Chapter 1

〖Introduction〗

"For many people in Bangladesh it can sometimes literally be a choice between death by arsenic poisoning and death by diarrhea."

Timothy Claydon, Country Representative of Water Aid

Arsenic (from the Greek word *arsenikon*, meaning "potent") is a metalloid present everywhere (i.e., water, soil and air). It enters into our body when the water we drink, the food we eat and the air we breathe. Even a person comes in contact with soil or water containing arsenic may have arsenic within the body. Some pathological changes only occur when we consume it more than the safe level. This consumption may be acute, previous, intermittent or chronic. There is no scope to discuss in this book about acute consumption. Previous exposure to arsenic is important when we look after the findings of Taiwan (Chen et al., 1962) and Chile (Unicef, 2008). Chronic consumption of high concentration of arsenic affects any organ of the body. However, there may be no symptom, particularly in skin or failure of correlation between the arsenic consumption and involvement of other organ(s) which may be called preclinical. Most of the people in arsenic endemic area consuming arsenic are in preclinical state. Only a small percentage (?) of people consuming arsenic for a long time show skin manifestations (mostly non-malignant). There may be involvement of internal organs. Arsenic is a class A human carcinogen, which causes an increased risk of cancer usually originating from the skin, lungs, liver, kidneys and urinary bladder.

People in arsenic endemic area consume arsenic unknowingly or knowingly due to its physical characteristics (no odor, no color, and no taste). If we consider the history, the mummified bodies in Chile showed signs of arsenic exposure from as long as 7,000 years ago (Arriaza et al., 2010). Arsenic (Figure 1.1) has been known as a 'silent toxin' since ancient times. It was only two decades ago that it received overwhelming worldwide public attention (Jean et al., 2010).

Figure 1.1 *Alchemical symbol of arsenic.*

1.1 Multiple Terminologies

Health problems after chronic consumption of arsenic have more than 10 terminologies. These are chronic arsenic poisoning, chronic arsenic toxicity, arseniasis, arsenism, arsenicism, arsenicalism, hydroarsenicism, HACRE (Spanish word: Hidroarsenisismo Crónico Regional Endémico), arsenicosis, chronic arsenicosis, arsenicosis patient or arsenical dermatosis. It has also local name like "Kai Dam" in Thailand, "Bell Ville" in Argentina and "Blackfoot disease” in Taiwan. Bell Ville is the name of an area near Córdoba city, Argentina, where cases of arsenicosis were first diagnosed. Blackfoot literally means “black and dry snakes”. Some of the terminologies are used for certain period. For example, arsenicalism was used between 1950s and 1990s. The number of terminologies is due to regional variations and time variation.

When you enter the three terminologies ‘chronic arsenic poisoning’, ‘chronic arsenic toxicity’ and ‘arsenicosis’ into the internet www.scholar.google, the results show that chronic arsenic poisoning is the most preferred term whereas chronic arsenic toxicity is the least (Table 1.1). In each case, prevalence, diagnosis, prevention and treatment were added for search.

Table 1.1 *Hits in Google Scholar (up to May 2014).*

Terminology	Prevalence	Diagnosis	Prevention	Treatment
Chronic arsenic poisoning	1280	1670	1470	3060
Arsenicosis	1230	1130	1390	1130
Chronic arsenic toxicity	663	711	739	1450

However, the term “arsenicosis” may be more acceptable. The term “arsenicosis” was first detected in a paper (Journal of Association of Physicians India) in 1976 written by D. V. Datta and M. K. Kaul (Datta & Kaul, 1976). It is difficult to say who first coined this terminology. There is no need to use the word “chronic” when “arsenicosis” is used. Similarly “arsenicosis patient” is not necessary to use. The word “arsenicosis” is self-explanatory. The next option is the “chronic arsenic toxicity”. That is, toxicity develops following chronic ingestion of high concentration of arsenic in drinking water.

In scholarly journals, some authors choose the term “keratosis” whereas others use the term “hyperkeratosis”. This leads to confusion between keratosis and hyperkeratosis. Keratosis means growth of the keratin layer on the skin or on mucous membrane. Hyperkeratosis is the severe form of keratosis. It is better to avoid the term “hyperkeratosis”. The term “arsenical keratosis” may be used as because keratosis may develop from other causes. Keratosis in the palm or sole may be more appropriately accepted as “palmar arsenical keratosis” or “plantar arsenical keratosis”.

1.2 Definition

A working group of World Health Organization (WHO) regional office at New Delhi in 2003 defined arsenicosis as a “chronic health condition arising from prolonged ingestion (not less than six months) of arsenic above a safe level, usually manifested by characteristic skin lesions, with or without involvement of internal organs” (Caussy, 2005).

In this definition, emphasis was given on the presence of non-malignant skin manifestations. Therefore, arsenicosis may be better defined as “pathological changes develop in any organ of the body due to chronic or previous consumption of high concentration of arsenic”. The skin, body’s largest organ, is primarily affected. The patient attends the doctor with complain for treatment. Arsenicosis is difficult to diagnose when organ(s) other than skin are affected due to absence of any specific biomarker.

1.3 Types of Arsenicosis

Arsenicosis can be classified into three types based on method of contamination. These are medicinal arsenicosis, occupational arsenicosis, and dietary arsenicosis. Cases of medicinal arsenicosis were reported first, followed by occupational arsenicosis and dietary arsenicosis. When we consider the extent of arsenicosis, only limited numbers of cases were reported as medicinal and occupational arsenicosis. On the other hand, the extent of dietary arsenicosis is severe. Arsenicosis due to high concentration of arsenic in air (as arsenic trioxide; As_2O_3) is only reported in China.

Initially it was thought that the presence of arsenic in surface and groundwater was due to mining (Sambu & Wilson, 2008). Cases of arsenicosis were detected in Hungary in 1940s. A survey conducted by the Hungarian Public Health in 1982 concluded that the high level of arsenic was due to natural biogeochemical process instead of anthropogenic activities (Csalagovits, 1994).

Medicinal arsenicosis: Arsenic had been used as medicine for at least 2,500 years. Hippocrates (460-377 BC) used orpiment (As_2S_3) and realgar (As_2S_2) as escharotics, a caustic material that burns flesh away. Aristotle (384-322 BC) and Pliny the Elder (23-79 AD) also wrote about the medicinal properties of arsenicals. Galen (130-200 AD) recommended a paste of arsenic sulfide for the treatment of ulcers. Paracelsus (1493-1541) used elemental arsenic extensively (Jolliffe, 1993).

For the last two centuries, it was used by the physicians to treat dermatitis herpetiformis, asthma, syphilis, epilepsy, psoriasis, and amebiasis. Cases of arsenical dermatitis were reported in 1884 (White, 1884). Sir Jonathan Hutchinson, in 1887, first clearly related the development of keratosis and skin cancer to long-term ingestion of arsenic as Fowler's solution (1% potassium arsenite, $KAsO_2$). Fowler's solution was first discovered in 1786 and was also used as medical tonic. In 1912 arsenic was recognized as the best agent in the Pharmacopoeia (Frost, 1977). It is also used in the form of Donovan's solution (AsI_3), and the Asiatic pill (As_2O_3). Asiatic pill was taken with pepper or opium. German physician Paul Ehrlich and Japanese student Sahachiro Hata produced their 606th preparation of an arsenobenzene compound (salvarsan) in 1907. Ehrlich watched on 31 August, 1909, as Hata injected chemical No. 606 into a rabbit with syphilitic ulcers. Subsequently it was used in the treatment of syphilis. Inorganic arsenic (when arsenic combines with oxygen, sulfur or chloride) is still available in Traditional Chinese Medicine preparations (Espinoza et al., 1996). For example, the Chinese herbal ball named 'An Gong Niu Huang Wan' (in English: Calm the palace pill with cattle gallstone) is used in the treatment of high fever, irritability, restlessness, delirious speech contains high concentration of arsenic (3.21 to 36.6 mg per herbal ball).

When the cases of arsenicosis were identified due to intake of arsenic as medicine, then the prescriptions of arsenic containing medicines were stopped. However, in 2000, arsenic trioxide was approved by Food and Drug Administration (FDA) for the treatment of acute promyelocytic leukemia (FDA, 2000). About 75 percent of acute promyelocytic leukemia patients can be cured with other combination therapies, but those who do not achieve remission or who relapse can be treated with arsenic trioxide.

Occupational arsenicosis: Occupational arsenicosis may be due to a) working in mining, b) use of pesticide or fertilizer, c) sweeping chimney, and d) use of arsenic contaminated paint or timber. Keratosis was observed in female workers in a chemical plant who were exposed to arsanilic acid (0.065 mg/m^3; Chou et al., 2007). Copper arsenite was used as a pigment for making wall paper and paint. Arsine gas exposure was found following ore smelting, electroplating, manufacturing brass, dyeing or gold extraction.

Pesticide: Paris green (copper acetoarsenite) was first used against the potato beetle in the Western USA in 1865 and its use was well established in 1868 (Frear, 1942). Between 1880 and 1900, Paris green was probably the most commonly used insecticide, with London purple (an arsenic compound) a close second (Frear, 1942). Arsenic trioxide was used as insecticide, rat poison, weed killer, sheep dip and hide preservative. Lead arsenate and calcium arsenate were used as insecticide.

The pesticides monosodium methane arsonate (MSMA), disodium methane arsonate (DSMA), calcium acid methane arsonate (CAMA), and cacodylic acid were used as herbicides on cotton and other agricultural crops. All uses of DSMA, CAMA, and cacodylic acid were canceled on September 30, 2009. The use of MSMA was prohibited after December 31, 2013.

Sweeping chimney: In 1775, the English Surgeon Sir Percivall Pott (1714-1788) first reported the case of skin cancer at scrotum among the chimney sweeper (Pott, 1775). In 1820, the English physician John Ayrton Paris (1785-1856) first reported the association between arsenic and the development of cancer as occupational (Blejer & Wagner, 1976). While sweeping the chimney, these patients were exposed to soot that contained sulfur dioxide and arsenic.

Wood preservative: Chromated copper arsenate was introduced as wood preservative by an Indian mining engineer in 1933. Arsenic releases into the soil and raised the concentration of arsenic. Thus, children sickened by contact with playground equipment built from arsenic-treated wood. Similarly, burning arsenic-treated wood can result in elevated arsenic levels in smoke. It is no longer used since 2003.

Dietary arsenicosis: Arsenicosis develops due to intake of high arsenic contaminated drinking and cooking water [as inorganic arsenate (AsO_4^{3-}) or arsenite (AsO_2^{-})], and foodstuffs. Arsenical keratoses of the palms and soles were first described by Erasmus Wilson in 1873 (White, 1885). In 1900, about 3,000 people developed arsenicosis in Manchester, England, as a result of drinking beer which had been sweetened with glucose containing arsenic (McNeer, 1934).

As early as in 1809, William Lambe expressed the belief that arsenic in potable water may be the cause of malignant disease (Eggers, 1931). The contamination of drinking water resources by geogenic arsenic was first described in Argentina in 1913 (Goyenechea, 1917). The river water in some areas of Argentina and Chile is contaminated with high concentration of arsenic. Subsequently it was detected in other countries. In Taiwan the arsenic exposure occurred between 1910s and 1970s due to use of water from artesian well (Hsueh et al., 1995), and the blackfoot disease was first diagnosed in 1954 (Table 1.2). In India, arsenic pollution of groundwater was first discovered in Chandigarh in 1976 by doctors (Datta, 1976)

Table 1.2 *Detection of first case of arsenicosis.*

Country	Year of first detection
Argentina	1917
Taiwan	1954
Mexico	1958
Chile	1962
China	1980
Iran (Kurdistan)	1981
India	1976
Thailand	1987
Mongolia	1990
Bangladesh	1993
Nicaragua	1996
Nepal	2003
Cambodia	2006

after a patient who died of liver disease was found to have high levels of arsenic in all internal organs. The presence of large number of cases of arsenicosis was reported in Kolkata, West Bengal in 1984 (Garai et al., 1984). The first case of arsenicosis due to chronic consumption of drinking water in Bangladesh (Chapai Nawabganj, a district close to the border of West Bengal, India) was diagnosed in 1993. The groundwater of Bangladesh and India (West Bengal) is contaminated with high concentration of arsenic (Misbahuddin et al., 2011). The amount of arsenic in hand pump tube wells of different sites on an endemic area varies with wide range.

Sea food contains high concentration of organic arsenic (when arsenic combines with hydrogen and carbon). Foodstuffs in arsenic endemic area are contaminated with high concentration of arsenic which is due to contamination of soil by geological or anthropogenic cause. Flood or mining affects the level of arsenic in soil. Irrigation of agricultural land by arsenic contaminated deep tube well water is an important factor of contamination of soil in Bangladesh and India. On the other hand, soil of gardening area near the house is less contaminated with arsenic. All foodstuffs are not equally contaminated with arsenic. The staple food of some countries, for example, rice is contaminated with arsenic.

Arsenicosis due to inhalation of arsenic: When air containing arsenic dusts is breathed in, the majority of the dust particles settle onto the lining of the lungs (Chen et al., 2006). High level of arsenic is present in air of some areas in China. The arsenic concentration in kitchen air following coal burning is 160-760 $\mu g/m^3$ (average: 445 $\mu g/m^3$). Coal can contain very high levels of arsenic, up to 3.5% arsenic by weight. Millions of people around the world burn coal in the household in non-ventilated stoves for cooking, heating the room during winter season, and in some cases for drying food. Arsenic-contaminated coal, when used for these purposes, may cause arsenicosis. This is particularly apparent in some areas in Guizhou Province of China.

Cow dung is found to cause arsenicosis in West Bengal, India (Pal et al., 2007). The cow dung, from cows fed contaminated rice straw, is dried in the sun and used as fuel in domestic ovens. When the cow dung cakes are burnt arsenic is released into the air, which is then inhaled by the people.

Seekh kebab is a popular diet of South East Asian countries where coal is burned to prepare it. The fume produced from coal is inhaled by the cook. The extent of arsenic while preparing seek kebab is not known.

Arsenicosis cases were first documented in patients following chronic administration of Fowler's solution as medicine. Subsequently paints and pesticides were responsible for the development of arsenicosis. These were man-made and the number of cases was reduced after stoppage of usage. Later surface and groundwater were identified for the development of arsenicosis.

1.4 Outline of Sources of Contamination

The presence of high concentration of arsenic in the environment for human consumption is due to geogenic, anthropogenic or biogenic (Figure 1.2).

Geogenic sources of arsenic contamination are geothermal/volcanic activities and weathering of rocks and minerals. Geothermally active zones occur to plate boundaries, in tectonic rift areas and at "hot spots" where mantle-derived plumes ascend. In Taiwan, groundwater from artesian wells completed in black shales, muds and fine sands are contaminated with arsenic. The presence of arsenic in surfaces and groundwater in Latin America is associated with tertiary and quaternary volcanism in the Andes Mountains.

Himalayas has formed the extensive alluvial plain and delta through which the Ganges, Brahmaputra and Meghna rivers flow and which form aquifers in India and Bangladesh. Anthropogenic contamination of arsenic is due to human activities includes mining and processing of ores and manufacturing using arsenic-bearing sulfides. The use of organic arsenic-based pesticides in agriculture causes contamination of groundwater in Mexico, USA and India. Biogenic sources of arsenic contamination include plants, animals and microorganisms.

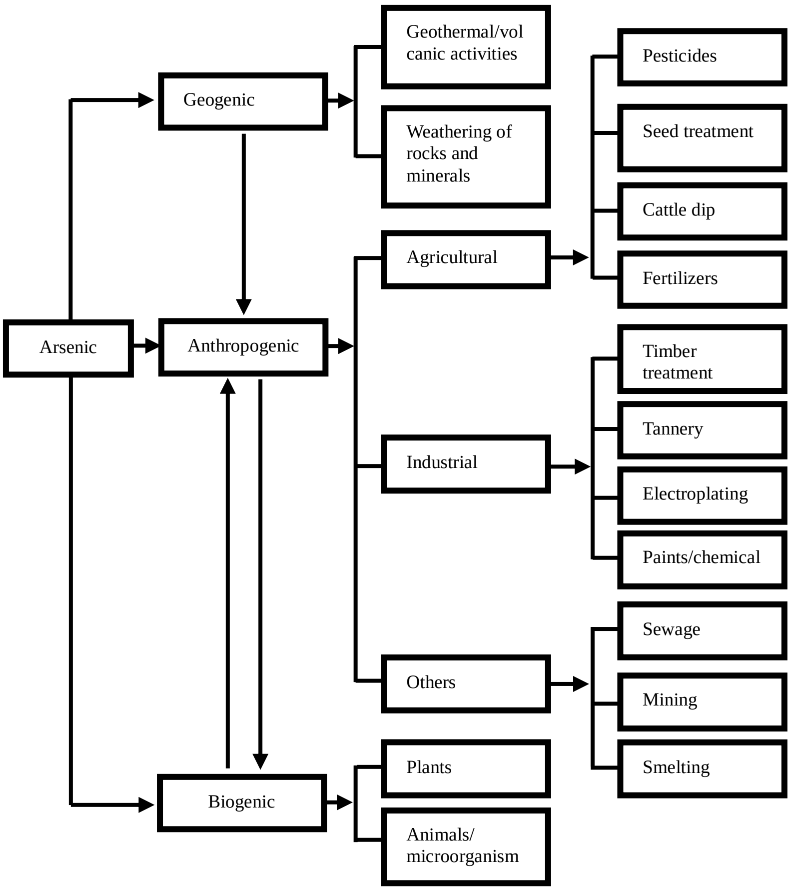


Figure 1.2 *Major sources and routes of arsenic in soil and aquatic ecosystems (Mahimairaja et al., 2005).*

1.5 Safe Level of Arsenic

The concentrations of arsenic vary: nanogram per cubic meter level is present in air, microgram level per liter in water and milligram level per kg in soil (Table 1.3). That is, there are thousand time differences in each level. There is also regional variation. The word 'safe', here, means the level of arsenic when exposed chronically to human body does not produce any adverse effect after a long time. However, in true sense, it is difficult to measure.

Air: The usual level of arsenic in air is 1-3 ng/m^3 in rural area and 20-100 ng/m^3 in urban area in USA. In European regions, it is between 0.2-1.5 ng/m^3 in rural areas, 0.5-3 ng/m^3 in urban areas and no more than 50 ng/m^3 in industrial areas (DG Environment, 2000). In England, the mean concentration is 5.4 ng/m^3, with a declining trend over the period 1957-1974 (Salamon, 1978). In Canada, the mean level is 1 ng/m^3 (range 0.5-17 ng/m^3) (Hughes, 1994).

Table 1.3 *Safe level of arsenic.*

Site	Amount of arsenic
Air (rural area, USA)	1-3 ng/m^3
Air (urban area, USA)	20-100 ng/m^3
Soil (USA)	7.2 mg/kg
Water	5, 7, 10, 25, 50 ppb
Food	??
Human	
Blood	<1 ppb
Urine	<100 ppb
Nail	<1 ppm
Hair	<1 ppm

Soil: Arsenic is present in soil at levels ranging from 0.2 to 40 mg/kg. It is rarely more than 10 mg/kg.

Drinking water: The safe level of arsenic in drinking water is still confusing (5, 7, 10, 25 or 50 ppb). WHO in 1958 recommended drinking water standard of 200 ppb which was reset to 50 ppb in 1963 and 10 ppb in 1993.

For American, it is 10 ppb whereas 50 ppb for Bangladeshi (Table 1.4). It is not clear about the discrepancy. Skin manifestations of arsenicosis are found in some Bangladeshi patients where their drinking water levels are below 50 ppb level. Therefore, 10 ppb may be considered as safe level.

Is it possible to change the safe level of arsenic to 10 ppb where it is 50 ppb? If we look after this case in USA, a developed country, it took about 10 years to implement 10 ppb from 50 ppb. The main problem of implementing 10 ppb in developing countries, like Bangladesh, is the absence of sensitive method for the estimation of arsenic. There may be involvement of other factor(s) including genetic factor.

Table 1.4 *Country-wise safe level of arsenic in drinking and cooking water.*

Safe level of arsenic in water	Country
5 ppb	USA (State of New Jersey)
7 ppb	Australia
10 ppb	Alaska, Argentina, Austria, Bolivia, Brazil, Chile, Colombia, Costa Rica, El Salvador, Finland, France, Germany, Greece, Guatemala, Honduras, Hungary, Itali, Japan, New Zealand, Nicaragua, Panama, Russia, Spain, Sweden, UK, USA, Vietnam
25 ppb	Canada, Mexico
50 ppb	Bangladesh, China, Cambodia, India, Laos, Myanmar, Nepal, Pakistan

Food: Bangladesh or India has not yet set standards for arsenic in foods, but the Chinese government in 2005 fixed a limit of 0.15 mg/kg inorganic arsenic in rice. WHO has established a provisional Maximum Tolerable Daily Intake (MTDI) of 2.1 µg/kg body weight inorganic arsenic that should include exposure from food and water.

With the exception of some kinds of seafood, most foods contain low levels of arsenic, normally less than 0.25 mg/kg. However, rice and vegetables in Bangladesh as well as India are contaminated with high concentration of arsenic.

Seafood is the primary source of arsenic in the diet of Japanese and Spanish. Arsenic concentrations in seafood are 2.4-16.7 mg/kg in marine fish, 3.5 mg/kg in mussels (Buchet, 1994) and more than 100 mg/kg in certain crustaceans.

Speciation study shows that seafood in Japanese diet mainly contains arsenobetaine (47.9-75.2%). Others are inorganic arsenic (5.7-17.0%), monomethylarsonate (MMA; 1.1-3.6%), and dimethyl-arsinate (DMA; 6.6-27%; Yamauchi & Fowler, 1994).

Wine is also contaminated with arsenic when grapes are sprayed with arsenic containing pesticides (up to 500 ppb) in the As^{III} form (Hughes, 1994).

The daily intake of arsenic by the people of different countries is reported for comparison (Figure 1.3). Spanish showed the highest consumption of arsenic that is followed by Japanese, Indian and French. The data of Bangladeshi are not shown which may be similar to the Indians. High consumption of arsenic by Spanish or Japanese is due to high intake of seafood whereas by Indian or Bangladeshi is due to consumption of arsenic contaminated water.

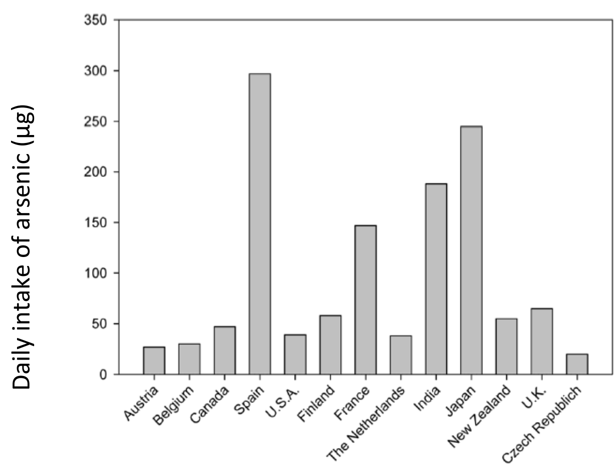


Figure 1.3 *Daily intake of arsenic by the people of different countries (Carbonell-Barrachina et al., 2009).*

Human body: In arsenic non-endemic areas, the level of arsenic in human blood is <1 ppb, urine <100 ppb, nails ≤1 ppm and hair ≤1 ppm (Table 1.3). The amount of arsenic in nail is comparatively higher than that of hair. Blood is the principal vehicle for the transport of arsenic following absorption, and arsenic is cleared relatively rapidly from it. It is rather surprising that arsenic concentration, after entering into blood, remains very low. It may be due to rapid distribution in different tissues or rapid excretion. However, arsenic reduces the erythrocyte glutathione level indicating that while it stays in blood, it produces oxidative stress in erythrocytes. The mean reduced glutathione level in red blood cell of arsenic affected patient was 55.3 mg/dL, in arsenic exposed family member was 57.8 mg/dL, and in the control group was 88.7 mg/dL (Sinha et al., 2003).

Data on human body are mainly based on autopsy result. The muscles, bones, kidneys and lungs have the highest absolute amounts of arsenic, but skin and excretory/storage organs, such as nail and hair, have the highest concentrations. Tissue distribution of arsenic indicates that levels of arsenic in the kidneys, liver, bile, brain, skeleton, skin and blood are 2-25 times higher for the As^{III} than for the As^{V} form and are greatly increased at higher doses.

1.6 Prevalence

Over 226 million people from more than 105 countries, from Bangladesh to Bolivia, are consuming high concentration arsenic (Murcott, 2012). The numbers of people affected in Asia are more than the rest of the world (Ravenscroft et al., 2009). The worst situation is in Bangladesh and India (West Bengal). Most of them are from drinking water of groundwater source. In Latin America, 14 out of 20 countries are affected with high concentration of arsenic in drinking water with total exposed people of about 14 million (Bundschuh et al., 2012). The exact number of cases of arsenicosis is not known. The countries having large number of arsenic exposed people and cases of arsenicosis are described below:

Bangladesh: Bangladesh is a densely populated area. Its total population is 157 million. About 95% of total population is using groundwater for drinking and cooking purposes. People of urban areas are using water of deep aquifer whereas hand pumped tube wells are used by rural people. There are in total 8.6 million hand pump tube wells (?) of which 4.7 millions are screened for arsenic mainly by ket methed. Although kit method is not a reliable method, the data shows that 1.4 million hand pumped tube wells are contaminated with more than 50 ppb arsenic (Unicef, 2008). There are more than 8,000 villages (total number of villages within the country: 87,319) where 80% of all hand pump tube wells are contaminated.

About 36 million people are consuming arsenic contaminated drinking water (>10 ppb) of hand pump tube wells (Chakraborti et al., 2010). This data is based on 52,202 water samples throughout the country analyzed by flow injection hydride generation atomic absorption spectrometry. Estimation of total arsenic by atomic absorption is more reliable than kit method. About 43% of the estimated hand pump tube wells contain arsenic >10 ppb (Table 1.5). The amount of arsenic above 300 ppb is about 6%. The water of deep tube wells is also contaminated. Multiple Cluster Indication Survey of 2009 conducted a survey in 15,000 households across Bangladesh and showed 7.7% deep tube wells were contaminated with unsafe concentration of arsenic (Unicef, 2011). More than 90% of drinking water is as As^{III} (Huq & Naidu, 2003).

Sixty out of total 64 districts of Bangladesh are affected by arsenic contaminated drinking water. Area wise distribution of arsenic contaminated drinking water is clearly shown only in Bangladesh. High levels of arsenic in groundwater occur in the districts of Chandpur, Comilla, Noakhali, Munshiganj, Brahmanbaria, Faridpur, Madaripur, Gopalganj, Shariatpur, and Satkhira. Irrigation of cultivated land with arsenic contaminated water has polluted the soil leading to the presence of arsenic in foodstuffs.

Table 1.5 *Percentage of hand pump tube wells containing different concentrations of arsenic in water.*

Concentration of arsenic (ppb)	**Percentage of tube wells**
<10	57.0
10-50	15.8
51-99	7.1
100-299	12.4
300-499	4.3
500-699	1.8
700-1,000	1.0
>1,000	0.5

(Chakraborti et al., 2010)

According to the report of the Directorate General of Health Services, Government of Bangladesh, 50,000 people are suffering from non-malignant skin lesions of arsenicosis. In reality, the number will be 2-3 times more which is due to poor statistical data. The capital city Dhaka is supplied by tap water which is not contaminated but the people (about 15 million) living within the city are consuming foodstuffs which are supplied from some of the arsenic endemic areas.

Only a few cohort studies have been done in Bangladesh. A study conducted at Matlab, Bangladesh (an arsenic endemic area) shows that there were 504 confirmed cases of non-malignant skin lesion of arsenicosis among the total population of 166,934 (>4 years of age). That is, 3 per 1,000 are affected by arsenicosis (Rahman et al., 2006). A cross-sectional study in another arsenic endemic area in Bangladesh shows that there were 714 cases of non-malignant skin lesion among 11,438 subjects (Argos et al., 2007). The incidence rate is 6.2%. That is, the incidence rate in two arsenic endemic areas varies a wide range. A study conducted by the Massachusetts Institute of Technology (MIT) estimated the arsenic health burden through a model of dose-response function (Yu et al., 2003). The research group predicted that long-term exposure will result in approximately 1 million cases of melanosis, 350,000 cases of keratosis, 8,500 cases of skin cancer, and 6,500 fatalities per year from internal cancer (Table 1.6). Among the arsenic-induced fatal cancers, males will be more affected than female.

Table 1.6 *Estimated health impact of arsenic contamination of tube well water in Bangladesh.*

Illness	Males	Females	Combined
Fatal cancer/year	3,809	2,718	6,528
Non-fatal cancer/year	1,071	1,024	2,095
Total number of cancer fatalities accumulated over 50 years	190,450	135,900	326,400
Arsenicosis			
Hyperpigmentation	654,718	316,511	971,230
Keratosis	277,759	74,473	352,233
Cough	21,823	68,887	90,712
Breathlessness	93,247	176,874	270,122
Glucosuria	67,887	63,551	131,439
Hypertension	94,396	88,366	182,762
Total arsenicosis cases in each year	1,209,830	788,662	1,998,498

(Koundouri, 2005; Maddison et al., 2004)

Among the non-malignant skin lesions, all the patients have melanosis and leucomelanosis. About 50% have keratosis. It is rare where the patient is suffering from keratosis without melanosis or leucomelanosis. Only a few cases of Bowen's diseases are reported. The number of reported skin cancer due to arsenic is low. Latency period of symptoms are 10-15 years. One study shows that on average, 16.6% of arsenicosis had died of cancer during the last 9-12 years (Chakraborti et al., 2010). There is dose-response relationship between inorganic arsenic exposure and risk of hypertension (Rahman et al., 1999).

India: The total population in India is 1,256 million. The states of West Bengal, Bihar, Jharkhand, Uttar Pradesh, Assam, and Manipur are reported to be contaminated with high concentration of arsenic in drinking water. West

Bengal is the most severely affected area. The total number of Indians consuming high concentration of arsenic is not clear.

West Bengal – Out of 19 districts, 9 districts of West Bengal are severely affected by arsenic contaminated drinking water. Badly affected districts are Malda, Murshidabad, Nadia, North-24-Parganas, South-24-Parganas, Bardhaman, Howrah, and Hoogly. About 26 million people of West Bengal are exposed to high concentration of arsenic (Chakraborti et al., 2009). On the basis of estimating arsenic level of 140,150 hand pump tube wells using atomic absorption spectrometer, about 50.1% of tube wells contain more than 10 ppb (Table 1.7; Chakraborti et al., 2010). The amount of arsenic above 300 ppb is about 3.4%. The extent of arsenic contamination is more or less similar to Bangladesh. Screening of 86,000 people show that 8,500 people were suffering from arsenicosis (9.7%; Chakraborti et al., 2002). The same research group reported that about 300,000 cases of arsenicosis with symptoms of non-malignant skin lesion are present in West Bengal (Chakraborti et al., 2002).

Table 1.7 *Percentage of hand pump tube wells containing different concentrations of arsenic in West Bengal.*

Amount of arsenic (ppb)	Percentage of tube wells
<10	49.9
10-50	26.2
51-99	9.3
100-299	11.2
300-499	2.3
500-699	0.7
700-1,000	0.3
>1,000	0.1

(Chakraborti et al., 2009)

Bihar – The total population in Bihar is 50 million. In total, 7,218 out of 27,061 hand pump tube wells were tested which had arsenic concentration of more than 10 ppb. That is 26.7% tube wells are contaminated. The water contains high concentration of As^{III} (87%). More than 13.85 million people are drinking high arsenic contaminated water (>10 ppb) in Bihar. Out of 38 districts, 16 districts are severely affected by arsenic contaminated drinking water. Among them the badly affected districts are Bhojpur, Buxar, Vaishali, Bhagalpur, Samastipur, Khagaria, Katihar, Chapra, Munger and Darbhanga. Non-malignant skin lesions of arsenicosis are mainly reported. In addition, there are non-pitting edema, liver and kidney disorders.

Jharkhand – Only 320 villages were screened in December 2003 and 30% of the hand pump tube wells had arsenic concentration >10 ppb. Only 87 cases were diagnosed as arsenicosis (Mukherjee et al., 2006).

Uttar Pradesh – The total population of Uttar Pradesh is 166 million. Only three districts (Ballia, Gazipur & Varanasi) out of 70 districts were screened. About 45% of the hand pump tube wells are contaminated with arsenic (>10 ppb; Ahamed et al., 2006). The number of patients is only 154.

Assam – A survey conducted (between 2005 and 2010) jointly by the State Public Health Engineering Department, UNICEF and the IIT, Guwahati showed that 7,22,603 people of 18 districts (out of 24 districts) are at risk of chronic arsenic poisoning. The affected districts are Goalpara, Dhubri, Bongaigaon, Barpeta, Nalbari, Kamrup, Darrang, Sonitpur, Lakhimpur, Sivasagar, Jorhat, Golaghat, Nagaon, Morigaon, Cachar, Hailakandi, Karimganj and the BTAD areas. The total number of arsenicosis is 2,581.

In Chandigarh and adjacent areas, high concentration of arsenic (>500 ppb) is present not only in hand pump tube wells but also in surface water like ponds and canals.

There is 6-fold increased risk of stillbirth following exposure to high concentrations of arsenic (200 ppb) during pregnancy (von Ehrenstein et al., 2006). No association was found between arsenic exposure and spontaneous abortion or overall infant mortality. Women had lower risks than men of developing skin lesions and showed little evidence of respiratory effects (shortness of breath at night, morning cough in smokers and shortness of breath in nonsmokers; von Ehrenstein et al., 2005).

China: The total population in China is 1,387 million. The Chinese government in 1994 declared arsenicosis as an endemic disease throughout the nation and conducted a massive screening program to sample wells in about 12 per cent of the counties. Because of the large size of China, it will take several decades to complete the screening of million of wells to determine the spatial occurrence and magnitude of arsenic contamination throughout the country. The total area at risk is around 580,000 km^2 (about 4 times the size of Bangladesh).

The affected areas include 8 provinces (Xinjiang, Inner Mongolia, Shanxi, Guizhou, Henan, Jilin, Ningxia, and Qinghai provinces) and 37 counties in China. The population exposed to high concentration of arsenic is estimated to be more than 20 million, and more than 30,000 arsenicosis cases have been confirmed. Drinking water of hand pump and deep tube wells are contaminated with arsenic.

In southwest China, arsenic-rich coal is used to dry chili peppers and corn, exposing people to arsenic both through inhalation and by contaminating food. Coal in Guizhou has undergone mineralization and thus produces high concentrations of arsenic. However, arsenic concentrations in the drinking water are within the normal range. The estimated sources of total arsenic exposure in this area are from arsenic-contaminated food (50-80%), air (10-20%), water (1-5%), and direct contact among coal-mining workers (1%). The use of arsenic-contaminated coal in some areas in Guizhou Province of China is also responsible for contamination. At least 3,000 arsenicosis cases were found in the Southwest Prefecture of Guizhou, and approximately 200,000 imhabitants are at risk for such over exposures (Liu et al., 2002).

The estimated arsenic intakes from rice and calculating the associated excess cancer risk for the Chinese population is to be 152 per 100,000 (Meharg et al., 2009).

Chile: The total population in Chile is 17 million. The cities having the highest exposure to arsenic are Antofagasta, Calama, Santiago, Ancagua, Taltal, Tocopilla and San Pedro de Atacama. Approximately 500,000 inhabitants are exposed to arsenic contamination. Lung and bladder cancer mortality rate increases about 10 years after high arsenic exposure commenced and continued to rise until peaking in 1986-1997 (Marshal et al., 2007). In this population, arsenic in water contributed more to mortality than did cigarette smoking.

People exposed to very high concentration of arsenic (averaging between 500 and 600 ppb) drinking water back in the 1950s and 60s are still showing a higher-than-normal risk of cancer of urinary bladder or lungs, years after the arsenic problem was brought under control. In Antofagasta, the incidence of urinary bladder cancer (2009) among men was about 16 cases per 100,000 while it was under six per 100,000 for the rest of Chile. Females suffer in less in number. It was 13.5 cases for every 100,000 women while it was 2.5 per 100,000 in the rest of Chile. At the peak, arsenic-induced cancers were responsible for the deaths of 1 in 20 females, and 1 in 10 males.

Like Taiwan, blackfoot disease is also reported in Chile (Borgono et al., 1997).

Argentina: The total population in Argentina is 41 million of which about 2 million people are exposed to high level of arsenic. The affected provinces are Cordoba, Salta, La Pampa, Santa Fe, Tucuman, Santiago del Estero, San Luis, and parts of Buenos Aires which are four times larger than the Bengal-basin area (India and Bangladesh) (Nicolli et al., 2012). The most important effects of arsenicosis are keratosis, warts, melanosis, leukomelanosis, basal cell carcinoma and cancer of the urinary bladder. It has been shown that arsenical keratosis predominates over melanosis. The types of cancer found were skin cancer and internal cancers (66% of which were in the lungs).

Taiwan: The total population in Taiwan is 23 million. In limited areas of southwest coast of Taiwan, 100,000 inhabitants used artesian well water containing high concentration of arsenic (mainly As^{V}, small amount of As^{III}; Wang et al., 2001) from 1920s to 1970s. A survey on 40,421 inhabitants in 37 villages in the affected area showed 18.5% had skin manifestations of arsenicosis.

About 30,000 cases have been identified as arsenicosis (Sun, 2001). The new cases of blackfoot disease were rarely reported since 1970 when tapewater was used for drinking instead of groundwater. Since 1990, no more new cases of blackfoot disease were reported.

The blackfoot disease was prevalent before 1970 in the southwest coast of Tainan, especially in Beimen, Hseuchia, Jiangjing and Yenshui Townships of Tainan County as well as Budai and Yichu Townships of Chiayi County. There were 1,455 reported cases of blackfoot disease in Tainan from 1954 to 1977 (Cheng, 1977).

Melanosis, keratosis and skin cancers were found among people who drank from arsenic contaminated wells water (but no effect was seen below 150 ppb, which might therefore be a biological threshold) and a very high incidence of lungs, bladder and other cancers was found (Chen et al., 1986). The prevalence of melanosis (18.4%), keratosis (7.1%) and skin cancer (1.1%) in the arsenic endemic area was high (Tseng et al., 1968). There were increasing water arsenic concentrations (170, 470, and 800 ppb) resulted in mortality rate ratios for lung cancer of 1.8, 3.3, and 4.5 for males, and 2.8, 4.3 and 8.8 for females, respectively, using lungs cancer mortality in the general Taiwanese population for comparison. Overall prevalence rate in 1968 was 0.89% (Tseng et al., 1968).

Mexico: The total population is 122 million. It is estimated that around 450,000 people are exposed. In Mexico, the amount of arsenic contaminant in groundwater varies from 10 to 5,000 ppb (Del Razo et al., 1990). The presence of arsenic in drinking water is severe in Durango, Coahuila, Zacatecas, Morelos, Aguas Calientes, Chihuahua, Puebla, Nuevo Leon, Guanajuato, San Luis Potosi and Sonora aquifers and the Lagunera region. More than 50% of the potable drinking water in the Lagunera Region of northern Mexico have arsenic concentrations >50 ppb (Del Razo et al., 1990). The predominant type of arsenic in 90% of the samples was As^{V}. The prevalence of blackfoot disease in Mexico is 0.7%.

Peru: The total population in Peru is 30 million. Traces of arsenic have been found in some of the rivers; for example, the River Locumba (500 ppb), which flows through Puno and Moquegua (the Ilo valley), where approximately 250,000 inhabitants are exposed to arsenic.

USA: It is estimated that 13 million Americans live in areas where the concentration of arsenic in public water supply exceeds >10 ppb. Arsenic concentrations found in at least 25% of groundwater samples based on 31,350 samples in each county (Ryker, 2001). Arsenic concentrations in groundwater are generally highest in the west. Parts of the midwest and northeast also have arsenic concentrations >10 ppb. Arsenic concentrations appear to be lower in the southeast, based on a smaller amount of data. Even at sampled locations, concentrations might differ between hand pump and deep tube wells water.

These data illustrate how arsenic concentrations vary across broad regions of the country.

Exposure to 50 ppb of arsenic in drinking water can cause 31 cases of skin cancer per 1,000 inhabitants.

Nepal: The total population in Nepal is 28 million. Maximum concentration of arsenic in hand pump tube wells of Nawalparasi, Bara, Parsa, Rautahat, Rupandehi, and Kapilvastu districts were 571, 254, 456, 324 and 2,620 ppb, respectively (Maharjan et al., 2006). The population at risk for arsenicosis was estimated to be 3.5 million (Pokhrel et al., 2009). About 5,000 cases of arsenicosis are suffering symptoms of melanosis and keratosis on the palms, trunk, and soles of the feet (Nepal, 2011). Nawalparasi is the most affected district among those six districts, where about 3.6% people have prevalence of arsenicosis.

Pakistan: The total population in Pakistan is 183 million. The arsenic (>10 ppb) affected provinces are Punjub (about 20% population) and Sindh (about 36% population) (Ahmed et al., 2004).

Punjab – In Punjab, 18 districts out of 34 had arsenic contamination in both hand pump and deep tube wells water (>50 ppb). 36,000 samples were estimated for arsenic of which 31% contain 10-50 ppb, while 9.0% had arsenic over 50 ppb. Maximum arsenic contaminated samples 250-500 ppb found in southern and eastern Punjab. More than 65% of the people living in Lahore are consuming water contaminated with arsenic. Southern Punjab is facing serious threat which is causing cancer, stillbirth, post-neonatal mortality and other diseases. A study shows that about 28,000 people in seven districts of the Punjab had elevated arsenic in finger nails of people drinking >50 ppb. The prevalence rate of arsenicosis is 0.1%. It was estimated that 6 million people in the Punjab drink water with arsenic level >10 ppb (Ravenscroft et al., 2009).

Sindh – High contamination of arsenic over 1,000 ppb has been found in two central districts in Sindh. About 23% tube wells in Khairpur district are contaminated with arsenic and the prevalence of melanosis and keratosis is 13 and 3.4 per 1,000 (Fatmi et al., 2009).

Cambodia: The total population in Cambodia is 15 million. Arsenic contamination of the Mekong River and groundwater is putting million of residents at risk of developing arsenicosis. Arsenic contamination of groundwater has been identified in at least 10 provinces of Cambodia with Kandal being one of the most heavily impacted. Six provinces were found to have elevated arsenic risk: Kampong Cham, Kampong Chnang, Kampong Thom, Kandal, Kratie, and Prey Veng. Over 100,000 people are at high risk in Kandal Province of Cambodia.

Levels in some areas approach 3,500 ppb. In total 320,000 people are at risk of arsenicosis. The groundwater arsenic pollution in the Mekong delta ranged up to 1,610 ppb in Cambodia (average 217 ppb) (Berg et al., 2007).

Vietnam: The total population in Vietnam is 88.8 million. Both Red River Delta (flat plain formed by the Red River) and Mekong Delta (region in southwestern Vietnam where the Mekong River approaches and empties into the sea) are affected. The groundwater arsenic pollution in the Red River Delta is up to 3,050 ppb (average 159 ppb) whereas it is up to 845 ppb (average 39 ppb) in the Mekong delta of southern Vietnam (Berg et al., 2007). The population at risk of arsenicosis is estimated to be 10 million in the Red River delta and 0.5-1 million in the Mekong delta.

Thailand: The total population in Thailand is 67 million of which 250,000 people are exposed to high concentration of arsenic. The prevalence of skin manifestation from arsenicosis is 26.3% in Ronpibool district (Ekpalakom & Rodcline, 1994). It can be estimated that there would be around 5,000 cases of non-malignant skin lesions of arsenicosis and more than 10,000 people had arsenic levels higher in hair and nail. More than two-thirds of the drinking water supplies were contaminated with arsenic and about 2% had an arsenic level higher than the safety limit. Another study shows high arsenic intake from cooked food with the level of 726.8 μg/person/day.

Iran: Some villages in Kurdistan and West Azerbaijan provinces of Iran are contaminated with high concentration of arsenic in drinking water (maximum concentration: more than 1,000 ppb; mean concentration 290 ppb). Patients show skin lesions-keratosis, pigmentation, and even blackfoot disease in some villages.

Hungary and Romania: Groundwater resources in the Pannonian Basin (Hungary, Romania, Croatia and Serbia) are known to contain high concentration of arsenic (>10 ppb). Published data show that nearly 500,000 people are exposed through drinking water, making it the largest area so affected in Europe (Rowland et al., 2011). An estimated 300 Hungarians die each year as a result of consuming arsenic-contaminated groundwater.

In conclusion, Table 1.8 shows the most affected 25 countries of arsenic contamination of drinking water with number of arsenicosis cases.

The relative risks of lung cancer were higher in Taiwan where exposures were higher and of longer duration than in Chile. Lower relative risks were found in Argentina where exposures were lower.

Table 1.8 *Top 24 countries with areas where water is contaminated with high concentrations of arsenic.*

Sl. No.	Country	People exposed to arsenic	Area	Number of arsenicosis
1	Bangladesh	36 million	Chittagong coastal plain, Bengal basin	50,000
2	India	26 million	West Bengal, Assam, Nagaland, Thoubal (Manipur), Tripura, Chennai, Vapi (Gujarat), Chandigarh, Himachal Pradesh, Uttar Pradesh, Bihar	300,000
3	China	20 million	Xinjiang, Inner Mongolia, Henan, Shandong and Jiangsu provinces	30,000
4	Pakistan	6 million	Sindh (Indus plain), Punjab (Indus plain and valleys of tributaries)	
5	Vietnam	5.8 million	Red River, Mekong river delta	
6	Nepal	3.5 million	Terai, Kathmandu valley	5,000
7	Argentina	2 million	NW Argentine Andean highland, e.g. San Antonio de Los Cobres and many other localities, Chaco plain, Pampa plain, Copahue	
8	Ukraine	1.6 million	Cities of Donets, Makeevka, Yasinovataya	
9	Chile	500,000	Antofagasta, Calama, Santiago, ancagua, Taltal, Tocopilla and San Pedro de Atacama	
10	Hungary, Romania, Croatia and Serbia	500,000	Pannonian Basin	
11	Mexico	450,000	Durango, Coahuila, Zacatecas, Morelos, Aguas Calientes, Chihuahua, Puebla, Nuevo Leon, Guanajuato, San Luis Potosi and Sonora aquifers and the Lagunera region	
12	Laos	400,000	Mekong river plain	
13	USA	350,000	Appalachian Highlands; Massachu-setts to Maine, Appalachian Highlands; NE Ohio, Interior Plains: E Michigan, Interior Plains: Upper Midwest, Interior Plains: NE Wiscon-sin, Interior Plains: Upper Midwest, Interior Plains: Upper Midwest, Interior Plains: S Dakota, Interior Plains: central Oklahoma, Rocky Mountains: Yellowstone National Park, Intermontane Plateaus: Oregon, Intermontane Plateaus: Carson desert, Nevada, Pacific Mountain System, Pacific Mountain System: NW Washington, Pacific Mountain System,	

Sl. No.	Country	People exposed to arsenic	Area	Number of arsenicosis
			Pacific Mountain System: Arizona, Pacific Mountain System: southern San Joaquin valley, Arizona; Fairbanks, Alaska, Akutan island (Aleutian islands), Kilahuea, Hawai, Soda Dam/Valles Caldera (Manzano Mountains), New Mexico, SW Florida between Tampa and Ft. Myers	
14	Cambodia	320,000	Mekong river delta	
15	Peru	250,000	Puno, Ilo	
16	Thailand	250,000	Hat Yai, Nakorn Chaisi, Rhon Phibun district, Tin belt (Naknon Si Thammarat province)	2,000
17	Colombia	180,000	Caldas, Departments of S Tolima, Nari ño	
18	Mongolia	99,000	Govi Altai-Hovd, Arkhangai, Dornod steppe	1,774
19	Bolivia	20,000	El Alto (La Paz), Oruro, Poop ó basin, North of Potos ídept., Lip éz and south of Potos ídept.	
20	Indonesia		Citarum river, Aceh	
21	Iran		Kurdistan	
22	Japan		Shinji plain, Fukui, Niigata plain, Sendai, Takatsuki, Osaka, Kyushu island	
23	Kazakhstan		S Mangyshlak	
24	Taiwan		Guandu plain, Lanyang plain, Chianan plain	
25	Turkey		Emet-Hisarcik area, Afyon, Heybeli spa, Izmir province	

After several years of low level arsenic exposure, various non-malignant skin lesions appear. These are manifested by melanosis, leucomelanosis and keratosis. After a dozen or so years skin cancers may develop. Twenty or thirty years after exposure to 500 ppb of arsenic, internal cancers (lung, kidney, liver and bladder) appear among 10% of all exposed.

Basal cell carcinoma is the most frequent type of among Euro-Americans, whereas Bowen disease is the most frequent type among Asians (Abernathy et al., 1999).

At low doses, the risk of cancer is assumed to be linear and lifetime exposure at 10 ppb is predicted to result in 6 excess skin cancer cases per 10,000 people exposed (6 x 10^4). This is relatively high risk for drinking water; risk targets are usually fixed at one additional death per 100,000 people exposed (1 x 10^5). The US National Academy of Sciences has noted that as many as 1 in 100 (1 x 10^2) additional cancer deaths could be expected from a lifetime exposure to drinking water containing 50 ppb arsenic.

1.7 Double Edged Sword

Chronic consumption of arsenic may lead to cancer particularly skin cancer. On the other hand, it is still an effective drug for the treatment of chronic promyelocytic leukemia. Its dual role is not clear. Like arsenic, beta-carotene, retinol also act as a double edged sword. Here, dose may be a factor that is not yet established.

Lifetime risks of dying cancer from arsenic in tap water of the USA are shown in Table 1.9.

Table 1.9 *Lifetime risks of dying cancer from consuming tap water with arsenic.*

Concentration of arsenic (ppb)	Approximate total cancer risk
0.5	1 in 10,000
1	1 in 5,000
3	1 in 1,667
4	1 in 1,250
5	1 in 1,000
10	1 in 500
20	1 in 250
25	1 in 200
50	1 in 100

Assuming arsenic contaminated water of 2 liters consumed per day (Based upon the National Academy of Sciences' 1999 Risk estimates).

1.8 Biomarker of Arsenicosis

Estimation of total arsenic in urine, hair, and nail are usually used to confirm the diagnosis of arsenicosis. These samples can be easily collected from the patient. Still now no dependable biomarker is identified.

Presence of arsenic in urine indicates the recent exposure of arsenic whereas high amount of arsenic in hair or nail indicates long-term exposure to arsenic.

In absence of dependable marker, the diagnosis of arsenicosis involving organs other than the skin is difficult to confirm. How many people are suffering from arsenicosis is still not yet known.

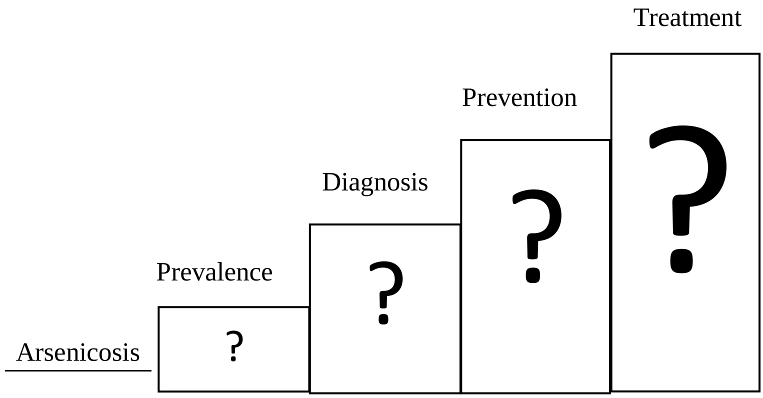
1.9 Providing Arsenic Safe Drinking Water

Since 1993 international donor agencies mobilized fund to Bangladesh. Extensive researches were conducted how to provide arsenic safe drinking water. Several methods were suggested, but none is suitable for the Bangladeshi arsenicosis with non-malignant skin lesions. There are more chances of bacterial infection using these options for providing arsenic safe drinking water.

1.10 Vitamins and Minerals

Retinol, ascorbic acid, alpha-tocopherol, zinc, and selenium are either alone or in combination is considered to be effective in reducing non-malignant skin lesions. Prolonged duration of treatment is required ranging from 6 to 14 months. These all are antioxidants. Antioxidants in high doses may serve as pro-oxidant. Stoppage of supplementation of these vitamins and minerals recur the symptoms.

1.11 Big Questions



The prevalence of arsenicosis is not clear. A small question mark is determined by this aspect. It is much more complicated task to diagnose the cases if the patient has no melanosis or keratosis. About prevention of disease, a number of approaches were tried. Extensive works were done. But not a single one is appropriate for Bangladeshi. Some antioxidant vitamins and minerals were identified to be effective, but their role in the total cure shows big question.

A group of authors wrote a book "The Taiwan Crisis: A showcase of the global arsenic problem" (Jean et al., 2010). They wrote:

In the 1950s, the residents of the southwestern coastal areas of Taiwan suffered greatly from blackfoot disease due to the consumption of arsenic-contaminated groundwater. Groundwater with high levels of arsenic in southwestern and northeastern Taiwan received much attention. After arsenic-safe tap water was utilized for drinking instead of groundwater in the 1970s, blackfoot disease cases decreased greatly. After 1990, no new blackfoot disease cases were reported, and as a consequence, blackfoot disease problems disregarded. However, arsenic is still present in the groundwater.

The title of this book should be “The Bangladeshi Crisis: A mummified case of the global arsenic problem”. It is not a joke. It is real as because:

During 1997-1998, two specialists from World Bank and WHO came to Bangladesh to assess the situation. Subsequently considerable research funds were mobilized. Most of the research funds were used to provide arsenic safe drinking water. Only a small fraction of funds were utilized in health issues of arsenicosis. At present the flow of funds is almost nil (Adams, 2013) and research activities are also related to the fund. However, the number of diagnosed patients is increasing.

The limitations of the studies are a) group rather than individual measures of drinking water arsenic; b) lack of biomarkers to confirm arsenic exposure; and c) the underestimation of confounders such as cooking water and contaminated food (Wang et al., 2007).

1.12 Questions to be Raised

1. High concentration of arsenic was found in the mummified human body as long as 7,000 years, but arsenic was used as medicine for at least 2,500 years. Why is such discrepancy?

2. Arsenic causes cancer in skin, lungs and urinary bladder. Is it due to exposed part of these organs?

3. Previous exposure of arsenic may cause cancer. When a population of an arsenic endemic area is already exposed to arsenic, is it necessary to take preventive measure of arsenic exposure?

4. The amount of arsenic in water is closely related to the effect. What is the role of arsenic in food?

5. Prolonged exposure means 6 months or more. What is the scientific basis of this criterion.

6. In West Bengal (India), 26 million people are exposed to high concentration of arsenic of which 300,000 shows arsenicosis (non-malignant skin lesions). On the other hand, 36 million Bangladeshi are exposed to arsenic of which 50,000 are suffering from arsenicosis (non-malignant skin lesions). Why?

7. Why the involvement of liver in arsenicosis of Indians are more than Bangladeshi patients?

8. Why the cases of blackfoot disease are limited in Taiwan and a small extent in Chile and Mexico? Is there any relationship between the ratio of As^{III} and As^{V} in drinking water in the development of blackfoot disease?

9. Is there any regional variation in the development of skin cancer and the concentration of arsenic in drinking water. For example, ingestion of 50 ppb of arsenic in drinking water can cause skin cancer among Americans but not among Bangladeshi.

References

[1] Abernathy, C. O., Liu, L. P., Longfellow, D., Aposhian, H. V., Beck, B., Fowler, B., Goyer, R., Menzer, R., Rossman, T., Thompson, C., & Waalkes, M. (1999). Arsenic: Health effects, mechanisms of actions, and research issues. *Environmental Health Perspectives*, 107(7), 593-597.

[2] Adams, P. (2013). In Bangladesh, funds dry up for arsenic mitigation research. *Lancet*, 382, 1693-1694.

[3] Ahamed, S., Sengupta, M. K., Mukherjee, A., Hossain, M. A., Das, B., Nayak, B., Pal, A., & Mukherjee, S. C. (2006). Arsenic groundwater contamination and its health effects in the state of Uttar Pradesh (UP) in upper and middle Ganga plain,

India: A severe danger. *Science of the Total Environment*, 370 (2-3), 310-322.

[4] Ahmed, T., Kahlown, M. A., Tahir, A., & Rashid, H. (2004). People-centred approaches to water and environmental sanitation: Proceedings of the 30th WED conference, Lao national cultural hall, Vientiane, Lao PDR, 2004. In 30th WED international conference, Viantiane, p 662.

[5] Argos, M., Parvez, F., Chen, Y., Hussain A. Z. M. I., Momotaj, H., Howe, G. R., Graziano, J. H., & Ahsan, H. (2007). Socioeconomic status and risk for arsenic-related skin lesions in Bangladesh. *American Journal of Public Health*, 97(5), 825-831.

[6] Arriaza, B., Amarasiriwardena, D., Cornejo, L., Standen, V., Byrne, S., Bartkus, L., & Bandak, B. (2010). Exploring chronic arsenic poisoning in pre-Columbian Chilean mummies. *Journal of Archaeological Science*, 37(6), 1274-1278.

[7] Berg, M., Stengel, C., Trang, P. T. K., Viet, P. H., Sampson, M. L., Leng, M., Samreth, S., & David Fredericks, D. (2007). Magnitude of arsenic pollution in the Mekong and Red River Deltas: Cambodia and Vietnam. *Science of the Total Environment*, 372, 413-425.

[8] Blejer, H. P., & Wagner, W. (1976). Inorganic arsenic: Ambient level approach to the control of occupational cancerigenic exposures. *Annals of New York Academy of Science*. 271, 179-186.

[9] Borgono, J. M., Vincent, P., Venturino, H., & Infante, A. (1997). Arsenic in the drinking water of the city of Anotgagasta: Epidemiological and clinical study before and after the installation of a treatment plan. *Environmental Health Perspective*, 19, 103-105.

[10] Buchet, J. P. (1994). Assessment of exposure to inorganic arsenic following ingestion of marine organisms by volunteers. *Environmental Research*, 66(1), 44-51.

[11] Bundschuh, J., Litter, M. I., Parvez, F., Román-Ross, G., Nicolli, H. B., Jean, J. S., Liu, C. W., López, D., Armienta, M. A., Guilherme, L. R. G., Cuevas, A. G., Cornejo, L., Cumbal, L., & Toujaguez, R. (2012). One century of arsenic exposure in Latin America: A review of history and occurrence from 14 countries. *Science of the Total Environment,* 429: 2-35.

[12] Carbonell-Barrachina, A. A., Signes-Pastor, A. J., Vázquez-Araújo, L., Burló, F.,

& Sengupta, B. (2009). Presence of arsenic in agricultural products from arsenic-endemic areas and strategies to reduce arsenic intake in rural villages. *Molecular Nutrition & Food Research*, 53(5), 531-541.

[13] Caussy, D. (2005). A field guide for detection, management and surveillance of arsenicosis cases. New Delhi, World Health Organization, pp 5-18.

[14] Chakraborti, D., Das, B., Rahman, M. M., Chowdhury, U. K., Biswas, B., Goswami, A. B., & Das, D. (2009). Status of groundwater arsenic contamination in the state of West Bengal, India: A 20-year study report. *Molecular Nutrition & Food Research*, 53(5), 542-551.

[15] Chakraborti, D., Rahman, M. M., Das, B., Murrill, M., Dey, S., Mukherjee, S. C., Dhar, R. K., Biswas, B. K., Chowdhury, U. K., Roy, S., Sorif, S., Selim, M., Rahman, M., & Quamruzzaman, Q. (2010). Status of groundwater arsenic contamination in Bangladesh: A 14-year study report. *Water Research*, 44(19), 5789-5802.

[16] Chakraborti, D., Rahman, M. M., Paul, K., Chowdhury, U. K., Sengupta, M. K., Lodh, D., Chanda, C. R., Saha, K. C., & Mukherjee, S. C. (2002). Arsenic calamity in the Indian subcontinent: What lessons have been learned? *Talanta*, 58(1), 3-22.

[17] Chen, C. J., Chuang, Y. C., You, S. L., & Lin, H. Y. (1986). A retrospective study on malignant neoplasms of bladder, lung and liver in blackfoot disease endemic area in Taiwan. *British Journal of Cancer*, 53(3), 399-405.

[18] Chen, K. P., Wu, H. Y., & Wu, T. C. (1962). Epidemiologic studies on blackfoot disease (BFD) in Ta ïwan 3: Physicochemical characteristics of drinking water in endemic BFD areas. *Memorial College Medicine National Taiwan University*, 8, 115-129.

[19] Chen, W., Yang, J., Chen, J., & Bruch, J. (2006). Exposures to silica mixed dust and cohort mortality study in tin mines: Exposure-response analysis and risk assessment of lung cancer. *American Journal of Industrial Medicine*, 49, 67-76.

[20] Cheng, C. S. (1977). Introduction of blackfoot disease. In: Reports of blackfoot disease. Cheng, C. S. (ed). Institute of blackfoot disease, Tainan, p 2 (in Chinese).

[21] Chou, S., Harper, C., Ingerman, L., Llados, F., Colman, J., Chappell, L., Osier, M., Odin, M., & Sage, G. (2007). Toxicological profile for arsenic. US Department of

Health and Human Service, Agency for Toxic Substances and Disease Registry.

[22] Csalagovits, I. (1994). Geological Institute of Hungary.

[23] Datta, D. V. (1976). Letter: Arsenic and non-cirrhotic portal hypertension. Lancet, 1(7956), 433.

[24] Datta, D. V., & Kaul, M. K. (1976). Arsenic content of drinking water in villages in Northern India: A concept of arsenicosis. *Journal of Association of Physicians India*, 24(9), 599-604.

[25] Del Razo, L. M., Arellano, M. A., & Cebrián, M. E. (1990). The oxidation states of arsenic in well-water from a chronic arsenicism area of northern Mexico. *Environmental Pollution,* 64(2), 143-153.

[26] DG Environment. (2000). Ambient air pollution by As, Cd and Ni compounds, position paper, working group on arsenic. Cadmium and nickel compounds, DG Environment European Commission.

[27] Eggers, H. E. (1931). Etiology of Cancer, *Archives of Pathology*, 12, 983.

[28] Ekpalakom, V., & Rodcline A. (1994). The prevalence survey of chronic arsenic poisoning in Ronpibool District, Nakorn Sri Thammarat Province. Unpublished report. Division of Epidemiology, Office of the Permanent Secretary, Ministry of Public Health.

[29] Espinoza, E. O., Mann, M. J., Bleasdell, B., DeKorte, S., & Cox, M. (1996). Toxic metals in selected traditional Chinese medicinals. *Journal of Forensic Science*, 41, 453-456.

[30] Fatmi, Z., Azam, I., Ahmed, F., Kazi, A., Gill, A. B., Kadir, M. M., Ahmed, M., Ara, N., & Janjua, N. Z. (2009). Health burden of skin lesions at low arsenic exposure through groundwater in Pakistan. Is river the source? *Environment Research*, 109(5), 575-581.

[31] Food and Drug Administration (FDA). (2000). FDA approves arsenic trioxide for leukemia treatment in record time for a Cancer Drug Development Program, 26 September 2000.

[32] Frear, D. E. H. (1942). Chemistry of insecticides and fungicides. D. Van Nostrand Co., pp 1-300.

[33] Frost, D. V. (1977). The arsenic problems. *Advanced Experimental & Medicinal Biology*, 91, 259-279.

[34] Garai, R., Chakraborty, A. K., & Dey, S. B. (1984). Chronic arsenic poisoning from tube well water. *Journal of Indian Medical Association*, 82, 34-35.

[35] Goyenechea, M. (1917). Sobre la nueva enfermedad descubierta en Bell-Ville. *Review of Medicine Rosario*, 7, 485.

[36] Hsueh, Y. M., Cheng, G. S., Wu, M. M., Yu, H. S, Kuo, T. L., & Chen, C. J. (1995). Multiple risk factors associated with arsenic-induced skin cancer: Effects of chronic liver disease and malnutritional status. *British Journal of Cancer*, 71, 109-114.

[37] Hughes, K. (1994). Inorganic arsenic: Evaluation of risks to health from environmental exposure in Canada. *Environmental Carcinogenesis & Ecotoxicology Reviews*, 12, 145-149.

[38] Huq, S. M. I., & Naidu, R. (2003). Arsenic in groundwater of Bangladesh: Contamination in food chain. In: Arsenic contamination: Bangladesh prspective. ITN-Bangladesh. Ahmed, M. F. (ed). Bangladesh University of Engineering and Technology, Dhaka, Bangladesh, pp 203-226.

[39] Jean, J., Bundschuh, J., Chen, C., Guo, H., Liu, C., Lin, T., & Chen, Y. (2010). The Taiwan Crisis: A showcase of the global arsenic problem (Arsenic in the environment). CRC Press.

[40] Jolliffe, D. M. (1993). A history of the use of arsenicals in man. *Journal of the Royal Society of Medicine*, 86, 287-289.

[41] Koundouri, P. (2005). The economics of arsenic mitigation. World Bank Technical Report-II, Paper-4. Arsenic contamination of ground water in South and East Asian Countries, p 242.

[42] Liu, J., Zheng, B., Aposhian H. V., Zhou, Y., Chen, M. L., Zhang A., & Waalkes, M. P. (2002). Chronic arsenic poisoning from burning high-arsenic-containing coal in Guizhou, China. *Environmental Health Perspective*, 110(2), 119-122.

[43] Maddison, D., Luque, R. C., & Pearce, D. (2004). The economic cost of arsenic contamination of groundwater in Bangladesh. Water and Sanitation Program, p 32.

[44] Maharjan, M., Roshan, R., Shrestha, R., Ahmad, S. K. A., Watanabe, C., &

Ohtsuka, R. (2006). Prevalence of arsenicosis in Terai, Nepal. *Journal of Health Population & Nutrition*, 24, 246-252.

[45] Mahimairaja, S., Bolan, N. S., Adriano, D. C., & Robinson, B. (2005). Arsenic contamination and its risk management in complex environmental settings. *Advance Agronomy*, 86, 1-82.

[46] Marshall, G., Ferreccio, C., Yuan, Y., Bates, M. N., Steinmaus, C., Selvin, S., & Smith, A. H. (2007). Fifty-year study of lung and bladder cancer mortality in chile related to arsenic in drinking water. *Journal of National Cancer Institute*, 99(12), 920-928.

[47] McNeer, G. (1934). Arsenical kératoses and epitheliomas. *Annals of Surgery*, 99(2), 348-353.

[48] Meharg, A. A., Williams, P. N., Adomako, E., Lawgali, Y. Y., Deacon, C., Villada, A. et al. (2009). Geographical variation in total and inorganic arsenic content of polished (white) rice. *Environmental Science & Technology*, 43(5), 1612-1617.

[49] Misbahuddin, M., Khandker, S., & Jakariya, M. (2011). Arsenic contamination of drinking water and foodstuffs. In: Drinking water contaminants in Bangladesh: Focuses on arsenic, fluoride, pesticides, manganese and cyanobacteria. Misbahuddin, M., & Khandker, S. (eds). Germany, LAP LAMBERT Academic Publishing, pp 12-57.

[50] Mukherjee, A., Sengupta, M. K., Hossain, M. A., Ahamed, A. S., Das, B., Nayak, B., Lodh, D., Rahman, M. M., & Chakraborti, D. (2006). Arsenic contamination in groundwater: A global perspective with emphasis on the Asian scenario. *Journal of Health Population and Nutrition*, 24(2), 142-163.

[51] Murcott, S. (2012). Arsenic contamination in the world: An international sourcebook. IWA Publishing.

[52] Nepal, G. D. (2011). Research on mitigation options of arsenic contaminated groundwater in Nepal. Rural Water Supply and Sanitation Project, Western Nepal.

[53] Nicolli, N. B., Bundschuh, J., Blanco, M. C., Tujchneider, O. C., Panarello, H. C., Dapeña, C., & Rusansky, J. E. (2012). Arsenic and associated trace-elements in groundwater from the Chaco-Pampean plain, Argentina: Results from 100 years of research. *Science of Total Environment*, 429, 36-56.

[54] Pal, A., Nayak, B., Das, B., Hossain, M. A., Ahamed, S., & Chakraborti, D. (2007). Additional danger of arsenic exposure through inhalation from burning of cow dung cakes laced with arsenic as a fuel in arsenic affected villages in Ganga-Meghna-Brahmaputra plain. *Journal of Environmental Monitoring*, 9, 1067.

[55] Pokhrel, D., Bhandari, B. S., & Viraraghavan, T. (2009). Arsenic contamination of groundwater in the Terai region of Nepal: An overview of health concerns and treatment options. *Environment International,* 35(1), 157-161.

[56] Pott, P. (1775). Chirurgical observations relative to the cataract, the polypus of the nose, the cancer of the scrotum, the different kinds of ruptures, and the mortification of the toes and feet. London, Hawes, Clarke & Collins, pp 7-13.

[57] Rahman, M., Tondel, M., Ahmad, S. A., Chowdhury, I. A., Faruquee, M. H., & Axelson, O. (1999). Hypertension and arsenic exposure in Bangladesh. *Hypertension,* 33(1), 74-78.

[58] Rahman, M., Vahter, M., Wahed, M. A., Sohel, N., Yunus, M., Streatfield, P. K., Arifeen, S. E., Bhuiya, A., Zaman, K., Chowdhury, A. M. R., Ekström, E. C., & Persson, L. A. (2006). Prevalence of arsenic exposure and skin lesions: A population based survey in Matlab, Bangladesh. *Journal of Epidemiology & Community Health,* 60, 242-248.

[59] Ravenscroft, P., Hugh Brammer, H., & Richards, K. (2009). Arsenic pollution: A global synthesis. Wiley-Blackwell, pp 318-386.

[60] Rowland, H. A. L., Omoregie, E. O., Millot, R., Jimenez, C., Mertens, J., Baciu, C., Hug, S. J., & Berg, M. (2011). Geochemistry and arsenic behaviour in groundwater resources of the Pannonian Basin (Hungary and Romania). *Applied Geochemistry*, 26, 1-17.

[61] Ryker, S. J. (2001). Mapping arsenic in groundwater. Geotimes, 46(11), 34-36.

[62] Salamon, L. (1978). Retrospective trend analysis of the content of U. K.: Air particulate material 1957-74. *Science of the Total Environment,* 9, 161-200.

[63] Sambu, S., & Wilson, R. (2008). Arsenic in food and water: A brief history. *Toxicological and Industrial Health,* 24(4), 217-226.

[64] Sinha, S. K., Misbahuddin, M., & Ahmed, A. N. N. (2003). Factors involved in

the development of chronic arsenic poisoning in Bangladesh. *Archive of Environmental Health*, 58, 699-700.

[65] Sun, G. F., Liu, S., Li, B., Li, X., Sun, X., Guo, X. Y., & Pi, J. B. (2001). Current situation of endemic arsenicosis in China. *Environmental Science*, 8, 425.

[66] Tseng, W. P., Chu, H. M., How, S. W. Fong, J. M., Lin, C. S., & Yeh, S. (1968). Prevalence of skin cancer in an endemic area of chronic arsenicism in Taiwan. *Journal of National Cancer Institute*, 40, 453-463.

[67] Unicef. (2008). Arsenic mitigation in Bangladesh. http://www.unicef.org/bangladesh/Arsenic.pdf.

[68] Unicef. (2011). Bangladesh national drinking water quality survey of 2009. Unicef and Bangladesh Bureau of Statistics.

[69] von Ehrenstein, O. S., Guha Mazumder, D. N., Yuan, Y., Samanta, S., Balmes, J., Sil, A., & Smith, A. H. (2005). Decrements in lung function related to arsenic in drinking water in West Bengal, India. *American Journal of Epidemiology*, 2005(6), 162-533.

[70] Von Ehrenstein, O. S., Guha Mazumder, D. N., Hira-Smith, M., Ghosh, N., Yuan, Y., Windham, G., Ghosh, A., Haque, R., Lahiri, S., Kalman, D., Das, S., & Smith, A. H. (2006). Pregnancy outcomes, infant mortality, and arsenic in drinking water in West Bengal, India. *American Journal of Epidemiology*, 163(7), 662-669.

[71] Wang, C. H., Hsiao, C. K., Chen, C. L., Hsu, L. I., Chiou, H. Y., Chen, S. Y., & Chen, C. J. (2007). A review of the epidemiologic literature on the role of environmental arsenic exposure and cardiovascular diseases. *Toxicology & Applied Pharmacology*, 3, 222-315.

[72] Wang, H. C., Wang, H. P., Peng, C. Y., Liu, S. H., & Yang, Y. W. (2001). Speciation of As in the blackfoot disease endemic area. *Journal of Synchrotron Radiation*, 8, 961-962.

[73] White, J. C. (1884). Cases of arsenical dermatitis. *Boston Medcal & Surgery Journal*, 111, 433-435.

[74] White, J. C. (1885). Psoriais – verruca – epithelioma: A sequence. *American Journal of Medical Science*, 89, 163-173.

[75] Winkel, L. H. E., Trang, P. T. K., Lan, V. M., Stengel, C., Amini, M., Ha, N. T., Viet, P. H., & Berg, M. (2011). Arsenic pollution of groundwater in Vietnam exacerbated by deep aquifer exploitation for more than a century. *Proceedings of National Academy of Sciences*, 108, 1246-1251.

[76] Yamauchi, H. & Fowler, B. A. (1994). Toxicity and metabolism of inorganic and methylated arsenicals. In: Arsenic in the environment. Part II: Human health and ecosystem effects. Nriagu, J. O. (ed). New York, John Wiley & Sons, pp 35-53.

[77] Yu, W., Harvey, C. M., & Harvey, C. F. (2003). Arsenic in groundwater in Bangladesh: A geostatistical and epidemiological framework for evaluating health effect and potential remedies. *Water Resources Research*, 39(6), 1-17.