–1836) [99].

Napoleon Bonaparte
It has been suggested that Napoleon Bonaparte (1769–1821) suffered and died from arsenic poisoning during his imprisonment on the island of Saint Helena. Forensic samples of his hair did show high levels, 13 times the normal amount, of the element [100].

Simón Bolívar
South American independence leader Simón Bolívar (1783–1830), according to Paul Auwaerter from the Division of Infectious Diseases in the Department of Medicine at the Johns Hopkins University School of Medicine, may have died due to chronic arsenic poisoning further complicated by bronchiectasis and lung cancer [101].

Charles Francis Hall
American explorer Charles Francis Hall (1821–1871) died unexpectedly during his third Arctic expedition aboard the ship Polaris [102].

Clare Boothe Luce
Clare Boothe Luce (1903–1987), the American ambassador to Italy from 1953 to 1956, did not die from arsenic poisoning, but suffered an increasing variety of physical and psychological symptoms until arsenic was implicated [103].

Guangxu Emperor
In 2008, testing in the People's Republic of China confirmed that the Guangxu Emperor was poisoned with a massive dose of arsenic; suspects include his dying aunt, Empress Dowager Cixi, and her strongman, Yuan Shikai [104].
Munir Said Thalib
A human rights activist from Indonesia named Munir Said Thalib was poisoned with arsenic on a flight from Jakarta to Amsterdam on September 7, 2004.

CONCLUSION

In the presented review the authors have made an attempt to summarize all the facts about the arsenic and its toxicity. Arsenic exposure occurs mainly through drinking water, food and air. Inorganic arsenic is more toxic than organic arsenic. Chronic arsenic toxicity includes so many effects on skin and various body organs. Urine, hair and nails and blood are the possible biomarkers for the diagnosis of arsenic toxicity. Arsenic causes a variety of carcinomas. Their treatment is possible only if detected in the early stages. Hence arsenic toxicity must be prevented by taking utmost precautions and care. This review will be helpful for the readers to know about the details of complications caused by arsenic on human body and measures of its prevention. So the researchers must work on to develop formulations which should be used in the treatment of arsenic induced carcinomas like Bowen’s disease and other malignancies.

REFERENCES