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Assessment of Health Risk Due to Arsenic Exposure

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ABSTRACT

Present review reveals the health risk due to arsenic exposure. The risks of Arsenic and arsenic covering compounds induced uncontrolled cell growth through the epidemiologic research on inorganic arsenic exposure have been studied. Exposure to arsenic occurs occupationally (by Inhalation route) in several industries, including mining pesticide, pharmaceutical, glass and microelectronics, while ingestion of contaminated drinking water is the predominant source of significant environmental exposure globally. Still presence of arsenic or arsenic compounds in drinking water results in public health issues. Various studies reveals the Acute and chronic arsenic exposure of As in drinking water has been reported in many countries of the world like Bangladesh, United States, Mexico, where a large proportion of drinking water is contaminated with high concentrations of arsenic. Arsenic associated health abnormality includes Heart disease, hypertension, sexual dysfunction, genetic abnormality, developmental anomalies, neurodegeneration, behavioral, abnormality, glucose intolerance, chronic liver disease, hematologic disorders (anemia leucopenia and eosinophilia) and uncontrolled cell growth, multiple cancers: significantly higher standardized mortality rates and cumulative mortality rates for cancers of the skin, lung, liver, urinary bladder, kidney and colon in many areas of arsenic pollution. This paper exposes the outline of the effects of arsenic and related compounds on the human body and organ dysfunction. This review delivers a broad assessment of the epidemiologic confirmation and should be used to monitor future research on arsenic's injurious effects on health.

1. INTRODUCTION

Arsenic occurs in various arsenic derived compounds with many oxidation states like −3, 0, 3 and 5. It is commonly present throughout Earth's crust, frequently as arsenic sulfide or as metal arsenates and arsenide. In water, it is oxygenated with oxidation state 5 which is represent as arsenate, and under reduced conditions (<200 mV), it is represent as arsenite, with an oxidation state of 3 (IPCS, 2001). In spite of the World Health Organization's (WHO) mentioned limit of 10 µg/L, there are more than 100 million exposed to harmful levels of inorganic arsenic in drinking water (Noujokas et al., 2013). For example, arsenic has been predictable to be present in drinking water at levels exceeding 1,000 µg/L in Bangladesh (Chakrabarti et al., 2003), 800 µg/L in the United States (Sonders et al., 2012), and 800 µg/L in Mexico (SVG et al., 2002). Given its toxicity and high environmental prevalence, inorganic arsenic is ranked as the highest priority agent by the Agency for Toxic Substances and Disease Registry (ATSDR, 2015).

1.1 Arsenic compounds [7, 8, 9, 10, 11, 12]

Arsenic has both metallic and nonmetallic properties, which is chemically classified as a metalloid compound. It is a steel-gray solid material but in nature found in combination with other elements. When metallic arsenic combined with oxygen, chlorine, and sulfur it is called inorganic arsenic, but combined with carbon and hydrogen it is called organic arsenic. (ATSDR, 2000) Inorganic arsenic is more harmful than organic arsenic compounds. Arsenic inorganic forms mainly present in water are AsIII and AsV. Organic arsenic mostly found in marine food (mainly fish) which is about more than 85%. Another arsenic compound group is arsenic-containing ribofuranoside, known as arsenosugars, but there is insufficient information regarding their toxicity. (Feldmann and Krupp, 2011).Arsenic compounds have been used for the treatment of syphilis, yaws (childhood infectious disease), human intestinal amebiasis and trypanosomiasis. In 1887, Hutchinson first mentioned that patient of psoriasis and other skin disorder under treatment of arsenic compounds become more vulnerable to skin cancer (Hutchinson, 1887a, Hutchinson, 1887b). Arsenical drugs are used in the treatment of infectious diseases that mostly occur in hot, humid situation such as African trypanosomiasis and amoebic dysentery, filariasis in dogs and blackhead in turkeys and chickens (Washington, 1977). In recent times, arsenic has been used as an anticancer agent in the treatment of acute promyelocytic leukemia (W.B.Cs abnormality), and its therapeutic action has been identified to the induction of programmed cell death (apoptosis) in leukemia

cells (Rousselot et al., 1999). A large number of populations is globally uncovered to the arsenical compounds. Intake of arsenic or its compounds occur through the oral route (ingestion), inhalation, dermal contact, and the parenteral route to some level (ATSDR, 2000).

1.2 Arsenic exposure [7, 12]

Arsenic exposure represents a major public health hazard for worldwide. Arsenic is a universal element identified in low concentrations in almost all conservation media. It is represent in environmental and occupational health (ATSDR, 2000). More than 80% of arsenic mixtures are used to manufacture products with agricultural uses such as insecticides, herbicides, fungicides, algaecides, sheep dips, wood preservatives, dye-stuffs, and medicines for the suppression of tapeworms in sheep and cattle (Washington, 1977). Arsenic also occurs naturally, its concentrations in air in isolated locations range from 1 to 3 mg/m^3, whereas concentrations in cities may range from 20 to 100 mg/m^3. In water, the concentrations of arsenic are commonly less than 10 μg/L, while higher concentrations can occur natural mineral deposits or men made sources. Normal levels of arsenic in soil commonly range from 1 to 40 mg/kg but pesticide application or waste disposal can produce much higher values. It is also found in many foods at concentrations ranging from 20 to 140 mg/kg (ATSDR, 2000). Diet, for most individuals, is the largest source of exposure, with an average intake of about 50 μg per day from food. Intake from air, water, and soil are usually much smaller.

2. Mechanism [13, 14]

The complex mechanisms are arsenic-associated changes to the epigenome and their role in arsenic-induced toxicity. The mechanisms by which arsenic utilizes its toxic effect is through impairment of cellular respiration by the inhibition of various mitochondrial enzymes, and the separation of oxidative phosphorylation. Maximum toxicity is caused by the interaction with sulfhydryl group of proteins and enzymes and various biochemical reactions of phosphorus (Goyer, 1996). Arsenic *in vitro* reacts with protein sulfhydryl groups to inactivate enzymes, such as dihydrolipoyl dehydrogenase and thiolase, thereby producing inhibited oxidation of pyruvate and beta-oxidation of fatty acids (Belton et al., 1985).

2.1 Arsenic-induced changes in DNA methylation [15, 16, 17, 18, 19, 20]

The several forms of epigenetic modifications occur, and DNA methylation is the most systematically examined. CpG (cytosine-phosphate guanine) dinucleotide, methyl groups can be transferred from SAM to cytosines to form 5-methylcytosine (5-MeC). These processes are facilitated by the DNMT enzyme family (Robertson, 2001). CpG methylation has been designated as a transcriptional silencing mechanism, and the addition of methyl groups inhibits transcription factor binding to DNA to initiate transcription. More specifically, the transcription blockade is thought to be the result of the recruitment of methyl-CpG-binding domain proteins to the binding site or through direct methylation of the binding site (Newell-Price et al., 2000).There are three major mechanisms by which inorganic arsenic is proposed to impact DNA methylation. First, arsenic can alter the activity and expression of DNMT, the enzyme that facilitates DNA methylation (Ruiz-Hernondez et al., 2015). Second, the availability of SAM has been shown to be reduced in the presence of arsenic (Reichard and Puga, 2010). S-adenosine methionine (SAM) is one of the main substrates that DNMT uses as a methyl donor to execute CpG methylation and a major cofactor required for arsenic metabolism (Chiang et al., 1996). Third the alterations of gene-specific DNA methylation patterning in response to environmental contaminants (Martin and Fry, 2016). This theory states that targeted DNA binding by transcription factors changes the contact of DNMT to the targeted DNA sequence ((Martin and Fry, 2016). This combined effect suggests that arsenic directly impacts the process of DNA methylation by altering the availability and activity of enzymes that simplifyCpG methylation processes.

2.2 Arsenic-induced changes in histone modifications [21]

Another potential mediator of mRNA expression and an environmentally responsive epigenetic mechanism is histone modification. The histones are proteins which serve as a structure around which DNA can supercoil. This wrapping of DNA results in a condensed structure is termed as nucleosome and comprises chromatin (Grewal and Jia, 2007). Histone modifications can impact chromatin structure and allow for the necessary regions of DNA to be manageable for their respective DNA binding elements (Grewal and Jia, 2007). The acetylation of histones has been correlated with increased gene and protein expression due to a weakening of DNA-protein contact (Grewal and Jia, 2007). Conversely, histone deacetylation has been correlated with decreased gene and protein expression due to increased DNA-protein contact (Grewal and Jia, 2007). In the histone methylation has been

shown to have a mutable effect on transcriptional activity due to the specific location and quantity of the methyl groups on the histone tails (Grewal and Jia, 2007). Histone modifications are mediated by the enzyme families: histone acetyltransferases (HAT), histone deacetylases (HDAC), histone methyltransferases, histone demethylases, serine and threonine kinases, and phosphatases (Grewal and Jia, 2007).

2.3 Arsenic-induced changes in miRNA expression [22, 23, 24, 25, 26, 27, 28, 29, 30]

The microRNAs (miRNAs) represent a third type of epigenetic regulator. miRNAs are small, non-coding RNA sequences about 21-33 nucleotides. In some cases, miRNAs have been connected to transcriptional activation but associated in gene silencing activity through the targeting of specific transcripts for degradation (Breving and Esquelu-Kerscher, 2010).As with mRNAs, miRNAs are transcribed within the nucleus. However, after transcription inside the nucleus, miRNAs form hairpin structures and withdrawal the nucleus as pre-miRNA. The pre-miRNA is then processed further into mature miRNA and incorporated into RISC complexes (Breving and Esquelu-Kerscher, 2010). The mechanisms underlying arsenic-induced miRNA expression changes are not well characterized, however, it is well established that transcription factors represent critical regulators in the control of miRNA appearance (Arora et al., 2013). The study of the interplay between miRNAs and transcription factor regulation represents a current area of investigation, (Arora et al., 2013). Arsenic may changemi RNA appearance is through the induction of environmentally-responsive transcription factors (Sollome et al., 2016). In support of this, a recent meta-analysis has confirmed that there is an enrichment for common transcription factor binding site in the promoter region sequences of the arsenic-responsive miRNAs (Sollome et al., 2016). Future research of a population of studies that investigate arsenic-induced miRNA expression changes have been conducted in vitroand spanned the use of human lymphocyte (TK-6), human bladder carcinoma (T24), and human liver carcinoma (Hep-G2) cell lines (Roy et al., 2014). HepG-2cells treated with 4 μM arsenic trioxide for 24 hours displayed upregulation of miR-24,miR-29a, miR-30a, and miR-210 (Meng et al., 2011). These findings are particularly relevant to the field of epigenetically-mediated disease as miR-29a demonstrated a therapeutic effect in liver carcinoma cells through the induction apoptosis and inhibition of cellular growth and proliferation, making this miR a potential target for hepatocellular carcinoma therapy (Meng et al., 2011). Only a few human population-based studies that have examined the relationships between altered miRNA expression in response

to arsenic exposure and the potential for these alterations to result in disease development (Roy et al., 2014). For example, in a study that investigated the health impacts from prenatal exposure ranging up to 236.0 µg/L in drinking water in Mexico, researchers found a set of differently expressed miRNAs and mRNAs that were implicated in innate and adaptive immune response (Contone et al., 2011). Analyses of these differentially expressed miRNAs revealed enrichment in pathways associated with inflammatory disease and response, cancer, diabetes, and respiratory disease, among others mRNA analysis demonstrated several mRNAs to also be implicated in immune response (Rager et al., 2014). The expression levels of arsenic associated mRNAs and miRNAs were evaluated and miRNA expression levels were found to be negatively associated with mRNA levels, which indicates miRNAs may be responsible for reducing expression or silencing of important genes involved in immune response (Rager et al., 2014). In prenatal exposure to arsenic is associated with an increased incidence of infant infections (Farzan et al., 2013). Future research is needed to examine miRNAs in response to arsenic exposure in human populations. *In vitro* studies have identified arsenic exposure has a variable effect on miRNA expression profiles depending on specific cell type, duration, and dose of exposure (Roy et al., 2014). Given the few studies of miRNAs expression in humans, it is not surprising that there is little overlap between observed miRNA expression in human populations exposed to arsenic and cell lines. Nevertheless, several studies have confirmed altered miRNA expression to be implicated in disease development and immune response, which makes miRNAs a possible mediator for arsenic-induced disease development (Rager et al., 2014, Mendell and Olson, 2012).

3. Pharmacokinetics [31, 32, 33, 34, 35, 36, 37, 38,39, 40, 41]

Arsenic is poorly absorbed and largely eliminated in unchanged form. Soluble arsenic compounds which are rapidly absorbed from G.I.T. (Hindmarsh & McCurdy, 1986). The Organic arsenic are rapidly and almost completely eliminated through the kidneys (Buchet et al., 1981a; Luten et al., 1982; Tam et al., 1982). Inorganic arsenic may collect in skin, bones, liver, kidneys and muscles (Ishinishi et al., 1986). The half-life in humans is between 2 and 40 days (Pomroy et al., 1980). Inorganic arsenic is eliminated from the body by the rapid urinary excretion of unchanged arsenic in both the trivalent and pentavalent forms and by sequential methylation to MMA and DMA in both 3 and 5 valence states (Buchet & Lauwerys, 1985; Lovell & Farmer, 1985). The studies on humans indicate that the capacity to methylate inorganic arsenic is progressively, but not totally, saturated when daily intake more

than 0.5 mg (Buchet et al., 1981b). The concentrations of metabolites of inorganic arsenic in urine from individuals with no known exposure to arsenic are reported to be generally below 10 μg/l in European countries. However, in West Bengal, India, and Bangladesh, urinary arsenic concentrations above 1 mg/l have frequently been observed (IPCS, 2001). In humans, inorganic arsenic does not appear to cross the blood–brain barrier; however, transplacental transfer of arsenic in humans has been reported (Gibson & Gage, 1982).

The metabolism of arsenic is complex and metabolites is depend on the received arsenic compounds, through route of administration, and cell type used for the elimination of arsenic (Stice et al., 2016). In the metabolism of arsenic, those arsenic compounds are formed, methylated arsenicals such as DMAV (Dimethylarsinic acid), MMAV (Monomethylarsonic acid), DMAIII (Dimethylarsinous acid), and MMAIII (Monomethylarsonous acid) and As-glutathione (GSH) and recently determined type of arsenicals, thiolated as compounds, including DMMTAV (Dimethylmonothioarsinic acid), DMDTAV (Dimethyldithioarsinic acid) and DMMTAV (Dimethylmonothioarsinic acid) conjugates. Although it has been recognized in which human tissues these metabolites are present, their role in toxicity has not yet been full clarified (Rehman and Naranmandura, 2012). However, certain metabolites are known to be more likely to cause some toxicity. As shown that MMA III and DMA III are more genotoxic, and DEMTAV is more cytotoxic (Mass et al., 2001; Kojima et al., 2005). Usually, trivalent arsenicals has additional toxic than pentavalent arsenicals (Styblo et al., 2000). Besides their toxicity, some specific arsenic combinations are used in treatment of certain cancers (Antman, 2001). For example, arsenic trioxide (As2O3, ATO, Trisenox) has been used in treatment of acute promyelocytic leukemia (APL) (Liu et al., 2012).

4. Overdose and toxicity effects

In the epidemiological studies, ingestion of inorganic arsenic is involved in non-carcinogenic health effects in several organs or systems with cardiovascular, dermal, reproductive, neurological, respiratory, hepatic, hematological, renal, and gastrointestinal.

4.1 Dermatologic Effects [42, 43]

The chronic dermal effect of arsenic show a characteristic form of non-carcinogenic effects that begins with spotted hyper-pigmentation and may later include palmar and plantar hyperkeratosis. (Mazumder et al., 1998). The mechanisms for those latter dichotomous effects would be unique and interesting. Characteristic skin lesions of arsenic toxicity may be

used as an indicator of high exposure and are unique in contrast to other clinical appearances of arsenic intoxication.

On the basis of investigation & study, it was found that adverse effect of arsenic was found in the region of Gangetic plain of West Bengal, India and Bangladesh where more than 30 millions people were consuming water with arsenic containing which concentration was more than 50 μg/L.

This study showed a higher prevalence rate of arsenic skin lesions in males than females, with a clear dose-response relationship. (Chowdhary et al., 2000)Through a scientific study conducted a cross sectional survey of the prevalence of hyperpigmentation and palmar-plantar keratosis in a region of West Bengal, India with groundwater arsenic concentrations ranging from nondetectable to 3,400 μg/L (Mazumder et al., 1998). This study found that males were more affected than females for both hyperpigmentation and palmar-plantar keratosis. Several studies found an association between skin lesions and arsenic ingestion in India and Inner Mongolia. (Tucker et al., 2001)

4.2 Cardiovascular Effects [42, 44, 45, 46, 47, 48, 49, 50, 51]

The cardiovascular system is most important organs system of human body which plays an important role in respiration and blood flow in whole body. In the epidemiological studies have shown that the cardiovascular system is particularly sensitive to long-term ingestion of arsenic in drinking water. Visible effects include hypertension and increased cardiovascular disease mortality (NRC, 2001). The cross-sectional estimation of blood pressure in 1,595 adults (above 30 years of age) who resided all their life in a rural area of Bangladesh (Rahman et al., 1999). The area had a high level of arsenic exposure resulting from the use of contaminated groundwater for drinking water; wells were drilled because of microbial contamination of surface water. At the time of this study, no subjects were taking antihypertensive medication. The diet, lifestyle, and socioeconomic status of all subjects were similar. The study found that increasing arsenic in drinking water increased the incidence and severity of hypertension (Rahman et al., 1999). An increased risk of coronary heart disease has been related to long-term exposure to inorganic arsenic. Blackfoot disease patients have been reported to have increased mortality from ischemic heart disease (ISHD) (Chen et al., 1988). Arsenic is a major risk factor for what is known as black foot disease, that is peripheral atherosclerosis resulting in dry gangrene and spontaneous amputation of affected

extremities. The disease was named for its most striking clinical feature blackish discoloration of the feet or hands (Tseng, 1989). A new study has informed a biological gradient between cumulative arsenic exposure through consuming artesian well water and lethal ischemic heart disease (ISHD) in Taiwan (Chen et al., 1996). In the environmental exposure to inorganic arsenic through drinking water has been associated with increased mortality from cardiovascular disease in Chile (Zaldiver, 1980) and Japan (Tsuda et al., 1990), and from cardiovascular disease among chimney sweeps, copper smelter workers, and glass blowers exposed to arsenic in their working environments (Hsuch et al., 1998).

In India, individuals exposed to elevated inorganic arsenic levels in drinking water showed a range of health effects including peripheral vascular disease, noncirrhotic portal fibrosis, nasal septum perforation, bronchitis, and polyneuropathy. In Taiwan, skin pigmentation changes and hyperkeratosis were the most superficial signs of inorganic arsenic exposure (Mazumzder et al., 1998).

4.3 Reproductive and Developmental Effects [52, 53, 54, 55, 56, 57, 58, 59, 60, 61]

Although arsenic exposure has been associated with a number of adverse health outcomes, relatively little consideration has been focused toward the potential effect of arsenic on human reproductive system, despite studies in both humans and experimental animals demonstrating that arsenic and its methylated metabolites cross the placenta (Conch et al., 1998).

Evidences of adverse effect on reproductive impacts of offspring of Swedish were documented (Nordstrom et al., 1978a,-1979b). Female workers gave birth to lower weight infants than women who resided outside the smelter area, and the difference was greater if the mothers worked in the more highly exposed jobs (Nordstrome et al., 1979b). An incremental development in the rates of spontaneous abortions was observed with increasing occupational and residential exposure (Nordstrome et al., 1978b, Nordstrome et al., 1979b). Congenital abnormalities appeared to be more frequent if the expectant mother was employed in highly exposed jobs during pregnancy (Nordstrome et al., 1978b). In Bulgaria, the incidence of toxemia of pregnancy and the mortality from congenital abnormalities were significantly higher in an area near a smelter with environmental contamination from various metals than the national rates (Zelikoff et al., 1995). In the studies of populations exposed to arsenic from drinking water have found increased rates of spontaneous abortions and stillbirths in Hungary

(Borzsono et al., 1992) and Argentina. (Costro, 1982) In the United States, three studies reported adverse reproductive effects, including increases in mortality from congenital cardiovascular anomalies (Engel and Smith, 1994, Zieler et al., 1988) and spontaneous abortions (Aschengrou et al., 1989). A study in Texas found an increase in the rates of stillbirths in relation to residential exposures from an arsenic pesticide plant (Ihrig et al., 1998).

4.4 Neurological Effects [62, 63, 64, 65, 66, 67, 68]

In the past, studies of arsenic prompted neurological effects have usually focused on central nervous system effects following acute, high-dose intoxication, and on the peripheral neuropathy that occurs following chronic exposure (NRC, 1999). Two studies have focused on subtle cognitive effects in children following chronic exposure to arsenic. Siripitayakunkit et al investigated the effect of arsenic between environment and IQ of children in the district of Thailand which were contaminated with arsenic (Siripitayakunkit et al., 1999). To prove a significant association between arsenic and growth, head-hair arsenic concentrations and performance on the Weschler Intelligence Scale Test for children (WISTC) in 529 schoolchildren were analyzed in a crosssectional evaluation. High arsenic levels measured in hair affect height but not weight. Only 2 epidemiological studies on the effects of arsenic on children's growth exist in the literature. In these studies, males were more liable than females, and stature was more affected than weight (Poigen et al., 1987, Schwartz et al., 1986). Anorexia, malabsorption, and weight loss may be present because of low-dose arsenic ingestion (Moton and Dunnette, 1994). Two follow-up studies of arsenic-poisoned Japanese victims found that the victim group showed retarded growth from the age of one year to school age with average height of the victims less than that of a same-age group (Yamashita et al., 1972). Across-sectional study in San Luis Potosi, Mexico (Colderon et al., 2001) examined the effect of arsenic and under-nutrition on the neuropsychological performance of school children aged 6 to 9 years.

An observation was found on subject in which 41 children were included which were living near Morales Zones where arsenic concentration was more and other 39 children were living upwind from Martinez zones. The total concentration of arsenic in urine was found to be more in the Martinez childrens. It is due to lower status of maternal and paternal education attainment in the Martinez group.

Neuropsychological performance was assessed using the Weschler Intelligence Scale for children revised version, for Mexico (WISC-RM). The Morales children scored considerably lower than the Martinez children on the full-scale IQ test and other neuropsychological subscores (Colderon et al., 2001).

4.5 Respiratory Effects [49, 69, 70, 71, 72, 73, 74, 75, 76, 77, 78]

The respiratory effects have been reported in populations exposed to arsenic in drinking water (NRC, 1991), but the database is scant. In the recently reported association between arsenic ingestion in drinking water and the prevalence of respiratory disorders (Mazumder et al., 2000). Respiratory effects in West Bengal were first noted in 1995 when 57% of the 156 patients who lived in arsenic-affected villages described having chronic cough (Guha Mazumder et al., 1997). Furthermore, epidemiological studies in Chile have previously suggested an association between arsenic and nonmalignant respiratory effects. The survey data collected from 1968 to 1972 in Antofagasta, Chile, Zaldivar, and Ghaireported that the prevalence of cough among 398 children correlated with mean drinking water arsenic concentrations (Zoldivar and Ghei, 1980). Zaldivar also reported that the prevalence of bronchiectasis was 23-fold greater among children with arsenic-induced skin-lesions living in Antofagasta compared to children living in the rest of Chile (Zaldivar, 1980). In 1976 it was found that 144 school children was affected with arsenic induced skin related problems and bronchio pulmonary diseases which was more than 2.5 times in comparison to children with normal skin (Borgona et al., 1977). In a study, Smith et al. found high relative rates for chronic obstructive pulmonary disease (COPD) mortality among young men and women living in the same arsenic exposed region in Chile that includes Antofagasta (Smith et al., 1998). A few professional studies conducted in the1950s in Sweden have also reported nonmalignant respiratory effects in copper smelter workers exposed to airborne arsenic. In one of the clinical study of copper smelter workers cited by (Gerhard et al., 1988), a syndrome characterized by lesions of the mucous membranes of the upper respiratory system, emphysema, and reduced pulmonary function, was described (Gerdhart et al., 1978). The relationship between ingested arsenic and nonmalignant respiratory effects has so far only been informed fromChile (Chiou et al., 1995), India (Madal et al., 1996), and Bangladesh (Milton et al., 2001). The Studies from arsenic-affected regions in Taiwan, Chile, and Argentina show clear increases in lung cancer mortality. The specific feature of arsenic is that it seems to increase both malignant and nonmalignant respiratory disease following ingestion.

Milton et al reported an association between chronic arsenic ingestion and chronic bronchitis in a small cross sectional study of 94 individuals in Bangladesh with arsenic associated skin lesions.

Chronic bronchitis was found with more cough with sputum in three consecutive months for more than 2 successive years on the basis of physical examination. It were at greater risk in male than female (Milton et al., 2001).

4.6 Hepatotoxic Effect [79, 80, 81, 82]

The hepatotoxicity disturbs the function of liver which is most important role play in metabolism of food through enzymatically. In the studied liver function in individuals from three towns in the region of Lagunera, Mexico. They determined the serum activity of aspartate aminotransferase (SAT) and alanine aminotransferase (ALT) as indicators of hepatocellular injury and that of gamma-glutamyl-transpeptidase (GGT) and alkaline phosphatase (ALP) as indicators of cholestatic injury (Hernandez-Zavala et al., 1998). The key findings of this study were principally conjugated hyperbilirubinemia and increased serum ALP activity which were related to the concentration of total arsenic in urine, suggesting the presence of cholestasis in arsenic exposed individuals. Armstrong et al also observed increased concentrations of total bilirubins in serum samples from 7 individuals ingested with arsenic via drinking water (Armstrong et al., 1984). Moreover, histological examination of livers of individuals chronically revealed to high arsenic concentrations has revealed the presence of portal tract fibrosis, which occasionally causes portal hypertension and bleeding from esophageal varices (Mazumder et al., 1988). In the study by Santra et al. bilirubin, it was diagnosed in patients with hepatomegaly of arsenicosis in West Bengal and India result was mild fibrosis and cirrhosis (Santra et al., 1999).

4.7 Hematologic Effects and Diabetes[47, 83, 84, 85, 86, 87]

Some enzymes activities was found in the heme biosynthesis pathway their relationship was with urinary porphyrin excretion in individuals exposed chronically to arsenic by consuming drinking water in region Langunera, Mexico (Hernandez-Zavala et al, 1999). The more evident alterations in heme metabolism observed were small but significant increases in porphobilinogen deaminase (PBG-D) and uroporphyrinogen decarboxylase (URO-D) activities in peripheral blood erythrocytes, increases in the urinary excretion of total

porphyrins, mainly due to coproporphyrin III (COPROIII) and uroporphyrin III (UROIII), and increases in the COPRO/ URO and COPROIII/COPROI ratios.

Not alteration occurred in uroporphyrinogen III synthase (UROIII-S) activity.

The interaction with enzymes and urinary porphyrins increased porphyrin excretion which is associated with PBG-D, whereas the increased URO-D activity would enhance coproporphyrin synthesis and exretion of uroporphyrin.

No, any human study report is available of prophyric response and enzymes inhibition in rodents.

The main focus of arsenic is on endocrine system between arsenic exposure and diabetes mellitus.

As part of an ecological study examining multiple causes of mortality in the area of Southwestern Taiwan where Blackfoot disease is endemic, Tsai et al examined mortality from diabetes mellitus in 4 townships, where artesian well water containing arsenic had been consumed from the early 1900s until the mid-to-late 1970s. Diabetes mellitus was listed as the underlying cause of death for 188 males and 343 females (Tsai et al., 1999). Tseng et al reported a prospective cohort study examining the incidence of diabetes mellitus in three villages from the arsenic endemic area of Southwestern Taiwan. The study population consisted of three villages where artesian well water (0.70 to 0.93 mg/L As) was used for drinking and cooking until the mid-to-late 1970s (Tseng et al., 2000). The population was subjected to a follow-up examination that includes fasting blood glucose and an oral glucose tolerance test. The results of this study show an association between long-term arsenic exposure and diabetes mellitus, as found in the previous prevalence study. The prevalence of diabetes mellitus was 2-fold higher in Southwestern area of Taiwan than in Taipei city and the Taiwan area in general. A dose-response relation between cumulative arsenic exposure and the prevalence of diabetes mellitus was also demonstrated after adjustment for multiple risk factors (Lai et al., 1994). Rahman and Axelson carried out a case-control study on Swedish copper smelter workers. Using the death records for 1960–1976, they compared three arsenic exposure categories with an unexposed group (Rahman and Axelson, 1995). They observed an increased risk of dying from diabetes mellitus with increasing arsenic exposure. In a similar study carried out among art glassworkers, indications of a relationship between arsenic exposure and diabetes mellitus have also been described. (Rehman et al.,

1996) In a community-based survey of diabetes mellitus in Bangladesh, (Rahman et al., 1999) Observed a dose-response trend between the occurrence of diabetes mellitus and the arsenic level in drinking water.

4.8 Hearing loss [88, 89, 90, 91]

The ototoxicity of arsenic was also supported with human studies sensorineural hearing loss was reported in individuals exposed to arsenic. In a study conducted in Inner Mongolia, a region in China rich, there was statistically significantly more hearing loss cases in an arsenic affected village, compared with an unaffected village (Guo et al., 2007).

According to study with Bencko and Symon the level of arsenic in blood, urine and hair samples detected hearing loss at 125 Hz, 250 Hz in children with age 10 years old which lived in polluted zones of arsenics (Bencko et al., 1977). Contrary to expectations, during an investigation of public schools near a copper smelter, six children with high urinary arsenic levels had no hearing loss in a pure tone audiometry test (Milham, 1977). In a national population-based study on individuals above the age of 50, urinary concentrations of environmental chemicals were measured and hearing loss was assessed using questionnaires (Shiue, 2013). It was found that urinary arsenic concentrations of acid and 2, 4, 5-trichlorophenol concentrations were significantly associated with hearing disorders.

4.9 Renal Effects[66, 74, 92, 93, 94, 95, 96, 97]

The main route of excretion of arsenic toxicity is kidney it damage the capillaries, tubules and glomeruli of the kidneys (Schoolmaster and White, 1980, Sauibb and Fowler, 1983, Winship, 1984). As in other organs, capillary damage seems to be a basic event leading to other cellular manifestations. Glomerular arterioles dilate, permitting hematuria. Damaged proximal tubular cells lead to proteinuria and casts in the urine. Mitochondrial damage is also prominent in tubular cells (Morton and Dunnette, 1994).

Oliguria is common symptoms appears but it produce shock and dehydration sufficiently, which actually hazard renal failure, although dialysis is effective to overcome this complication (Giberson et al., 1976).Acute cortical necrosis is an uncommon severe renal sign, but benefits from dialysis (Gerhardt et al., 1988). Arsenic-induced hemolysis is likely to cause acute tubular necrosis with partial or complete renal failure, requiring hemodialysis for removal of the hemoglobin-bound arsenic (Fowler and Weissbeg, 1974, Teitelbaum and Kier,

1969). Recovery may leave interstitial fibrosis and thickened glomerular basement membranes.

4.10 Gastrointestinal Effects[31, 92, 93, 98, 99, 100, 101]

Arsenic may produce direct irritant effects on gastrointestinal tissues with which it comes in contact, the greatest degree of damage is produced by local sub mucosal capillary damage from absorbed arsenic (Clarkson, 1991). The effects of oral administration by accident or with suicidal or dangerous intent, the direct effects on the gastrointestinal tract have been projecting harmful effect through tissues rupturing mechanism (Ellenhon and Barceloux, 1988, Gorby, 1988, Hindmorsh and Mccurdy, 1986, Schoolmaster and White, 1980, Sauibb and Fowler, 1983, Vahter, 1988). The vascular damage is thought the cause of submucosal vesicles, whose rupture can create grossly visible erosions and major fluid and protein loss. Nausea and vomiting can be severe, as can colicky abdominal pain and marked diarrhea. If sufficiently severe, the acute gastroenteritis can lead to circulatory collapse with renal damage and shutdown. Arsenic poisoning from smaller doses of arsenic may manifest as dry mouth and throat, heartburn, nausea, abdominal pains and cramps, and moderate diarrhea. Chronic low-dose arsenic ingestion may be without symptomatic gastrointestinal irritation or may produce a mild esophagitis, gastritis, colitis with respective upper and lower abdominal discomfort. Anorexia, malabsorption, and weight loss may be present (Morton and Dunnette, 1994).

5. Management [102, 103, 104]

There is no antidote which is effective for arsenic intoxication however, acute and chronic arsenic exposure can be managed. Two chelation therapies are available in the USA. Dimercaprol is the chelating drug for acute severe arsenic toxicity also known as British anti-lewisite. Meso-2,3-dimercaptosuccinic acid is the agent in the setting of ongoing arsenic exposure. To eliminate further exposure and contamination manageable sources such as mining and some pesticides and wood preservative contribute to human exposure should be organized to prevent environmental contamination. However, the great majority of exposure happens through naturally contaminated groundwater, through drinking-water, water used in food preparation and water used to moisten food crops, particularly rice. It is technically possible to achieve arsenic concentrations of 5 μg/l or lower using any of several possible treatment methods. However, this requires careful process optimization and control, and a

more reasonable expectancy is that 10 µg/l should be achievable by conventional treatment (e.g. coagulation). The ideal solution is to use alternative sources of water that are low in arsenic. However, it is important that this does not result in risk substitution—for example, if the alternative water source, although low in arsenic, increases exposure to waterborne pathogens and results in acute gastrointestinal infections, which are a major source of mortality and morbidity in many parts of the world (Howard, 2003). This is important for most alternative water sources other than water from tube wells. Water protection frameworks should be used during planning, installation and management of all new water points, mainly ones based on surface water and very shallow groundwater, to minimize risks from faecal and other non-arsenic contamination. Screening for arsenic and other possible chemical contaminants of concern that can cause problems with health or acceptability, including fluoride, nitrate, iron and manganese, is also important to ensure that new sources are acceptable. Random screening may also be required after a source is established to ensure that it remains safe. Where there are large urban supplies, resources are often available to treat water to remove arsenic or to exploit alternative low-arsenic sources, such as surface water that can be treated to avoid microbiological and other hazards. These low-arsenic sources can be used to blend with higher-arsenic sources to lower the concentration to acceptable levels while still retaining the resource. Many of the major problems lie in rural areas, where there are many small supplies sometimes down to the household level. At this level, water availability and financial and technical resources are all limited. There are several available approaches, but there is a basic requirement for education. In particular, there is a need to understand the risks of high arsenic exposure and the sources of arsenic exposure, including the uptake of arsenic by crops from irrigation water and the uptake of arsenic into food from cooking water.

A number of approaches have been successfully used in rural areas, including source substitution and the use of both high- and low-arsenic sources blended together. These sources may be used to provide drinking water and cooking water or to provide water for irrigation. High-arsenic water can still be used for bathing and clothes washing or other requirements that do not result in contamination of food. However, it is important to remember that there may be other contaminants present as well as arsenic, and so it is important to determine whether other contaminants of concern are present.

Low-cost approaches that have been developed to lower exposure to arsenic where contamination of groundwater is a problem include the following:

- Alternative sources, including dug wells that are properly protected to prevent microbiological contamination and rainwater harvesting, which may be possible for at least some months of the year, with steps taken to minimize contamination;

- Surface ponds, which require appropriate steps to minimize microbial and chemical contamination and also require treatment to ensure microbial safety before drinking;

- Identifying high- and low-arsenic tube wells by painting them different colures and sharing wells (spatial variability in groundwater arsenic contamination in Argentina, Chile and the river deltas of South and South-east Asia is very high, so there are mixtures of arsenic-contaminated and arsenic uncontaminated wells in most villages); sinking new wells into low-arsenic strata. This requires significant technical support to ensure that low arsenic levels are known and can be exploited without other problems arising. Deeper groundwater aquifers can be used to develop community water supplies, which generally succeed where there is community involvement in their establishment and operation;

- Removal of arsenic by low-cost village or household treatment systems, usually using absorptive media, such as elemental iron, iron or aluminum oxides and carbon. Shallow groundwater that is anoxic (e.g. in South and South-east Asia) is generally high in liquefied iron, so a pretreatment step involving the development and precipitation of iron hydroxide, which will then adsorb arsenic, is beneficial.

Many household treatment systems in Bangladesh and West Bengal, India, may fail prematurely because of high levels of phosphate, which competes with inorganic arsenic species for adsorption, in the water. Safe disposal of arsenic-contaminated wastes should also be considered.

In areas where there is observable arsenicosis, there is usually no problem in persuading the local population to follow arsenic mitigation measures, even though they often require significant extra effort. Involvement of individuals and communities in the planning, application and management of the mitigation strategy is a key factor for successful intervention. Studies in Bangladesh have shown that most rural households prefer sharing of

unpolluted wells or filtration of low arsenic surface water through sand to treatment of groundwater (Howard, 2003; Johnston, Hanchett & Khan, 2010).

Where arsenic levels are lower and the adverse effects of arsenic exposure are less obvious, there will be a much greater requirement for education in order for justification measures to be carried out effectively over an extended time period. Further information can be found in sources such as Howard (2003) and JICA/AAN (2004).

6. DISCUSSION [70, 105, 106]

In the world including India arsenic toxicity was found due to the result of arsenic – contaminated groundwater and major environmental health hazards. According to recent information chronic arsenic toxicity in humans was seen last two decades. Symptoms such as pigmentation and the specific skin lesions appeared due to chronic arsenic toxicity.

Others various systemic appearances, chronic lung diseases, peripheral neuropathy, and chronic liver diseases appeared to be the major cause morbidity reported by most of the investigators from different parts of the country or world.

A review of the epidemiological confirmation on arsenic exposure and cardiovascular diseases showed that various methods and limitations regulated the high exposure and outcome in Taiwan.

In other populations and in occupational setting, the evidence was inconclusive (Acien et al., 2005). There is planning in all the studies on pregnancy outcome with the finding that stillbirth occurs in significantly higher number of cases in pregnant women with chronic arsenic exposure. There is sufficient epidemiological confirmation to incriminate arsenic as an important cause of cancers of skin, lungs, and urinary bladder (IARC, 2004). Arsenic causing genotoxicity as a result of drinking arsenic-contaminated water has been extensively studied in West Bengal. Chromosomal deviation and increased frequency of micronuclei in different cell types have been found to be significant. Further studies are needed to ascertain whether these could be used as biomarker of chronic arsenic toxicity. The various possible mechanisms have been incriminated to cause DNA damage because of chronic arsenic toxicity and have been interconnected with disease manifestations. However, additional studies are needed to establish specific genotoxic effects of arsenic in causing cancer. There appears to be no consensus with the various findings of genetic polymorphism and disease

manifestation. The addressing the arsenic problem is to provide scientifically corrects information to the people at risk and develops comprehensive water-quality surveillance system. The important step is to organize for identification of arsenic-contaminated tube wells and make the people aware of not drinking arsenic-contaminated water. Management of health effect because of arsenic toxicity requires an integrated approach of collaboration of health personnel of Ministry of Health and engineering personnel of Public Health Engineering Department of the government. For its justification in a developing country, such as India, assistances may also be required from nongovernmental organizations and international agencies, for example, World Health Organization, United Nations Children's Fund, and World Bank. Research on epidemiology, including determination of disease burden in the population, difficult factors for inconsistency in disease manifestation, standardization of proper disease management protocol, and arsenic in food chain and human health are some of the issues that require further attention.

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