

# Advances made in understanding the effects of arsenic exposure on humans

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*Arsenic contamination of drinking water is a great concern for public health throughout the world. This alarming situation led to many independent research studies but there are only a few studies till date which collectively articulated all studies together with a multidisciplinary approach for better understanding. The present article is an effort towards collating the advances made in understanding the impacts of arsenic toxicity on human beings. It discusses the sources, mobility, sensing and metabolism patterns of arsenic. It also deals with understanding the impact of arsenic toxicity over clinical health, nutritional status, carcinogenicity, genomics, and social and economic status of human beings. Though many evaluative studies have been conducted, there are no easy and effective measures of sensing and remediation available till date. Hence, we conclude that more collective, multidisciplinary, advanced and target-specific studies are essential, the outcome of which can contribute in developing better prevention strategies and technological mitigation programmes for the betterment of human kind.*

**Keywords:** Arsenic, arsenite, arsenate, cytotoxic, genotoxic, carcinogenic.

ARSENIC contaminated drinking water and its impact on human health is of great concern with serious biological and social consequences (Figure 1), throughout the world<sup>1</sup>.

There are not many reviews available, addressing the worldwide scenario of arsenic contamination in drinking water. Despite this, it is found to be a major public health concern in many countries like Hungary, Chile, Mexico, USA, Vietnam, China, Bangladesh and India. At present with the discovery of newer sites worldwide, the global scenario of arsenic contamination is changing considerably, especially in Asian countries<sup>2</sup>.

Between 2000 and 2005, many new sites in Nepal, China, Mongolia, Myanmar, Afghanistan, Cambodia, DPR Korea and Pakistan have emerged with arsenic-related ground water problems. Among these, it is more prominent in countries like India, Bangladesh and Taiwan. The situation is most devastating in Bangladesh followed by West Bengal (India) (Figure 2)<sup>2</sup>, because of the number of people affected<sup>3</sup>.

In the context of the Indian sub-continent, the regions most affected by arsenic are along the river basin of Ganges and Brahmaputra in India and Meghna in Bangladesh. It is estimated that 6 million people in West Bengal and 25 million people in Bangladesh are exposed to arsenic-contaminated drinking water and ground water<sup>3</sup>.

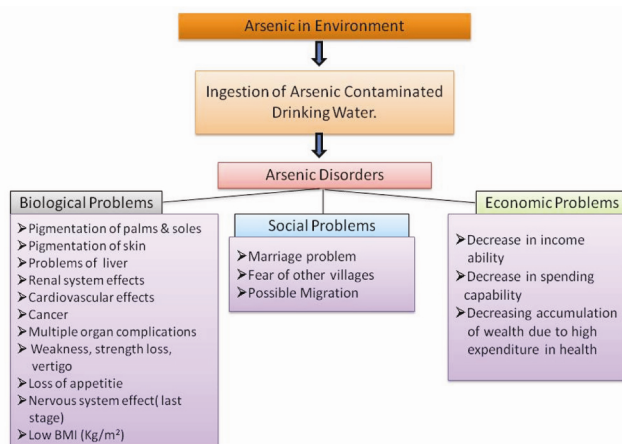
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Though many in-depth studies have been done specifically on the impacts of arsenic toxicity on humans, very few are done with a multidisciplinary approach on this issue. Hence, our main aim is to provide information on the latest advances in arsenic toxicity research for the inter and multidisciplinary researchers to develop better prevention and control measures.

## Source

Arsenic is an element, which stands in the 33rd spot of the periodic table between germanium and selenium. It is



**Figure 1.** Conceptual framework showing pathways of arsenic toxicity and its consequences among human beings.

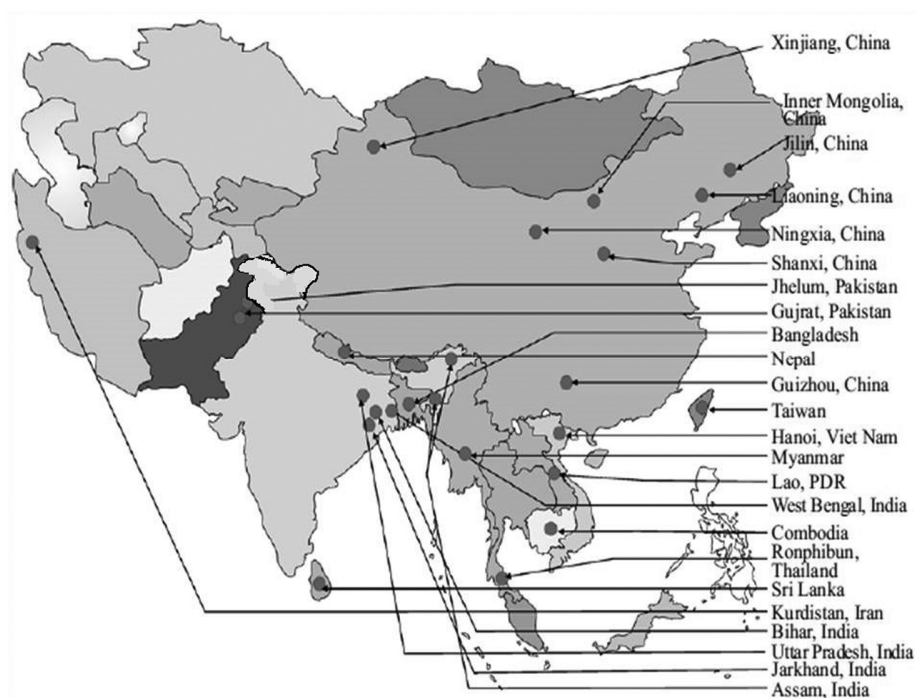


Figure 2. Distribution of arsenic in Asia.

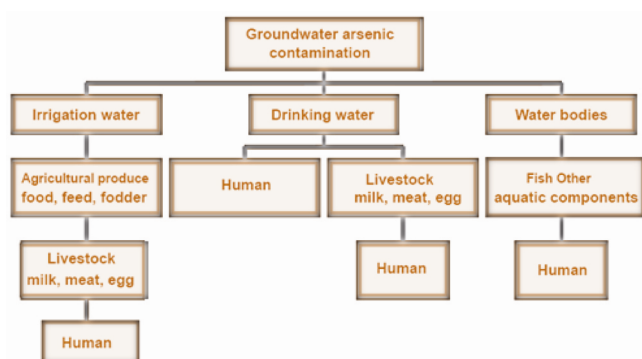


Figure 3. Sources through which humans get exposed to arsenic.

most commonly found in earth's crust, in the form of iron arsenide sulphide (FeAsS). It is also present in atmosphere in the form of arsenic trioxide dusts, a by-product of industrial smelting operations and through other anthropogenic activities. Arsenic is regarded to be a group I carcinogen for human beings (IARC monographs evaluating carcinogenic risk of chemicals on humans: some drinking water, disinfectants and contaminants including arsenic)<sup>4</sup>.

Exposure to contaminated drinking water by geological sources (Figure 3) is the major cause for human toxicity rather than anthropogenic sources. In addition, another route of human exposure to arsenic toxicity is through dietary consumption of arsenic-contaminated food. Both flora and fauna, an essential component of human diet, get exposed to arsenic through atmospheric emission

from anthropogenic activities like mining and smelting operations, and also through agricultural sources like insecticides, herbicides, wood preservatives, pesticides, fertilizers and growth stimulants for plants and animals<sup>3,5-8</sup>. Even though arsenic is bioconcentrated by flora and fauna, it does not get biomagnified in the food chain<sup>9</sup>.

### Mobility

Arsenic compounds are found in both inorganic and organic forms. They also exist in two different oxidation states, +3 (arsenite) and +5 (arsenate)<sup>10</sup>. This particular metal is considered to be more toxic, when it is in its inorganic forms, for e.g. sodium arsenite (NaAsO<sub>2</sub>), arsenic trichloride (AsCl<sub>3</sub>) and arsenous acid (H<sub>3</sub>AsO<sub>3</sub>). Arsenous acid and arsenate are different from each other in their charge at pH 7.4 and their ability to bind thiol containing compounds. Compounds containing arsenic, that binds to the protein are mainly in the form of arsenic (III) whereas arsenic (V) mostly remains in the free form<sup>10,11</sup>. Hence, arsenic compounds in trivalent state are much more harmful compared to its pentavalent state<sup>12</sup>.

### Arsenic sensing

Laboratory methods such as atomic absorption spectroscopy (AAS), atomic fluorescence spectroscopy (AFS), mass spectrometry or inductively coupled plasma-atomic emission spectrometry (ICP-MS or ICP-AES) are

most commonly used to detect arsenic at very low concentrations<sup>13</sup>. However, these techniques are expensive, bulky and sophisticated, and sample preparation is time-consuming<sup>14</sup>. Hence, these techniques are not feasible for field assays, especially in developing countries. At present, techniques like anodic stripping voltammetry (ASV), colorimetric methodology and laser-induced breakdown spectroscopy (LIBS) have shown potential and have been applied in arsenic field assays and are found to be compatible<sup>13</sup>. The advantages of using these techniques are that, they neither require use of reagents nor complicated pre-treatment of samples and analysis platforms for laborious fabrication. They also do not suffer from production of toxic substances, poor reproducibility, low sensitivity and extreme matrix interference problems<sup>14</sup>. Therefore, at present new techniques like surface-enhanced Raman scattering (SERS) have been attracting growing attention for its efficiency in detecting different arsenic species<sup>15</sup>.

### Metabolism of arsenic

Methylation is an important step that helps in conversion of inorganic arsenic to organic arsenic forms. In this process, first arsenite is methylated to monomethylarsinic acid (MMA) and thereafter methylated to dimethylarsinic acid (DMA). In some species arsenite is also methylated into trimethylarsine oxide (TMAO)<sup>10,11</sup>. Upon exposure to arsenic, humans excrete significant amount of MMA which is about 10–20% of total urine arsenic<sup>16</sup>. In mammals DMA is the end point of arsenic metabolism and is not further methylated<sup>17,18</sup>. It is found that 40–60% of arsenic remains are retained in skin, hair, nails, muscle, teeth and bones even after exposure to arsenic is ceased (ATSDR case studies in environmental medicine, agency for toxic substances and disease registry)<sup>19</sup>. The intensity of effect of arsenic toxicity completely relies on the level or degree of exposure. In the case of humans, the level or degree of exposure varies according to their geographical locations<sup>11</sup>.

### Effects of arsenic on human health

Exposure to chronic arsenic toxicity leads to effect on human health termed as arsenicosis<sup>3</sup>. Many countries worldwide suffer from problems of arsenicosis directly affecting the overall health of the population and indirectly the socio-economic status. Table 1 gives an overview of arsenic pollution and arsenicosis related problems from both global and Indian perspective<sup>2</sup>.

It has been investigated that susceptibility to arsenic toxicity is also influenced by several other factors like age, sex, health-status parameters, nutrition and various other lifestyle factors<sup>20</sup>. For instance, a study reveals that urinary arsenic levels are higher in men compared to

women<sup>16</sup>. According to the researchers, long exposure to arsenic may result in its accumulation in brain, bladder, heart, lungs, liver, kidneys, pancreas, spleen, muscles, skin and hair<sup>6</sup> as well as in fluids such as bile, blood and stomach juices<sup>21</sup>. Chronic exposure to arsenic toxicity also includes disruption of homeostasis mechanism of blood, spleen and liver by interfering with the uptake of essential chemicals, cardio toxicity<sup>22</sup>, peripheral vascular diseases (PVD)<sup>23</sup>, neuropathies, increased systolic blood pressure, skin lesions, declined nutritional status and elevated arsenic and glucose levels in urine. Apart from this, a dose-response relationship is also found with tumours of lung, skin, bladder and liver in arsenic-exposed human population<sup>20,24,25</sup>.

### Impact of arsenic toxicity on nutritional status

Epidemiological studies in Taiwan, Thailand, Bengal and Bangladesh<sup>20,26,27</sup> reveal that chronic energy deficiency (CED) and protein energy deficiency (PED) are strongly related to increased prevalence of arsenic carcinogenesis<sup>25</sup>. It is found that the crude prevalence ratio is high among arsenicosis individuals with poor nutritional status when compared to the unexposed population<sup>28–30</sup>. Findings from different studies across the world showed that poor nutritional status may increase an individual's susceptibility to chronic arsenic toxicity, or arsenicosis may contribute to poor nutritional status<sup>28</sup>. Association between the efficiency of arsenic methylation and body mass index (BMI) was found evident in a study involving three populations which were studied separately. Strong relationship was found between high BMI and low %  $\mu$ MMA and  $\mu$ DMA/ $\mu$ MMA which underscored the importance of BMI as a potential arsenic-related disease risk factor. Hence, it should be carefully considered for future studies associated with human arsenic metabolism and toxicity<sup>31</sup>.

### Molecular level effects of arsenic toxicity

Chronic exposure to arsenic is capable of altering expression of number of genes which are involved in different physiological processes in humans. For example, genes responsible for metabolism, stress responses, genes related to damage response and apoptosis, genes regulating cell cycle and the genes involved in cell signalling and altered growth factor<sup>10,11</sup>. However, is difficult to study the factors which affect arsenic toxicity, because of its ability to convert between oxidation states and organo-metalloidal forms<sup>32</sup>.

### Arsenic-induced cancer

It is evident that the study of arsenic toxicity is complex, because of its competition or interference with normal metabolic pathways. Therefore, very little information is

**Table 1.** Effect of arsenic pollution on global and Indian scenario

Countries	Regions	Concentration of arsenics	At risk	Clinical manifestations
Global scenario				
Afganistan	Ghazni	10 to 500 µg/l	0.5 million	
Argentina	Cordoba, Salta, La Pampa, Santa Fe, Tucuman, Santiago del Estero, San Luis, and parts of Buenos Aires.	10 to 720 µg/l	0.27 million	Skin cancer
Bangladesh	49 districts	50 to 3200 µg/l	105 million	Chronic arsenicosis with multiple chronic symptoms and poor nutritional status
Chile	Antofagasta, Calama, and Tocopilla	40 to 860 µg/l	0.3 million	Raynaud's syndrome, ischemia of the tongue, hemiplegic with partial occlusion of the carotid artery, mesenteric arterial thrombosis, and myocardial ischaemia
China	40 counties	50 to 2000 µg/l	3.4 million	Cirrhosis, ascites, polyneutitis, and skin cancer
Hungary	Great Hungarian Plain	60 to 4000 µg/l	Few thousand	Melanosis, hyperkeratosis, skin cancer, internal cancer, bronchitis, gastroenteritis or haematologic abnormalities
Iran	Kurdistan	10 to 1000 µg/l		Keratoses, pigmentation and even amputation due to gangrene
Mexico	11 counties	10 to 624 µg/l	0.6 million	Arsenicosis
Nepal	Terai	10 to 2620 µg/l	0.5 million	Arsenicosis
Taiwan	Southwest	400 to 600 µg/l	0.14 million	Diseases, such as cancer, diabetes mellitus, cardiovascular anomalies, hypertension, and cerebral apoplexy, occurred at significantly higher levels than in areas free of blackfoot
Vietnam	Hanoi and rural areas	1 to 3050 µg/l	Several million	Chronic arsenicosis
Indian Scenario				
West Bengal	3500 villages from 90 blocks	50 to 2500 µg/l	50 million	Lungs, kidney, liver cancer, Bowen's disease, skin lesions, poor nutritional status and multiple chronic symptoms.
Bihar	Middle Ganga Plain	Above 50 µg/l	Few lakhs	Skin lesions
Uttar Pradesh	Ballia, Ghazipur and Varanasi	Above 50 µg/l	Few thousand	Skin lesions
Andhra Pradesh	Hyderabad	0.87–12.8 mg/kg In Soil	Few thousand	High concentration in food chain but, no reports yet

available regarding arsenic uptake and efflux system. Arsenic acts as a potential carcinogenic agent, but the action mechanism of inorganic arsenic causing cancer remains indefinable. There are no evidences revealing how inorganic arsenic reacts with DNA, like other organic carcinogens<sup>24,26</sup>. Higher levels of 8-hydroxy-2'-deoxyguanosine are found in arsenic related skin neoplasm and arsenic keratosis. This study also suggests that DNA damage induced by arsenite is mediated by reactive oxygen species (ROS)<sup>33</sup>. Oxidative DNA damage and DNA-protein crosslinks are considered to be major DNA lesions caused by arsenite. A study on human lung adenocarcinoma, an arsenite-resistant variant cell line, revealed elevated levels of heme oxygenase (HO) and re-

sistive capability to arsenite could be blocked by tin-protoporphyrin. Tin-protoporphyrin, an inhibitor of HO, also enhances arsenite-induced DNA strand breaks and micro nucleus (MN)<sup>34-36</sup>. Later it was suggested that reactive species of oxygen are responsible for modification in DNA-bases and hence associated with arsenic-induced skin cancer<sup>37</sup>. The aberrant expression of oncogenes and tumour-suppressor genes has been found to be a result of hypo- and hyper-methylation of DNA. This in turn caused abnormality in cell proliferation leading to carcinogenesis, and few recent reports on arsenic-induced DNA methylation reinforced the carcinogenic potential of arsenic<sup>24,26,38</sup>. Further, a study regarding human lung adenocarcinoma A549 cells revealed that promoter

regions of tumour suppressor gene *p53* were methylated when exposed to arsenite<sup>39</sup>. Arsenic, to be a carcinogen, has to act in some way or the other to alter regulations of different cellular processes<sup>24</sup>. It has been found that arsenic species are responsible for disrupting the interactions between steroid receptors and their DNA response elements at non-cytotoxic cellular concentration<sup>40</sup>.

Arsenic altered multiple cellular pathways including suppression of cell cycle check point proteins, expression of growth factors, promotion of and resistance to apoptosis, alterations in DNA methylation, inhibition of DNA repair, decreased immune surveillance and increased oxidative stress, by disturbing the pro/antioxidant balance. These alterations played a prominent role in disease manifestations such as carcinogenicity diabetes, genotoxicity, cardiovascular and nervous system disorders<sup>33</sup>. Arsenite in the trivalent form is shown to increase cell proliferation via the production of keratinocyte-derived growth factor (KGF). Similar alterations in growth factor expression were also affirmed after analysing the gene expression of skin lesion samples collected from patients exposed to arsenic, via drinking water<sup>41</sup>.

### DNA, chromosomal aberrations and arsenic toxicity

It has been found that arsenite does not react directly with DNA. Rather, it is known to be pro-oxidant and thus found to cause lipid peroxidation, protein oxidation, enzyme oxidation and glutathione (GSH) depletion, DNA oxidation and DNA adducts<sup>42,43</sup>. The concept that arsenite increases oxidant levels is supported by many studies which have demonstrated the mechanism of protection against arsenite genotoxicity by GSH elevation and by antioxidants like vitamin E, catalyses, superoxide dismutase (SOD) and squalene<sup>44-49</sup>. Many studies revealed that arsenic generates reactive oxygen species like nitric oxide which produces poly adenosine diphosphate (ADP)-ribosylation, induces DNA strand-breaks and nicotinamide adenine dinucleotide (NAD) depletion. NAD depletion triggers poly ADP-ribose polymerase (PARP). PARP activation results in consumption of NAD and depletion of adenosine triphosphate (ATP) which is suggested to implicate in the pathogenesis of oxidant-induced cell death<sup>43</sup>. Sodium arsenite has been found to disrupt the structure of cisternae in mitochondria in human cancer cell line (HeLa) which might also lead to ATP depletion. It was further found that the depletion of ATP correlated with the cytotoxicity effects of arsenic<sup>50</sup>.

Another study obtained data from women and children who were exposed to arsenic-contaminated drinking water revealed genotoxic effects of micro nuclei in bi-nucleated cells and peripheral blood lymphocytes. It is considered to have been originated from a whole chromosome loss<sup>51</sup>. Arsenite is also found to alter the nuclear binding levels of transcription factors, AP-1, NF- $\kappa$ B, Sp-1 and YB-1 to

their respective *cis*-acting elements in human breast<sup>52</sup>. This indicates that arsenite influences particular signaling pathway within cells which selectively modulate the gene expression. Another study with human fibroblasts revealed that arsenite induced chromosome end-reduplication and thereafter inhibited ser/thr protein phosphatase activity and enhanced phosphorylation levels of small heat-shock proteins, hsp27 (ref. 53). If exposed to high toxic concentrations of arsenite, the A<sub>L</sub> cells which are Chinese hamster ovary (CHO)-K1 cells containing single copy of human chromosome 11 may suffer deletion<sup>44</sup>. Other than deletion and mutation, arsenite can also induce chromosome aberration, aneuploidy and MN formation<sup>54</sup>. It is found that chromosome aberrations and endo-reduplication is induced by arsenite (trivalent form) only, but not by arsenate (pentavalent form). Whereas a study in human fibroblasts and CHO cells revealed that both trivalent and pentavalent forms of arsenic caused sister chromatid exchanges (SCE) at concentrations as low as 0.01  $\mu$ M, but not in a dose-dependent manner<sup>53,55</sup>. In addition, increase in MN frequency confirms that clastogenesis or aneuploidy is induced due to exposure to toxic agents like arsenite<sup>56,57</sup>. Human fibroblasts and CHO cells when exposed to both low and high doses of arsenite induce MN; the low dose protocol results mainly in kinetochore positive (K<sup>+</sup>) MN, whereas high dose protocol results in kinetochore negative (K<sup>-</sup>) MN. K<sup>+</sup> MN are usually derived from whole chromosomes while K<sup>-</sup> MN are derived from fragments. Hence, at low dose, arsenite acts as an aneugen, whereas in high dose it acts as a clastogen<sup>58</sup>. Another study has detected MN in buccal cells, exfoliated bladder cells, lymphocytes and sputum cells of humans who were exposed to arsenic toxicity<sup>59,60</sup>. In Bengal region, frequencies of MN in peripheral blood lymphocytes were sensitive indicators of arsenic toxicity when compared with MN frequencies in buccal cells and exfoliated bladder epithelial cells<sup>61</sup>. It is also observed that population with long-term exposure to 400 ppb arsenic has increased chromosomal aberration in MN formation in ex-foliated oral mucosa cells, ex-foliated urinary bladder epithelial cells and lymphocytes, as well as in peripheral blood lymphocytes<sup>51,57,59-61</sup>. Huge inter-individual variations were found in an evaluative study of arsenite-induced aneuploidy in peripheral blood lymphocytes of human donors<sup>62</sup>. It was also found that donors sensitive to aneuploidy induced by arsenic were also found to be sensitive to arsenite-induced mitotic arrest as well as aberrations of chromosomes<sup>63</sup>.

### Socio-economic effects of arsenic toxicity

Apart from clinical symptoms, a number of social and economical problems aggravate the situation. Dissolution of marriages and isolation and avoidance of arsenicosis patients from both social and economical activities are

the most common problems reported from many of the affected areas<sup>64</sup>. Arsenic-affected individuals may not feel sick or look sick, other than some pigmentations on skin and skin discoloration, but their status in the society diminishes and they adopt a virtual identity as 'dangerous' people<sup>65</sup>. It is argued that the perception of symptoms of arsenic toxicity being contagious, separate families, creates boundaries between people. This also results in isolation of children in schools and leads to avoidance of people living in highly arsenic-contaminated regions by individuals living in other normal areas<sup>66</sup>, which directly affects their economic status too. This 'misperception' about the happenings also leads to problem associated with marriage and misunderstanding between the spouse and isolation<sup>67</sup>, which indirectly aggravates ones financial situation. Apart from these factors, there are other problems that increase the effects of arsenic on individuals living in contaminated zones. Reports from previous studies have confirmed that disorders, diseases and death caused by the impacts of arsenic toxicity were due to the lack of proper knowledge regarding the source of this heavy metal and its effects on human health<sup>68</sup>. Some researchers argue that clear perception of arsenic toxicity, proper distinction between arsenic-related disorders and other disorders, efficiency of measures taken to counter the diseases and better treatment practices might help in controlling the situation in arsenic-contaminated zones<sup>66</sup>.

### Minimizing the effects of arsenic toxicity

A multifaceted approach from different fields is being adopted worldwide in minimizing the impact of arsenic toxicity on human well being. It is found that there is a strong consensus that arsenic-associated problems can only be solved by complete removal of arsenic from the environment. Since arsenic cannot be totally removed from the environment, solution to this problem is by two means – first, with appropriate multi-directional non-technological based prevention strategies and management programmes, and second, with the use of advanced technology-based mitigation initiatives<sup>69</sup>.

Prevention strategies and management programmes like finding an alternative arsenic free water source, use of deep tube wells, well switching, rainwater harvesting, social awareness, educational programmes for children and adults, community-based educational programmes, proper information on irrigation and agriculture, strategies for reducing the cost burden, proper dietary supplements and constant monitoring of health and water quality, will control and minimize the impact of arsenic toxicity<sup>69-71</sup>. Furthermore, use of advanced technology-based mitigation initiatives like arsenic sensing using arsenic detection kits and use of modern water filtration units can effectively reduce the amount of arsenic in

drinking water and minimize the exposure. Removal of arsenic from water sources by biological and chemical procedures of oxidation, by coagulation-flocculation and by adsorption is also practised<sup>69,71</sup>. It is removed from human body using chelating agents<sup>71</sup>. Thus, the above methods are effective in controlling arsenic toxicity and improve human health.

### Discussion

Arsenic contamination of drinking water has a multifaceted influence over human life. It not only affects their health, but also affects their nutritional, social and economic status, thereby deteriorating the quality of human life. In this article we have put forward a brief collective effort focusing on the advances made in understanding the impact of arsenic toxicity from multiple aspects. There has been a collective effort in evaluating some core issues of the effects of arsenic on clinical health, nutritional status, carcinogenicity, genomics and social and economic status of human beings. Yet, there remains a huge lacunae in the fields of science and social science in solving certain issues. For instance, detailed studies relating to cellular level changes, arsenic altered cellular pathways and cell to cell communication, are few. In addition, well established, explanatory longitudinal animal models are not available. These aspects of the study are equally important in resolving the problem of arsenic toxicity. Though there has been more work on arsenic sensing, remediation and bioremediation, easy and effective measures of sensing and remediation are still not available. Regarding social awareness and economic prospects the mitigation programmes conducted for prevention and cure succeeded to a certain extent only. Hence, there is a need to employ multidisciplinary methodologies, for developing easy and effective solution for prevention and remediation of arsenic poisoning. Therefore, more collective, advanced and target-specific studies are essential in science and social sciences in tackling arsenic toxicity. This will further help researchers and administrators in developing appropriate and efficient prevention strategies and management programmes as well as technology-based mitigation initiatives for overall improvement of human welfare.

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