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Human health risk assessment for arsenic: a critical review

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Abstract

Millions of people are exposed to arsenic resulting in a range of health implications. This paper provides an up-to-date review of the different sources of arsenic (water, soil and food), indicators of human exposure (biomarker assessment of hair, nail, urine and blood), epidemiological and toxicological studies on carcinogenic and non-carcinogenic health outcomes, and risk assessment approaches. The review demonstrates a need for more work evaluating the risks of different arsenic species such as; arsenate, arsenite monomethylarsonic acid, monomethylarsonous acid, dimethylarsinic acid and dimethylarsinous acid as well as a need to better integrate the different exposure sources in risk assessments.

Keywords: total arsenic, arsenic species, exposure pathways, biomarker assessment, arsenic risk assessment, integrated risk assessment.

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1. Introduction

Arsenic is a toxic and carcinogenic chemical (International Agency for Research on Cancer, 2012; Pellizzari and Clayton, 2006; Hughes, 2006) that is a naturally occurring element and exists in the earth's crust at an average concentration of 5 mg kg^{-1} (Garelick et al., 2008). It is not, however, homogenously distributed in the crust and is more commonly associated with certain geological strata than others (Aronson, 1994; National Academy of Sciences, 1977). Whilst there are anthropogenic sources of arsenic, geological weathering is the primary cause of arsenic release into groundwater. This natural release of arsenic into ground or surface water poses a global public health risk for approximately 140 million people in at least 70 countries worldwide (Ravenscroft et al.,2009). Arsenic contaminated water also provides a pathway for arsenic to enter the food chain via irrigation as well as during food preparation and cooking (Bhattacharya et al.,2012; Fu et al.,2011; Mondal et al.,2010; Zavala and Duxbury, 2008; Zhao et al.,2010; Rahman and Hasegawa, 2011; Halder et al.,2014). Thus, ingestion of contaminated water and food is a significant exposure pathway for arsenic. Long-term arsenic exposure has been associated with the development of skin lesions, various types of cancer, developmental effects, cardiovascular disease, neurotoxicity and diabetes (Steinmaus et al., 2013; Martinez et al., 2011).

Arsenic in water, food and soil exists in many different chemical forms and oxidation states (International Agency for Research on Cancer, 2012) the most common inorganic and organic arsenic compounds found in water, food, soil and biomarkers referred to in this article are listed in Table 1.

Most of the trivalent and pentavalent arsenic species are absorbed in the body and transported via the blood stream to the body tissues (Capitani, 2011). Metabolism is mainly dependent on reduction-oxidation reactions causing inter-conversion of trivalent and pentavalent arsenic species and methylation of As^{+3} to yield methylated arsenic species. Generally, inorganic arsenic forms are reported by Pal (2015) to be more toxic than organo-arsenicals. As^{+3} is considered comparatively more toxic than As^{+5}, possibly due to interference of As^{+3} on enzymatic processes by bonding to sulfhydryl (–SH) or hydroxyl (–OH) functional groups (Kligerman et al., 2003; Mass et al.,2001; Hughes, 2002). Past studies have shown that trivalent methylated arsenicals are acutely more toxic and genotoxic than that of inorganic pentavalent arsenicals but the relative toxicity of individual arsenic species, such as MMA^{+3} or DMA^{+3} is still unknown (Tchounwou et al., 2003; Styblo et al., 2000; Viraraghaven et al., 1999). It has been suggested that the methylation of inorganic arsenic reduces toxicity but data are conflicting (Petrick et al., 2000; Petrick et al., 2001). Therefore, there are still uncertainties regarding the potential risks and relative toxicity of individual arsenic species in the human body. This critical review evaluates the current state of knowledge on the distribution and potential risks of different arsenic species from multiple exposure sources, through intake and uptake by the human body. It provides an overview of the associated health risks from environmental exposures, which can be used to eventually improve human health risk assessments.

2. Methodology: Literature search and selection strategy

A number of scientific publications databases: (Medline;PubMed), Environmental Sciences & Pollution Management (ESPM), the National Center for Biotechnology Information (NCBI) and University of Leeds Library Pro-quest were interrogated to identify peer-reviewed papers describing arsenic sources, exposure and risk, published between January 1961 and June 2015. An additional search was conducted on secondary literature such as books, reports and conference proceedings published around the world. Studies were selected based on the following selection criteria:

a. Concentrations reported for arsenic in surface and ground water, food items, soil, hair, nail, blood or urine.
b. Peer reviewed studies with methodological approach.
c. Potential health risks identified and associated to reported levels.
d. Risk estimates documented with variability and uncertainty.
e. Papers in English.

Of about 2000 items reviewed, 305 peer reviewed and published articles meeting the above criteria have been included in this review. In addition to the review, the relationships between total arsenic levels in water, soil, food and biomarkers identified in different studies reported across 22 countries (Tables 2-6) were evaluated using Pearson partial correlation analysis (SPSS 17.0, IBM, New York, NY, USA). Arsenic risk assessment techniques used for carcinogenic or non-carcinogenic risks estimates were also reviewed (Table 8) and critiqued to provide an overview of the current state of knowledge, knowledge gaps and further research needs.

3. Arsenic origin and mobilization

Arsenic is categorized into three main exposure sources based on its origin and mobilization i.e. geological, anthropogenic and biological (Figure 1). Arsenic occurs in combination with arsenopyrite or sulphide in more than 150 minerals (Budavari et al., 2001; Onishi and Sandell, 1955; Carapella, 1992). In addition to naturally occurring arsenic deposits and sediments, other geological sources such as geothermal springs and volcanic ash are common (Bhattacharya et al., 2006; Bundschuh et al., 2004; Nordstrom, 2002). Anthropogenic sources include metal mining and smelting which result in the release of arsenic sulphide (Straskraba and Moran, 1990). Other man made sources are the manufacture and use of pesticides (Tsuda et al., 1995; Mazumder et al.,1992; Gerald Matisoff et al.,1983; Kenzaburo Tsuchiya,1977), coal/wood burning, waste incineration, use in pharmaceutical and agricultural products/feeds, and electronics (United States Environmental protection Agency [USEPA], 1998; Sullivan, 1969). Many of these latter anthropogenic sources are now strictly controlled through regulation e.g. restrictions on use of copper chromated arsenate and other wood preservatives (European Economic Community, 2003; Edelstein, 1985).

Arsenic mobilization mechanisms from these different natural and anthropogenic sources include; arsenic adsorption by soil and its subsequent leaching into surface or ground water (World Health Organization, 2001; U.S Environmental Protection Agency, 1998), oxidation of pyrite or arsenopyrite (Mallick and Rajagopal, 1996; Mondal et al., 1996), microbial and/or chemical reductive dissolution of arsenic-bearing iron oxyhydroxides in the aquifer sediments (Berg et al.,2008; Charlet and Polya, 2006; Zheng et al.,2004; Dowling et al.,2002), desorption and microbial mobilization (Garelick et al., 2008), uncontrolled ground water abstraction and application of phosphate fertilizer (Acharyya et al., 1999).

4. Arsenic in water

Arsenic mobilised from the aforementioned sources has been reported at concentrations up to 24000 $\mu g\ l^{-1}$ in surface and groundwater sources (Table 2). World Health Organization (WHO) guidelines are 10 $\mu g\ l^{-1}$ having been reduced from 50 $\mu g\ l^{-1}$ in 1993, hence many regions around the world exceed the levels established for safe drinking water supplies.

High arsenic levels have been reported in Argentina, Australia, New Zealand, Mexico, India and Thailand (Figure 2). However, the highest levels of arsenic in water resources reported were for Bangladesh and India, where nine districts in West Bengal, India, (Chowdhury et al., 2000) and 59 districts in Bangladesh had arsenic levels in excess of the WHO guideline value (10 µg/l) (Chakraborti et al., 2010). About 20,000 deaths per year in Bangladesh have been attributed to exposure to arsenic, whereas an estimated 50 million people are considered at risk of health consequences (Pearce, 2001; Chaudhuri, 2004).

Most studies assessing arsenic concentrations in water (Table 2) have evaluated total arsenic levels with relatively few considering the different arsenic species. It is assumed that methylated-arsenic compounds are low in ground water unless special circumstances, such as pollution by arsenical herbicides or high biological activity, exist (Welch et al., 2000). Irgolic (1994) concluded that methylated species (MMA and DMA) would rarely be present in water supplies and thus their determination in water is unnecessary for regulatory purposes. There are a small number of studies that have evaluated arsenic species in water, particularly regarding the mobilisation from underlying geology to groundwater. For instance, Bhattacharya and co-workers (2006) reported concentrations of As^{+3} and As^{+5} in groundwater from geological sources, whilst Smedley and co-workers (2002) analysed aquifer pore waters for As^{+3} and As^{+5}. Earlier work by Smedley (1996) looked at As^{+3} and As^{+5} in groundwater in aquifers in Ghana, whereas, Rosas and co-workers (1999) examined the relationship between arsenic species (total arsenic, As^{+3}, As^{+5}) in soil and water. Chen and colleagues (1994) attempted to go one stage further by measuring As^{+3}, As^{+5}, MMA and DMA in water and linking it to human health outcomes with limited success. Understanding the metabolic fate and relative toxic effects of various chemical forms of arsenic may remain incomplete without drinking water source characterisation and exposure assessment of arsenic species.

5. Arsenic uptake by plants from soil and irrigation practices

Arsenic distribution in soils is reported within a widely variable range up to 43,500 mg kg^{-1} (Table 3). Arsenic above the European Union (EU) recommended maximum acceptable limit for agricultural soil (20 mg/kg; Rahman et al. 2007) has been associated with mining activities (Zhu et al., 2008), contaminated groundwater used for irrigation (Meharg and Rahman, 2003) and use of arsenical pesticides (Williams et al., 2007) as summarised in Figure 1.

Arsenic contamination of soil by irrigation water and subsequent uptake by crops poses a potentially significant public health risk. There are relatively few studies that have identified a positive correlation between arsenic concentrations in soil and irrigation water (Meharg and Rahman, 2003; Duxbury and Zavala, 2005; Das et al., 2004), and between arsenic uptake by rice and arsenic in soil water (Loeppert et al., 2005; Meharg and Rahman, 2003). Moyano and co-workers (2009) have shown that potatoes irrigated with arsenic-rich water have 35 times more arsenic compared with other crops. They have also confirmed the uptake of arsenic from contaminated irrigation water by beet, carrot and wheat crops. As for water, most monitoring studies have focused on total arsenic with few looking at the individual arsenic species present. Studies that have measured arsenic species in soils have reported higher levels of the less toxic As^{+5} compared to As^{+3} (Acosta et al., 2015; Matera et al., 2003). Similarly, Smith and co-workers (2008) have demonstrated that root, shoot and leaf tissues contained mainly inorganic As^{+3} and As^{+5} species, while rice grains contained predominantly DMA (85 to 94%) and As^{+3}. Generally, there are few studies that evaluate the quantification of the influence of arsenic contaminated irrigation water, accumulation of arsenic in top soils, land degradation pattern, relationship between water-soil-plant system and risks of arsenic contaminated irrigation water to crop production, specifically from the perspective of arsenic species.

6. Arsenic in the food chain

Evidence suggests that arsenic uptake by plants varies (Sharma, 2014), influenced by the water requirements of different crop types, levels of soluble arsenic species in soil, soil properties, redox and pH conditions, microbial activity, and plant species (Norra et al., 2005; Lehoczky et al., 2002). Arsenic can accumulate in the food chain if herbivorous animals are fed diets rich in arsenic-contaminated feedstock or drink from arsenic-contaminated water supplies. For humans, the main food sources have been suggested to be fish, crops (rice, cereals), vegetables, fruit, poultry and animal products (meat and milk) (Table 4).

The WHO has established a guideline permissible limit value of 0.1 mg kg^{-1} total arsenic in food which is frequently exceeded by many of the food groups that have been analysed (Table 4). Total arsenic detected in various food categories fall in the range of not detected to 1.9 mg kg^{-1} for cereals, 13 mg kg^{-1} for vegetables, 22.4 mg kg^{-1} for fruits and fruit juices, 42.6 mg kg^{-1} for animal products and 98 mg kg^{-1} for fish and sea food. Rice, however, demonstrates the highest levels of arsenic in food with the maximum level reported at 267.7 mg kg^{-1} (Nookabkaew et al., 2013). Rice is an efficient scavenger of arsenic and takes up ten times as much as other cereal crops probably due to growth in flooded fields (Sohn, 2014; Wang et al., 2013; Khan et al., 2010; Mehrag et al., 2009; Zvala et al., 2008). As such, arsenic exposure is likely to be greater for people who eat large amounts of rice every day and for infants, whose first solid meals are mainly rice-based baby food.

The relative toxicity of arsenic in foods depends on its chemical form and bioaccessibility (Juskelis et al., 2013). In contrast to water, arsenic species have been well studied in food items with both organic and inorganic species identified in a range of food items, from milk to fish and rice (Carey, 2010; Mehrag et al. 2009; Zvala et al., 2008; Norton et al., 2013; Schoof et al., 1999a; Jackson et al., 2012; Mehrag et al., 2008 and Li et al., 2003; Table 4). Studies have generally reported higher levels of toxic inorganic forms such as arsenite (As^{+3}) rather than the more mobile inorganic arsenate (As^{+5}) and organic species.

7. Human exposure pathways and bioavailability

Humans can be exposed to arsenic through a variety of exposure routes. Airborne arsenic released from industrial emissions result in occupational exposure through inhalation (U.S Public Health Service, 1989). For instance, peripheral neuropathy among smelter workers has been linked to exposures above the WHO air quality limit of 1 μg m^{-3} arsenic (Lagerkvist & Zetterlund, 1994, cited in WHO, 2000). Releases of 20 to 760 μg m^{-3} airborne arsenic associated with the burning of arsenic-rich coal in China have resulted in 3,000 patients with skin lesions on the hands and feet, pigmentation on the trunk, skin ulceration, and skin cancers (Liu et al., 2002).

Dermal contact, which might result from washing in contaminated water and/or handling products containing arsenic (e.g. wood preservatives), has also been suggested as a pathway of exposure but few studies have evaluated this in detail (Roels et al.,1980; Riedel et al., 1990; Malcolm Pirnie, 2001).

The ingestion of arsenic through drinking water, using contaminated water in food preparation, irrigation of food crops, food or beverage industrial processes and eating contaminated food are considered to be the primary exposure pathways (Tsuda et al., 1992). Water has long been considered the main exposure route for arsenic, with levels of As^{+3} or As^{+5} influenced by pH, redox potential or salinity of the water body (Smedley and Kinniburgh, 2002). Different opinions on the overall exposure contribution of arsenic in food exist. For example, a US study on arsenic toxicity concluded that inorganic arsenic exposure through food does not pose higher risks of carcinogenicity (Boyce et al., 2008). Meharg and colleagues (2009), however, assessed the health risks arising from consumption of arsenic-contaminated white rice; using country-specific rice consumption data for five countries, they reported an excess of cancer linked to total inorganic arsenic from 0.7 per 10,000 population in Italy to 22 per 10,000 in Bangladesh – almost a 30-fold increase in cancer risk. This is further supported by other studies, which suggest an association between arsenic in food and increased cancer risk (Meacher et al., 2002; Schoof et al., 1999b).

Linking exposure with potential health impacts depends on arsenic intake and uptake, which may be affected by type (inorganic or organic) and concentration of trivalent (As^{+3}, MMA^{+3} and DMA^{+3}) or pentavalent arsenic forms (As^{+5}, MMA^{+5} and DMA^{+5}) found in water or food, and how these different arsenic species are processed by the human body. In the human biological environment, As^{+3} and As^{+5} are considered comparatively more toxic than methylated organic (MMA^{+5} and DMA^{+5}) forms (Abedin et al., 2002; Meharg and Hartley-Whitaker, 2002). Quantification and risk assessment approaches may prove useful to understand the differences between individual arsenic species and person-to-person variation. People within a community or household sharing the same drinking water source may not be equally affected and show variable clinical manifestations (Huq and Naidu, 2005). This might be due to confounding factors such as nutritional deficiencies, low selenium intake, smoking and genetic factors, all of which have been observed to enhance the development of arsenicosis (Deb et al., 2013; Chen et al. 2001; Gamble et al., 2007; Spallholtz et al., 2004; Miyazaki et al., 2005; Lamm et al., 2006; Lamm and Kruse, 2005). The influence of these variables on the toxicity levels of various chemical forms of arsenic is yet to be explored in any detail.

8. Metabolic pathways and biomarkers of exposure

Arsenic metabolism within the human body is dependent on the inter-conversion of As^{+3} and As^{+5}. About 40-100% of total arsenic is absorbed as As^{+5} from the human gastrointestinal tract (Saha et al., 1999). As^{+3} can bind to bioactive protein molecules (National Research Council, 1999) but is less likely to be absorbed than soluble inorganic forms in water (European Food Safety Agency, 2009). Whilst all the processes involved in the metabolism of inorganic arsenic have not been fully elucidated, an overall metabolic pathway for arsenic has been proposed (Equation 1: Thomas et al., 2001; McKinney, 1992; Thompson, 1993).

$$As^{+3} \xleftrightarrow{Oxidation/reduction} As^{+5} \xrightarrow{methylation} MMA^{+5} \xrightarrow{reduction} MMA^{+3} \xrightarrow{methylation} DMA^{+5} \xrightarrow{possible\ reduction} DMA^{+3}$$

(Equation-1: simplified model of arsenic metabolism***)***

Certainly, metabolism of arsenic has a role in this effect. As a proxy to understanding this role, human biomarkers have been used as indicators. Biomarkers are quantifiable changes in biochemical, physiological or behavioural states within cells, tissues or whole individuals because of external stressors (Timbrell, 2002). Biomarkers are classified as markers of exposure, effect, or susceptibility (National

Academy of Science/National Research Council, 1989) and provide useful information on fate and metabolism of arsenic within human body. To evaluate the metabolic process and fate of arsenic within human body, samples of hair, nail, blood and urine have been examined for traces of arsenic (Tables 5-6). It has been suggested that arsenic accumulates in hair and fingernails due to preferential binding to proteins such as keratin (National Research Council, 1999). Biomarker analysis of hair and nails can therefore be used to confirm arsenic intake and associated accumulation of arsenic in the human body (Table 5). The highest level reported in hair is 1,500 mg kg^{-1} (Concha et al.,2006) whilst for nails it is 5406 mg kg^{-1} (Button et al., 2009) and urine 1000-6200 $\mu g\ l^{-1}$ (Lindberg et al., 2006): blood reveals the lowest levels of 1-14.3 $\mu g\ l^{-1}$.

There have been fewer arsenic speciation analyses carried out for hair and nails compared to urine possibly due to the more complex sample preparation required to remove contaminants adsorbed to the surface of the collected materials (Hindmarsh,1998; Mandal et al., 2003; Button et al., 2008). Urinary arsenic metabolites have been used to correlate arsenic exposure with arsenic intake rates, arsenic methylation mechanism, human bioaccumulation and excretion capacity and to determine carcinogenic or non-carcinogenic health impacts. Urinary metabolites studies (listed in Table 6) have indicated that most of the ingested arsenic is methylated and excreted as DMA (79–85%), with smaller amounts excreted as inorganic arsenic (8–16%) or MMA (5–6%) (Christian et al., 2006). Despite many studies on urinary arsenic metabolites, it is still far from clear what the processes are that control the uptake and excretion of arsenic species from different dietary sources and how these different exposures lead to health impacts. (Rivera-Núñez et al.,2012).

9. Arsenic Health Impacts

Chronic health problems result from prolonged exposure of humans to arsenic (Hong et al., 2014). Responses to arsenic exposure vary depending on genetics as much as exposure levels but it might be supposed that certain vulnerable groups, e.g. pregnant women, infants, children, the elderly, and immune-compromised groups are at greater risk of health impacts (European Food Safety Agency, 2009; Georgopoulos et al., 2008; Kordas et al., 2007). A number of epidemiological studies, from cohort to case-control, have evaluated the role of arsenic exposure for a number of health outcomes (Table 7). The Health Effects of Arsenic Longitudinal Study (HEALS), the largest cohort study in the world, evaluated individual-level total arsenic exposure for 12,000 people in Araihazar, Bangladesh (Ahsan et al., 2006). HEALS indicated the prevalence of risk at levels below the current WHO and USEPA permissible limit for arsenic in drinking water, shown by 24% of the participants drinking water with arsenic less than 10 µg l^{-1}. Biomarker samples of urine and blood were taken providing recent exposure data but chronic exposure proxies available via hair and nail samples were not evaluated. Whilst the study did model food intake, food samples were not collected and characterized as dietary sources other than drinking water were considered negligible.

The results of epidemiological studies (Table 7) are further supplemented by toxicological studies which used animal models to identify a link between gastrointestinal problems and lung cancer due to arsenic exposure (Afolabi et al., 2015; Santra et al.1999). As with all animal studies, caution is required when translating to humans particularly from rodent models (Tokar et al., 2010, International Agency for Research on Cancer, 2012).

In general, the health effects reported by most studies (Table 7) for various exposure levels were generally inferred on the basis of statistical correlation between total arsenic in drinking water, excreted urinary arsenic metabolites and existing physical symptoms (Chen et al., 2013; Agency for Toxic Substances and Disease Registry, 2000; Tsai et al.,1999). However, such analyses do not necessarily provide conclusive evidence of the role of individual arsenic species, particularly exposure over the long-term, in disease development. For instance, few studies have evaluated the toxicity of DMA (U.S Environmental Protection Agency, 1993) and MMA relative to As^{+3} (Petrick et al., 2000 & 2001) although a recent investigation by Huang and co-workers (2014) have concluded that MMA^{+3} potentially aggravates arsenic-associated cardiovascular disorders.

10. Arsenic permissible limits for water and food

The WHO international standards for drinking water established a maximum acceptable level of 50 μg l^{-1} in 1963 for total arsenic in drinking water (World Health Organization, 2008). This limit was reduced to 10 μg l^{-1} in 1993, based on concern regarding its carcinogenicity (World Health Organization, 2008; Smith and Smith, 2004). This lower guideline value has been adopted by many statutory bodies in industrialized nations, including the United States (U.S Environmental Protection Agency), Canada (Health Canada), and the European Union. However, many developing countries have generally kept the higher level of 50 μg l^{-1}. As such, millions of people in several developing countries (Bangladesh, China, India, Nepal, Thailand, Vietnam, Pakistan; Cambodia, Myanmar, Iran, Ghana, Argentina, Croatia) are still using drinking water with arsenic above 10 μg l^{-1} despite evidence of a carcinogenic effect (World Bank, 2005). The level of arsenic in drinking water below which no health effects can be observed, or the highest sensitive toxicity end-point, below which there is no risk of carcinogenicity, is yet to be confirmed. Following this, the limits of 10 and 50 μg l^{-1} apply to total arsenic only and do not consider the varying toxicity of different arsenic species – from highly toxic As^{+5} to less toxic organic species.

The WHO guideline limits only apply to water sources: exposure to arsenic–contaminated foodstuffs has only been considered by two national governments. Australia has established a limit of 1 mg $kg^{-1}$and China set a limit range of 0.05-1.5 mg kg^{-1} for vegetables, fruits, eggs, milk, rice, flour, beans/pulses fish and sea foods (Das et al., 2004; Islam et al., 2004; Jahiruddin et al., 2004; Japan International Cooperation Agency/Asia Arsenic Network, 2004; Abedin et al., 2002). Furthermore, the Current Codex Alimentarius, or 'food code', sets a maximum limit of 0.2 mg kg^{-1} of arsenic in white rice and 0.4 mg kg^{-1} for brown rice (Codex Committee on Contaminants in Foods, 2014). The development of limits imposed on foodstuffs demonstrates growing concern regarding arsenic availability in food and has important implications for food exports. As for water, the limits are based on total arsenic rather than individual arsenic species.

11. Risk assessment of arsenic species

Risk assessment tools identify likely health outcomes resulting from exposure to hazards and therefore are crucial first steps in determining the need for the development of risk management strategies and/or the need for regulation. A range of different risk assessment techniques, approaches or models have been used for arsenic (Table 8: Chen et al., 2010 & 2014; Mondal et al., 2008 & 2010; Ling et al., 2005; Liao et al., 2008).

Input variables for these methods have generally included estimates or measured concentrations of total arsenic in water; fewer studies have included a food source variable and these tend to have a restricted sample size or do not integrate the different exposure sources (Mondal et al., 2010; Saipan and Ruangwises, 2009). Similarly, few studies considered the risks posed by individual arsenic species specifically, trivalent (As^{+3}, MMA^{+3} and DMA^{+3}) or pentavalent species (As^{+5}, MMA^{+5} and DMA^{+5}) from different exposure sources: the few studies that do this tend to use predicted arsenic species calculated from total arsenic levels and focus on an ecological, rather than a human health risk assessment (Markley and Herbert, 2009; Du et al., 2015). For human health risk assessment, arsenic speciation and bioavailability are critical as arsenic species vary differ in their toxicity and bioavailability and thus influence the uptake dose resulting from dietary intake (Laparra et al., 2005). It is thus important to obtain information about the arsenic species absorbed from food, water, and soil, metabolized in the liver and kidneys, accumulated in nails and hair, and ultimately eliminated by urine and faeces.

12. Synthesis

There have been many studies evaluating the distribution of total arsenic in water, food, soil and human biomarkers but relatively few have included arsenic species characterisation (Tables 2-6). Understanding the contribution of individual arsenic sources to overall arsenic burden is important in developing the most appropriate risk mitigation strategies. Understanding the burden of each arsenic species and the interaction of species from source though intake and uptake to accumulation/metabolism and toxic effect is also a pressing need. Current literature provides good information on pathways from some sources, in particular drinking water, to health outcomes but the underlying biological mechanisms affecting the uptake and metabolism of different arsenic species from a range of sources are still not well understood.

As previously mentioned, linking environmental concentrations of arsenic to the levels identified in biomarker analyses have been carried out by relatively few studies. Comparing studies of similar geographical origin reported in Tables 2-6, Pearson's correlation analyses were undertaken as part of this review to examine relationships between total arsenic levels in water, soil, food and humans (as biomarkers) to help understanding of pathways of exposure and uptake. Positive and significant correlations were found between arsenic in soil and water ($r=0.830, p=0.000, n=20$), arsenic in water and hair ($r=0.563, p=0.029, n=15$), water and urine ($r=0.687, p=0.005, n=15$), hair and nail ($r=0.829, p=0.011, n=8$), and nail and urine ($r=0.925, p=0.024, n=5$). The linear correlations suggest that elevated levels of arsenic in the biomarkers are most likely a consequence of the intake of arsenic-contaminated water. The close correlation of the three biomarkers also demonstrates that they are inter-related.

Many of the models used to predict carcinogenic or non-carcinogenic health outcomes from arsenic exposure require data specific to an exposure scenario that might not always be available to the assessors. Hence, the use of generic exposure data, such as that available through the USEPA Exposure Factors Handbook (U.S Environmental Protection Agency, 2011) and the EFSA Comprehensive European Food Consumption Database (European Food Safety Authority, 2011), are often used and whilst a good surrogate where no data exist, this does lead to assumptions about consumption patterns and concentrations (e.g. total arsenic but not individual arsenic species).

Providing an integrated approach to arsenic risk assessment is likely to have been prevented by a number of factors including lack of speciation facilities, high cost of arsenic speciation, uncertainty levels of speciation modelling, and physiological differences of humans and animals for toxicological assessment. Nevertheless, such an approach would consider all possible exposure sources, ingestion pathways, response elements, and health outcomes, and include the contribution made by individual arsenic species to each step.

13. Conclusions and research needs:

Arsenic in water, food, soil and human biomarkers exists at various concentrations and in different chemical forms (As^{+3}, As^{+5}, MMA^{+3}, DMA^{+3}, MMA^{+5} and DMA^{+5}). Arsenic released from natural geological, anthropogenic or multiple sources enters groundwater and soil with levels reported up to 24000 μg l^{-1} and 43,500 mg kg^{-1} respectively for water and soil. Uptake by plants from soil or water has led to arsenic residues identified in many vegetable and cereal crops as well as fish and seafood, where it accumulates in the food chain. As such, different dietary sources including drinking water contribute to arsenic intake. Biomarker assessment in humans further demonstrates bioaccumulation, metabolism and excretion. Most studies evaluating human exposure to arsenic have concentrated on total arsenic; relatively few have looked at the role of individual arsenic species and this is a pressing research need. Furthermore, integrated approaches to exposure and thereafter risk assessment that consider all sources of arsenic exposure are not commonly reported, despite arsenic sources and exposure being relatively well studied. Nevertheless, the risks of arsenic exposure, both carcinogenic and non-carcinogenic, are well-reported and demonstrate the importance of developing risk assessment approaches that can fully elucidate the different sources of exposure and hence suggest appropriate mitigation and management steps to reduce exposure.

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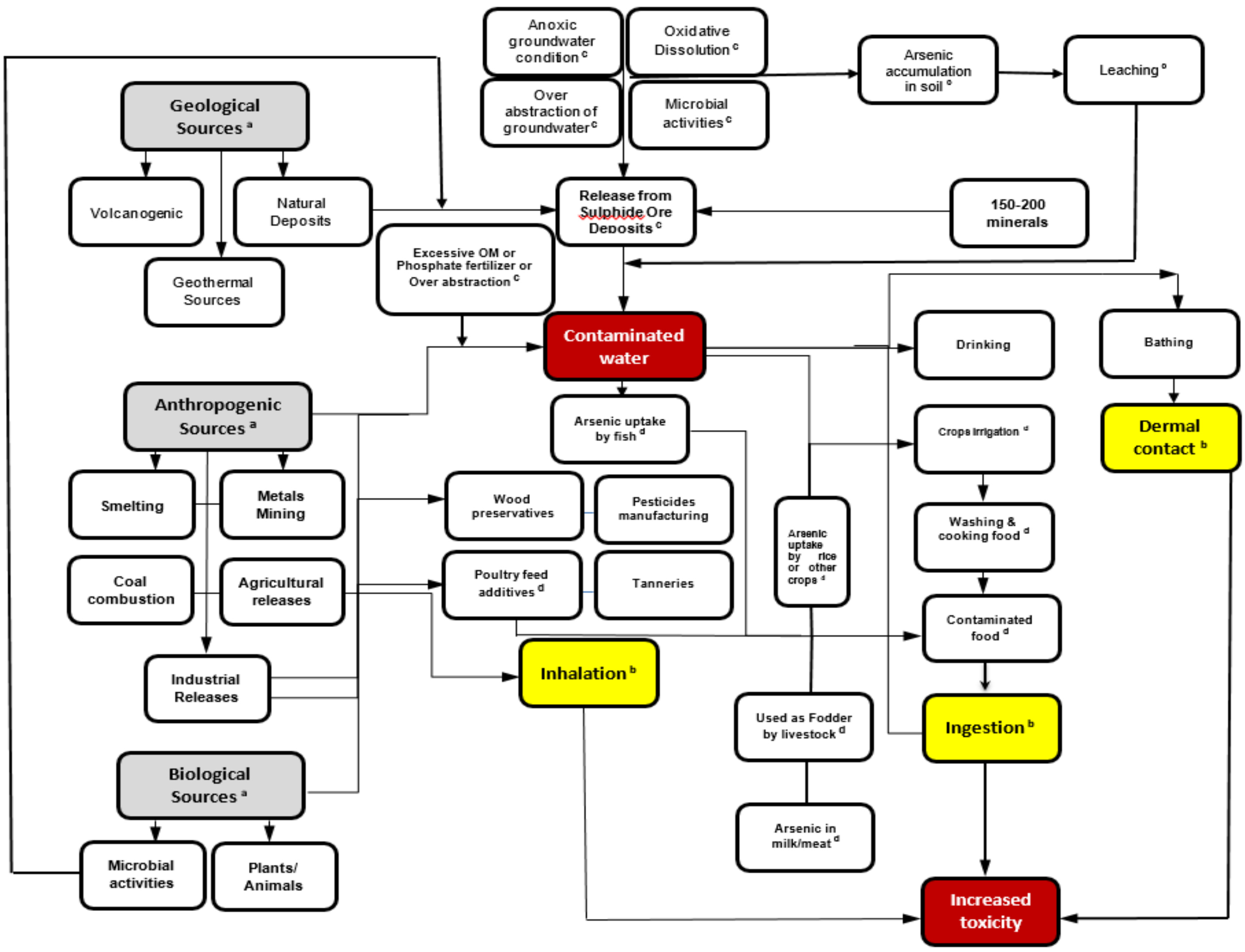

Figure 1: a) ***Arsenic Sources*** - showing the release of arsenic from geological, anthropogenic and biological sources into ground water; **b)** ***Human exposure pathways*** through ingestion, inhalation and dermal contact; **c)** ***Mechanisms of arsenic mobilization*** into ground water hypothesized as arsenic adsorption by soil and its subsequent leaching into surface or ground water, arsenic release due to oxidation of pyrite or arsenopyrite, microbial and/or chemical reductive dissolution of iron oxyhydroxides, desorption and microbial mobilization, uncontrolled ground water abstraction and phosphate fertilizer; **d)** ***Arsenic enters the food chain*** from natural or anthropogenic sources and uptake by plants and crops from ground water used for irrigation.

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Table 1: Inorganic and organic arsenic species

Arsenic type	Species	Abbreviation
Inorganic arsenic	Arsenate (arsenic acid)	As^{+5}
	Arsenite (arsenous acid)	As^{+3}
Organic Arsenic	Monomethylarsonic acid or methylarsonic acid	MMA^{+5}
	Monomethylarsonous acid or methylarsonous acid	MMA^{+3}
	Dimethylarsinic acid	DMA^{+5}
	Dimethylarsinous acid	DMA^{+3}
	Arsenobetaine	AsB
	Arsenocholine	AsC
	Arsenosugars	-

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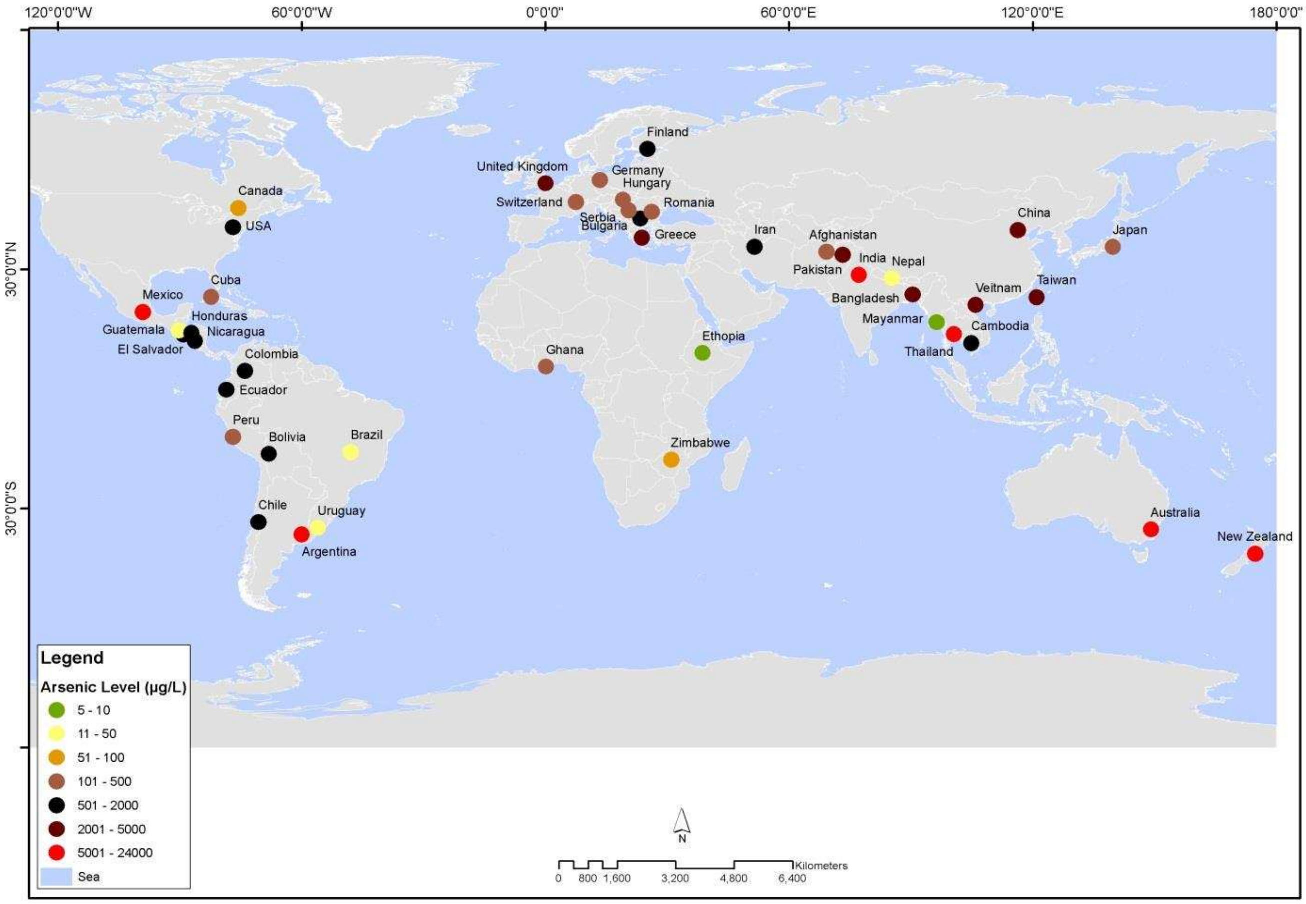

Figure 2: Global distribution of arsenic in water indicated by GIS (Geographical Information System) characterisation of levels of arsenic in water sources of 43 countries. Lowest range up to WHO guideline of drinking water ≥10 *µ*g l^{-1} indicated by green circle and highest level by red circle. See Table 2 for all references.

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Table 2: Arsenic levels reported in ground or surface water by mobilization source

Source	Type	Country	Average As concentration (μg l^{-1})	Arsenic testing performed as	Population at risk or affected (persons)	Reference
Natural Geological	Loess deposits, thermal springs, holocene volcanic ash layer	Argentina	Total arsenic: <1-14,969	Total arsenic	2,750,000	Mukherjee, et al. (2006) Bundschuh et al. (2003) Claesson and Fagerberg (2003) Sifuentes and Nordberg (2003) Bates et al. (2003) Nordstrom (2002) Nicolli et al. (1989)
			Total arsenic:7-14969 As^{+3} :1.2-1813 As^{+5} :5.7-13156	Speciation based analysis		Bhattacharya et al. (2006)
			As^{+3} : 1.2–8991	Speciation based analysis	9000	Smedley et al. (2002)
	Pyritic sediments, increased groundwater abstraction	Australia	>10-7000	Total arsenic		Appleyard et al. (2006)
	Alluvial sediments	Bolivia	>10-964	Total arsenic		Johnsson et al. (2010) Bergh et al. (2010)
	Older alluvial, Holocene, Pleistocene and Fluvio sediments, Microbial mediated degradation of organic matter and reductive dissolution of Fe-oxyhydroxide	Bangladesh	>50-4700	Total arsenic	35-79 million	Van Geen et al. (2014) Halim et al. (2009) Tareq et al. (2003) Bristish Geological Survey and the Department of Public Health Engineering. (2001) Chowdhury et al. (2000) Nickson et al. (2000) Smith et al., (2000) Chowdhury et al. (1999) Dhar et al. (1997) Khan and Ahmad (1997)
	inter-dune lake sediments	Brazil	>50	Total arsenic		Mirlean et al. (2014)
	Volcanic rocks Sulfide ore deposits Weathering products at the Andean volcanic chain Geothermal manifestations	Chile	750-800	Total arsenic	130,000-400,000	Bundschuh et al. (2012b) Bundschuh et al. (2009) Landrum et al. (2009) Bundschuh et al. (2008) Romero et al. (2003) Smith et al. (1998)
	Geological Arsenic ore reserves Spatial distribution of Fe oxides Natural; alluvial and lake sediments; high alkalinity	China	>50-2400	Total arsenic	3.0 million	Jing and Laurent (2013) Guangqian (2006) Sun (2004) Jin et al. (2003) Smedley et al. (2003) Jin et al. (2003) Nordstrom (2002) Guo X et al. (2001)
	Holocene sediments at depths >16 m Mekong and Bassac river channels.	Cambodia	0.21–1700	Total arsenic	0.5–1 million	Gault (2008) Berg et al. (2006) Polya et al. (2005)
	Proterozoic volcanic sedimentary rocks	Finland	17-980	Total arsenic	9000	Kurttio et al. (1999)
	Numerous volcanoes, hot springs, fumaroles, and geothermal wells	El Salvador	10-770	Total arsenic		Lopez et al. (2012) Lopez et al. (2009)
	geological	Ethiopia	<1-70	Total arsenic		Merola et al.(2014)
	Geothermal deltaic sediments hydrothermal activities Deeper anoxic waters	Greece	1- 3760	Total arsenic		Casentini et al.(2011) Kouras and Voutsa (2007) Ioannis and Katsoyiannis (2006)
	specific lithofacies sediments	Germany	<10-150	Total arsenic		Heinrichs and Udluft (1999)
	volcanic rocks	Guatemala	1-15	Total arsenic		Bundschuh et al. (2012)

	Geothermal springs	Honduras	70-1260	Total arsenic		Fraser et al. (1986)
	alluvial sediments and arsenic rich organic material	Hungary	4-310	Total arsenic	33,006	Lindberg et al. (2005) Varsanyi et al. (2005) Varsanyi et al. (1991) Varsanyi et al. (1989)
	Geological	Nepal	>10-50	Total arsenic	0.5 million	Yadav et al. (2011) Gurung et al. (2010) Shrestha et al. (2007) Tandukar (2000)
	Geothermal outflow from Volcán Telica volcanic rocks	Nicaragua	>10	Total arsenic	1000	Longley and Esperanzas (2012) McClintock et al. (2012) Aldana (2010)
	Geological	Mayanmar	>10	Total arsenic	03 (cases of Arsenicosis)	Tun (2003)
	Geological and Quaternary volcanic activity	Iran	11-1480	Total arsenic		Keshavarz et al. (2011) Mosaferi et al. (2003)
	Geothermal sources	New Zealand	9.8-8500	Total arsenic		Wilson and Brown (2009) Robinson et al. (1995) Ritchie (1961)
	Geological	Pakistan	>10-2400	Total arsenic	2.0 millions	Tahir and Hifza (2014) Fatmi and Ali (2014) Malana and Khosa (2011) Toor and Tahir (2008) Farooqi et al. (2006) Nickson et al. (2005) Kahlown et al. (2005) Ahmad et al. (2004)
	Geological	Romania	46.36 -179.98	Total arsenic	41,000	Gurzau and Pop (2012) Mukherjee et al. (2006)
	Geological	Serbia	5-420	Total arsenic		Stanisavljev et al. (2013) Dragana et al.(2010)
	Arsenic containing ore and sediments	Switzerland	>10-170	Total arsenic		EAWAG (2011)
	Arsenopyrite waste piles alluvial deposits	Thailand	1.25- 9000	Total arsenic	15000	Kohnhorst et al. (2002) Williams et al. (1996) Fordyce et al. (1995)
	Geological	Taiwan	Total arsenic: <0.15-3,000	Total arsenic	40,421 in 37 villages	Chen et al. (2010) Mukherjee et al. (2006)
	Geological	Taiwan	As^{+3} : 318-683 As^{+5} : 33-420 MMA: <1 DMA: <1	Speciation based analysis	1141 patients	Chen et al. (1994)
	Anoxic groundwater iron oxy-hydroxides sediments	Vietnam	>10-3050	Total arsenic	1 million	Merola et al. (2015) Duc et al. (2013) Lenny et al. (2010) Berg et al. (2001)
	sediments containing volcanic ash	Uruguay	18-30	Total arsenic		Bundschuh et al. (2012)
Anthropogenic sources	Smelter unit processing sulphide ores	Bulgaria	750-1500	Total arsenic		Nilsson et al. (1993)
	Gold mines	Cuba	25-250	Total arsenic		Toujaguez et al. (2013)
	Contaminated ballast water from old oil terminal, mine waters from the Cerramotoso nickel mine	Colombia	60-690	Total arsenic		Gray et al. (1997)
	Gold mining	Ecuador	390-670	Total arsenic		Cumbal et al. (2009)
	Gold mining	Ghana	Total arsenic: <1-175 As^{+3} : <3	Speciation based analysis	100,000	Smedley et al. (1996)

Combination of geological and anthropogenic sources	Fluvial inputs originating from the Deloro mining site Organic, marine and glaciomarine sediments	Canada	22-75	Total arsenic	27	Meranger and Subramanian (1984) Azcue and Nriagu (1995) Zheng et al. (2003) Wilson et al. (2013)
	Geological as arsenic rich sediment i.e Holocene, alluvia/delltaic sediments with high phosphate or organic matter deposits arsenical pesticides	India	10-5800	Total arsenic	100 million	Hoque et al. (2014) Chakraborti et al. (2013) Srivastava & Sharma (2012) Yano et al. (2012) Chakraborti et al. (2006) Mukherjee et al. (2006) Rahman et al. (2005) McArthur et al. (2004) Chakraborti et al. (2003) Chakraborti et al. (2003) Chakraborti et al. (2003) Nordstrom (2002) Smedley and Kinniburgh (2002) Mandal and Suzuki (2002) Acharyya (2002) Chowdhury et al. (2000) Pandey et al. (1999) Das et al. (1996) Das (1995) Mazumder et al. (1992)
	Geological, mining Industrial waste containing arsenic sulphide, arsenical containing insecticides	Japan	1-293	Total arsenic	18 (deaths from cancer)	Mukherjee et al. (2006) Mandal and Suzuki (2002) Tsuda et al. (1995) Tsuchiya (1977)
	Alluvial sediments Mining activities Over abstraction of ground water	Mexico	Total arsenic: 14-24000	Total arsenic	450,000	Bundschuh et al. (2012b) Muniz et al. (2012) Armienta et al. (2001) Rosas et al. (1999) Arroyo et al. (1997) Armienta et al. (1997) Del Razo et al. (1990)
			Total inorganic arsenic: 3.12-319 As^{+3} : 0.25-5.12 As^{+5} : 3.12-315	Speciation based analysis		Rosas et al. (1999)
	Mining and volcanic rock formations	Peru	>10-400	Total arsenic	250,000	George et al. (2014) Bundschuh et al. (2012b) Esparza (2002)
	Geological, mining and smelting	United Kingdom	11-5000	Total arsenic		British Geological Survey (2014) Aston et al. (1975)
	Geologic land use practices, volcanic rocks, bedrock wells gold and coal mining arsenical pesticides	USA	<1-1300	Total arsenic	35000-285,000	James et al. (2014) Peters et al. (2006) U.S Geological Survey et al. (2003) Alan et al. (2000) Lewis, et al. (1999) Brown and Fan (1994) Robertson (1989) Matisoff et al. (1983) Wilson and Hawkins (1978)
	arsenic rich abandoned mine dumps	Zimbabwe	13-96	Total arsenic		Jonnalagadda & Nenzou (1996)
Not Known		Afghanistan	>10-500	Total arsenic	500,000	Mukherjee et al. (2006)

Table 3: Summary of arsenic distribution in soil

Possible source	Reported arsenic levels (mg kg^{-1})	Arsenic testing performed as	Reference
Geological	5.0	Total arsenic	Reichert and Trelles (1921)
	0.32-18	Total arsenic	Mantylahti and Laakso (2002) RAKAS-project (2004-2007)
	0.50-22.9	Total arsenic	Wei et al. (1991)
	2.9-41.7	Total arsenic	Phuong et al. (2008)
	10-46	Total arsenic	Rahman and Naidu (2010) Meharg and Rahman (2003)
	9.38-57.1	Total arsenic	ONG et al. (2013)
	6.5-65	Total arsenic	Slekovec and Irgolic (1996)
	11-30	Total arsenic	Rosas et al. (1999)
	10-196	Total arsenic	Roychowdhury et al. (2002) Chakraborti et al. (2002)
	0.8-500	Total arsenic	Seyfferth et al. (2014) Kocar and Fendorf (2012)
Geothermal sources	40–116	Total arsenic	Flores-Tavizón et al. (2003)
Mining and tailing	2.1-183	Total arsenic	Skala et al. (2011)
	4 to 14,700	Total arsenic	Ongley et al. (2007)
	5.3-2035	Total arsenic	Baroni et al. (2004)
	11.4-439	Total arsenic	Norton et al. (2012)
	13-64 (as sum of total arsenic, As^{+3} and As^{+5})	Speciation based analysis	Acosta et al. (2015)
	34-1198	Total arsenic	Pfeifer et al. (2007)
Multiple sources: (geological, gold and copper mining, sulphide mineralization, pesticides application, industrial disposal of arsenopyrite (FeAsS), offshore oil fields and industrial waste)	0.72-38.2	Total arsenic	Limura (1980) Arao et al. (2010)
	0.8-99.5	Total arsenic	Overesch et al. (2007)
	1-3000	Total arsenic	Wenzel et al. (2002)
	1.21-56.17	Total arsenic	Weerasiri et al. (2013) Srinuttrakul and Yoshida (2012)
	1.8-830	Total arsenic	Pettry and Switzer (2001) Smith et al. (1998)
	1.8-60	Total arsenic	Ungaro et al. (2008)
	6.13-89.2	Total arsenic	Safaa et al. (2013)
	22-157	Total arsenic	Amonoo-Neizer and Busari (1980)
	100-43,500	Total arsenic	Krysiak and Karczewska (2007)
	280.3-1207.4	Total arsenic	Bidone et al. (2014)
	Total arsenic: 9400-13500 As^{+3} :<2-504 As^{+5} :4921-10504 MMA: <2 DMA:<2	Speciation based analysis	Matera et al. (2003)

Table 4: Summary of arsenic distribution in food items

Food item	Type	Reported arsenic levels (mg kg^{-1})*	Arsenic testing performed as	Reference
Rice	White rice (small-long grains)	0.01	Total arsenic	U.S Food and Drug Administration (2013)
	Polished (white) grain rice	Total arsenic: 0.5-85.2	Total arsenic	Wang et al. (2013) Khan et al. (2010)
		Total arsenic:0.05-0.28 As^{+3}: 0.049-0.572 As^{+5}: <0.005-0.095 DMA: 0.04-0.572	Speciation based analysis	Carey (2010) Mehrag et al. (2009) Zvala et al. (2008)
	Cooked rice	0.057	Total arsenic	Khan et al. (2010)
	Boro rice grain	0.45	Total arsenic	Bhattacharya et al. (2010)
	White rice	86.5–115.9	Total arsenic	Nookabkaew et al. (2013)
	Brown rice	203.7–267.7	Total arsenic	Nookabkaew et al. (2013)
Cereals	corn (*Zea mais*)	0.004-1.9	Total arsenic	Muñoz et al. (2002) Queirolo et al. (2000) Schoof et al. (1999a)
	Wheat flour	<0.05-0.01	Total arsenic	Schoof et al. (1999a) Liukkonen-Lilja (1993)
	grains and pulses	0.016	Total arsenic	Sancha and Marchetti (2009)
	rye flour	<0.02	Total arsenic	Liukkonen-Lilja (1993)
Vegetables	peas	0.005	Total arsenic	Schoof et al. (1999a)
	cucumber	0.004	Total arsenic	Schoof et al. (1999a)
	beet sugar	0.004	Total arsenic	Schoof et al. (1999a)
	spinach	0.02	Total arsenic	Schoof et al. (1999a) Khan et al. (2010)
	potato	0.01-0.86	Total arsenic	Norton et al. (2013) Bhattacharya et al. (2010) Queirolo et al. (2000)
	turmeric	0.003	Total arsenic	Bhattacharya et al. (2010)
	chili (*Capsicum*)	8.0	Total arsenic	Prieto-García et al. (2005)
	chayote squash (*Sechium edule*)	5.1	Total arsenic	Prieto-García et al. (2005)
	amaranth	0.023	Total arsenic	Khan et al. (2010)
	cabbage	0.02	Total arsenic	Wang et al. (2013)
	cauliflower	0.01-0.06	Total arsenic	Munoz et al. (2002)
	onion	0.35–5.4	Total arsenic	ITA (2006)
	carrots	3.8	Total arsenic	ITA (2006)
	yam roots	4.8	Total arsenic	Palmieri et al.(2009)
	bean grains	8.3	Total arsenic	Palmieri et al.(2009)
	broad beans	2.3- 2.9	Total arsenic	ITA (2006)
	salad, mix	0.06	Total arsenic	Norton et al.(2013)
	lettuce leafs	Total arsenic: 13 As^{+3}: 0-30.6 As^{+5}: 39.6-1913.9 MMA: 0-5.5 DMA: 0-24.3	Total arsenic & speciation based analysis	Norton et al.(2013)
Fruits and Fruit juices	currants	0.012	Total arsenic	Norton et al. (2013)
	grape juice	Total arsenic: 0.009 $\mu g\ l^{-1}$ As^{+3}: 2.60-35.65 As^{+5}: 2.06-15.30 MMA: <0.04-0.25 DMA: 0.27-2.07	Speciation based analysis	Schoof et al. (1999a)
	apple cider	Total arsenic: 5.41-15.27 $\mu g\ l^{-1}$ As^{+3}: 0.98-4.29 As^{+5}: 2.90-11.20 MMA: 0.80-0.81 DMA: 0.30-0.92	Speciation based analysis	Roberge et al. (2009)
	apple juice	10.8-22.4 $\mu g\ l^{-1}$	Total arsenic	Jackson et al. (2012)
	pear containing products	0.017	Total arsenic	Jackson et al. (2012)
	oil palm fruit	4.53	Total arsenic	Amonoo-Neizer & Amekor (1993)
	cane sugar	0.004	Total arsenic	Schoof et al.(1999a)
Animal products	raw milk	0.42-9.13 $\mu g\ l^{-1}$	Total arsenic	Perez Carrera & Fernandez Cirelli (2005)
	whole milk	Total arsenic: 2.78-7.92 $\mu g\ l^{-1}$* As^{+3}: <0.05-0.94 As^{+5}: 0.28-1.05 MMA: <0.04 DMA: <0.04	Speciation based analysis	Roberge et al. (2009)
	chicken broth	Total arsenic: 11.1-22.8 $\mu g\ l^{-1}$* As^{+3}: 0.17-1.38 As^{+5}: <0.06-0.78 MMA: <0.04 DMA: <0.04	Speciation based analysis	Roberge et al. (2009)
	beef broth	Total arsenic: 19.1- 42.6 $\mu g\ l^{-1}$ As^{+3}: 1.14-5.94 As^{+5}: 0.37-6.56 MMA: <0.04 DMA: <0.04-0.17	Speciation based analysis	Roberge et al. (2009)

	peanut butter	0.005	Total arsenic	Schoof et al. (1999a)
	eggs	0.0642	Total arsenic	Wang et al. (2013)
Baby foods	infant formulas and first foods	Total arsenic: 0.02–0.013 μg l^{-1} DMA: 19-40 μg l^{-1}	Speciation based analysis	Jackson et al. (2012)
	Baby rice	Total arsenic:0.15-0.47 DMA: 0.03-0.23	Speciation based analysis	Mehrag et al. (2008)
Fish and Sea food	Fresh water fish	Total arsenic :0.02-15.8	Total arsenic	Wang et al. (2013) Liang et al. (2012) New South Wales Food Authority (2010) Moreno López (2008) Stassen and van de Ven (2007) Mora et al. (2001) Quevillon et al. (1996) Amonoo-Neizer & Amekor (1993)
	Fresh water fish	Total arsenic :0.26-2.38 DMA: 0.045 AsB:0.13-1.73	Speciation based analysis	Li et al. (2003)
	blue shark	8.0	Total arsenic	Macedo (2010)
	Atlantic cod fish (haddock)	11.4	Total arsenic	Julshamn et al. (2004)
	prawns	62	Total arsenic	Julshamn et al. (2004)
	shell fish	Total arsenic: 0.24-0.37 DMA: LOD AsB: 0.15-0.24	Speciation based analysis	Li et al. (2003)
	crustaceans	Total arsenic: 0.45-7.54 DMA: LOD-0.029 AsB: 0.34-6.60	Speciation based analysis	Li et al., (2003)
	hijiki seaweed	77	Total arsenic	Food Standards Agency (2004)
	sea weeds	39.0	Total arsenic	New South Wales Food Authority (2010)
	mollusc specie (*Lapa negra*)	1.17-6.07	Total arsenic	Lavanchy Dougnac (1999)
	fresh water algae	98	Total arsenic	Diaz et al. (2009)
	blue mussels	3-15.8	Total arsenic	Sloth and Julshamn (2008)

*for beverages/liquid foods, the concentration unit is μg l^{-1}

Table 5: Summary of human studies measuring biological arsenic in hair, nail and blood

Biomarker type	Reported arsenic level	Unit*	Arsenic testing performed as	References
Hair	1.6-4.64	mg kg-1	Total arsenic	Rahman et al. (2006)
	2-5 (exposed cancer patient)	mg kg-1	Total arsenic	Wadha et al. (2011)
	0.10–4.57	mg kg-1	Total arsenic	Aldroobi et al. (2013)
	0.018–1.0	mg kg-1	Total arsenic	Normandin et al. (2013)
	4.2	mg kg-1	Total arsenic	Jinli Cui et al. (2013)
	nd-0.38	mg kg-1	Total arsenic	Ponpat Intarasunanont et al. (2012)
	0.01-57.21	mg kg-1	Total arsenic	Phan et al. (2011)
	2002: 0.48-10.83 2006: 0.27-8.25	mg kg-1	Total arsenic	Bin and Chen (2010)
	0.27-23.85	mg kg-1	Total arsenic	de Fatima Pinheiro Pereira et al. (2010)
	0.0059-0.0644	mg kg-1	Total arsenic	Essumang (2009)
	0.20 to 6.50	mg kg-1	Total arsenic	Gault AG et al. (2008)
	0.088-2.77	mg kg-1	Total arsenic	Agusa et al. (2006)
	20–1,500	mg kg-1	Total arsenic	Concha et al. (2006)
	4.20	mg kg-1	Total arsenic	Yanez et al. (2005)
	Total arsenic: 0.07-4.61 As^{+3} 0.21-2.64 DMA$^{+5:}$:0.02-0.13 MMA$^{+5:}$: 0.02-0.2 As^{+5} :0.08-1.54	mg kg-1	Speciation based analysis	Mandal et al. (2003)
	5.52	mg kg-1	Total arsenic	Hinwood et al. (2003)
	0.2-5.60	mg kg-1	Total arsenic	Pazirandeh et al. (1998)
	<0.006-0.582	mg kg-1	Total arsenic	Gebel et al. (1998)
	1.18-31.05	mg kg-1	Total arsenic	Das et al. (1995)
	0.43-5.74	mg kg-1	Total arsenic	Harrington et al. (1978)
Nails	Significant correlation between Arsenic in drinking water and nails (r = 0.49, *P*<0.001)	mg kg-1	Total arsenic	Merola et al. (2015)
	0.61-27.89	mg kg-1	Total arsenic	Rahman et al. (2005)
	Significant correlation between arsenic in toenails and drinking water	mg kg-1	Total arsenic	Merola (2014)
	0.19	mg kg-1	Total arsenic	Cottingham et al. (2013)
	0.008–1.4	mg kg-1	Total arsenic	Normandin et al. (2013)
	7.8	mg kg-1	Total arsenic	Jinli Cui et al. (2013)
	0-8.23	mg kg-1	Total arsenic	Ponpat Intarasunanont et al. (2012)
	Finger nail: 0.03-28.47 Toenail: 0.10- 21.89	mg kg-1	Total arsenic	Phan et al. (2011)
	0.10 to 7.95	mg kg-1	Total arsenic	Gault AG et al. (2008)
	Total arsenic: 5406 As^{+3} 11477 DMA$^{+5:}$ 84 MMA$^{+5:}$ 73 As^{+5} 2899	mg kg-1	Speciation based analysis	Button et al. (2008)
	0.02 to 2.11	mg kg-1	Total arsenic	Dominique S. Michaud et al. (2004)
	2.94	mg kg-1	Total arsenic	Wilhelm et al. (2005)
	Total arsenic: 1.47-7.39 As^{+3} 0.95-2.76 MMA$^{+3:}$:0.09-0.21 DMA$^{+3:}$:0.11-0.38 DMA$^{+5:}$: 0.04-0.09 As^{+5} : 0.27-1.31	mg kg-1	Speciation based analysis	Mandal et al. (2003)
	21.7	mg kg-1	Total arsenic	Hinwood et al. (2002)
	<0.01 to 0.81	mg kg-1	Total arsenic	Karagas et al. (2000)
	1.47-52.03	mg kg-1	Total arsenic	Das et al. (1995)
	4 (in 37% of persons)	mg kg-1	Total arsenic	Harrington et al. (1978)
Blood	3.29-8.82 (exposed cancer patients)	*μg l^{-1}*	Total arsenic	Wadha et al. (2013)
	1.31-10.37 (new borne blood)	μg l^{-1}	Total arsenic	Ponpat Intarasunanont et al. (2012)
	14.3	μg l^{-1}	Total arsenic	Hall et al. (2006)
	1.0-18.3	μg l^{-1}	Total arsenic	Vahter et al. (1995)

** units of concentration for solid samples is mg kg-1 and liquid samples is μg l^{-1}*

Table 6: Summary of human studies measuring biological arsenic in urine

Reported arsenic levels	Unit	Arsenic testing performed as	References
Exposed: 6.6 Unexposed: 5.0	$\mu g\ l^{-1}$	Total arsenic	Neamtiu et al. (2015)
Males: 124 Females: 130	$\mu g\ l^{-1}$	Total arsenic	Mazumder et al. (2013)
As^{+3}: 0.03-7.38 DMA^{+5} : 0.32-7.38 MMA^{+5} : 0.03-31.5 As^{+5} : 0.03-13.3	$\mu g\ l^{-1}$	Speciation based analysis	Normandin et al. (2013)
56.0 (sum of arsenic species)	$\mu g\ l^{-1}$	speciation based analysis	Jinli Cui et al. (2013)
117 ± 8.3	$\mu g\ g^{-1}$ of creatinine**	Total arsenic	Liu et al. (2013)
As^{+3}: 16.8 As^{+5}: 1.8 MMA: 1.8 DMA: 88.6	$\mu g\ l^{-1}$	Speciation based analysis	Hata et al. (2012)
15	$\mu g\ g^{-1}$	Total urinary arsenic	Robles-Osorio (2012)
Maternal urinary creatinine: 0-0.43	$\mu g\ mmol^{-1}$ (creatinine, lower than reference background level of 28 $\mu g\ mmol^{-1}$ creatinine)	Total arsenic	Ponpat Intarasunanont et al. (2012)
Total arsenic: 19.1 (As^{+3} + As^{+5} + MMA + DMA): 8.6	$\mu g\ l^{-1}$	Speciation based analysis	Sakuma et al. (2010)
(total arsenic+MMA+DMA) >3.5	$\mu g\ l^{-1}$	Speciation based analysis	Fillol et al. (2010)
Urinary iAs as (As^{+3} + As^{+5} + MMA + DMA): 9.1-1398	$\mu g\ g^{-1}$	Speciation based analysis	Valenzuela et al. (2009)
Females: 94.8 ± 250 Males: 59.7 ± 81.8	$\mu g\ g^{-1}$ creatinine**	Total urinary arsenic	Sirot et al. (2009)
260	$\mu g\ l^{-1}$	Total arsenic	Asante et al. (2009)
As^{+3} : <1-22.6 $MMA^{+5:}$ <1-20.3 $DMA^{+5:}$ 17.7-86 As^{+5} <1-35.1	$mg\ g^{-1}$ creatinine	Speciation based analysis	Agusa et al. (2006)
iAs: 1.1-1.6 iAs+MMA+DMA: 33.1-84.8	$\mu g\ l^{-1}$	Speciation based analysis	Hata et al. (2007)
Urinary arsenic: 1000-6200 DMA^{+5}: 20-98 MMA^{+5}: 3-33 Inorganic arsenic: 1.2-62	$\mu g\ l^{-1}$	Speciation based analysis	Lindberg et al. (2006)
172	$\mu g\ l^{-1}$	Total arsenic	Hall et al. (2006)
(total arsenic+MMA+DMA): 232-301	$\mu g\ l^{-1}$	Total arsenic species	Concha et al. (2006)
11.1-54.5	$\mu g\ g^{-1}$ of creatinine**	Total arsenic	Maharjan et al. (2005)
As^{+3} + As^{+5} : 7.1 $DMA^{+5:}$: 41.7 MMA^{+5} : 5.6 Total arsenic as sum of species: 47.9	$\mu g\ l^{-1}$	Speciation based analysis	Michael Wilhelm et al. (2004)
10.1% of the human subjects found with highest bladder cancer risk calculated from Urinary arsenic and cumulative arsenic exposure	$\mu g\ l^{-1}$	Speciation based analysis	Chen et al. (2003)
Inorganic arsenic: 11-509.4 MMA: 55-2192.5 DMA:6.8-687.4	$\mu g\ l^{-1}$	Speciation based analysis	Loffredo et al. (2003)
2.48-4.05	$\mu g\ g^{-1}$ creatinine**	Total arsenic	Spevackova et al. (2002)
2.2–106	$\mu g\ l^{-1}$	Total arsenic	Jörg Matschullat et al. (2000)
<0.1-18.32	$\mu g\ l^{-1}$	Total arsenic	Gebel et al. (1998)
30-2000	$\mu g\ l^{-1}$	Total arsenic	Das et al. (1995)
Total arsenic: 13-440 Inorganic As + MMA + DMA: 9-405	$\mu g\ l^{-1}$	Speciation based analysis	Vahter et al. (1995)
As^{+3} 0.5-35 $DMA^{+5:}$ 15-85 $MMA^{+5:}$ 4-36 As^{+5} 3-57	$\mu g\ l^{-1}$	Speciation based analysis	Harrington et al. (1978)

**Units vary in accordance with testing methods*
***Urinary arsenic reference value: 28 $\mu g\ mmol^{-1}$ creatinine*

Table 7: Summary of reported health effects of higher levels of arsenic

Organs targeted	Health impacts	Arsenic exposure level	Study type	No. of participants	parameters studied	References
Skin	Hyperpigmentation, Hyperkeratosis and Skin tumours	<50-3400 $\mu g\ l^{-1}$	cross sectional population survey	7683	total arsenic in water, examination of skin lesions	Mazumder et al. (1998)
	Prominent transverse white lines in the fingernails and toenails called Mee's lines	1 g of sodium arsenite in an apparent suicide attempt.	case-control study	1 (20 years old man)	urinary arsenic, neurological examination	Fincher and Koerker (1987)
	Skin lesions	<100 $\mu g\ l^{-1}$	prospective cohort study 668 with skin lesions and 10051 without lesions	11746	examination of pre-malignant skin lesions	Argos et al. (2007)
	-do-	115-380 $\mu g\ l^{-1}$	case control study based on	415 (256 identified cases)	total arsenic in water, medical examination of skin lesions	Haque et al. (2003)
	-do-	<100 $\mu g\ l^{-1}$	prospective cohort study (based on individual-level exposure assessment)	11,746 (married men and women)	-do-	Ahsan et al. (2006)
	Skin cancer	<500 $\mu g\ l^{-1}$	retrospective cohort study	3,179	well-use histories, medical history on dermatological examinations	Lamm et al. (2006)
Gastrointestinal system	Diarrhoea and stomach issues	slow poisoning case with 36000 $\mu g\ l^{-1}$arsenic	cross-sectional study	1(62-year-old man)	Total arsenic, autopsy findings, post-mortem toxicological findings	Poklis and Saady (1990)
	Non-cirrhotic portal fibrosis	5050-14200 $\mu g\ l^{-1}$	hospital-based and case control cohort follow-up studies	248 patients	Liver function tests, HBsAg status. Liver biopsy	Santra et al. (1999)
	Macro-nodular cirrhosis variceal bleeding	0.015–0.06 mg kg^{-1} per day	clinical study (8 patients, who received arsenical preparation for psoriasis as Fowler's solution)	8	total arsenic, clinical examination	Nevens et al. (1994)
	Liver dysfunction Haemangio endothelioma	240-2000 $\mu g\ l^{-1}$	retrospective cohort study (16 male patients with malignant tumours associated with arsenic-polluted water)	16	total arsenic in water	Zaldivar et al. (1981)
Cardiovascular system	Cardiovascular disease	3 to 295 $\mu g\ m^{-3}$	retrospective cohort study (based on causes of death among a group of 527 pensioners in a copper smelter)	527	airborne arsenic, urinary arsenic values	Pinto et al. (1977)
	-do-	<0.5->0.5 mg m^{-3}	case-control retrospective assessment of exposure	325 (74 referents and 251 individuals)	airborne arsenic, in a Swedish copper smelter	Axelson et al. (1978)
	-do-	0.9-21.65 mg m^{-3}	case-control study (based on copper smelter employees in Montana)	8,045 (302 died with respiratory cancer)	estimated measures of relations between respiratory cancer mortality and exposure to airborne arsenic	Lee-Feldstein (1989)
	-do-	>40 $\mu g\ l^{-1}$	case control study	298 cases and 275 controls	total inorganic arsenic in water and toenail samples (Nail arsenic above 1.38 µg/g concluded to be associated with an increased risk of cardiovascular disease)	Wade et al. (2015)
	-do-	≥ 108 $\mu g\ l^{-1}$	case–cohort prospective study	369 incident fatal and non-fatal cases of CVD	Blood pressure monitoring, verbal autopsy procedure, medical records, death certificates, determination of arsenobetaine (AsB), arsenocholine (AsC), As^{+5}, As^{+3}, MMA, and DMA in urine samples.	Chen et al. (2013)
	-do-	exposed to 50, 100 and 150 mg l^{-1} arsenic)	clinical study	based on male albino rats	induced lipotoxic and non-lipotoxic dyslipidemia at "low" or "medium" doses,	Afolabi et al. (2015)
	Hypertensive heart disease	14 to 166 $\mu g\ l^{-1}$	cohort mortality study (association of drinking	2,203 deceased cases	total arsenic in water	Lewis et al. (1999)

			water arsenic and mortality outcome)			
	Hypertension		case control study	40 (workers occupationally exposed to arsenic)	total arsenic in urine samples, determination of glycosylated haemoglobin (Hgb A1C)	Jensen and Hansen (1998)
	Ischaemic heart disease	267.05 ± 20.95 μg l^{-1}	cross sectional study	1081	Mean total arsenic of water 267.05 μg/L, urinary inorganic arsenic and its metabolites	Hsueh et al. (1998)
	Cardiac arrhythmias		patient based case control study	1(57-year-old man)		Goldsmith (1980)
	Peripheral vascular disease	80 μg l^{-1}	cohort (follow-up)	774 (129 adults, 645 school children)	total arsenic content in hair and nail clippings, vegetables and beverages samples, examination of cutaneous lesions attributed to arsenicism	Borgono et al. (1977)
	Peripheral vascular disturbances leading to gangrene, and; Black foot disease	>10 μg l^{-1}	cohort (follow-up) study	survey of 40,421 inhabitants and follow-up of 1,108 patients	total arsenic in water, examination of skin lesions, calculation of death rates specific for age for black foot disease	Tseng (1977)
Respiratory diseases	Restrictive or obstructive Lungs diseases, and bronchitis	0.015–0.08 mg kg^{-1} per day	cross-sectional survey	7683	total arsenic in drinking water, chest X-ray and HRCT	Mazumder et al. (1998 & 2000)
	Lungs diseases	780 μg l^{-1}	cohort (follow-up) study	20067	death certificates from Black Foot Endemic area of Taiwan from 1971 to 1994)	Tsai et al. (1999)
	-do-	Mean 800 μg l^{-1}	cohort (follow-up)	774 (129 adults, 645 school children)	total arsenic content in hair and nail clipping, vegetables and beverages samples, examination of cutaneous lesions attributed to arsenicism	Borgono et al. (1977)
	-do-	>250 μg l^{-1}	population-based prospective cohort study	20,033 adults	total arsenic in drinking water (tube-well), urine and blood samples collection of arsenic exposure history, smoking and demographic data Pulmonary function test	Parvez et al. (2013)
	Lung cancer	10- 1752 μg l^{-1}	cohort (follow-up) study	308 lungs cancer cases	death certificates of residents who died from cancers during the period from 1973 to 1986	Chen et al. (1992)
Endocrinology	Diabetes mellitus	0.11 mg kg^{-1} per day	case control study	40 (workers occupationally exposed to arsenic)	total arsenic concentration in urine samples, concentration of glycosylated haemoglobin (Hgb A1C) in 40 arsenic workers,	Jensen and Hansen. (1998)
	-do-	500-1000 μg l^{-1}	case–control (case–comparison)	163 exposed subjects and 854 unexposed individuals	Total arsenic in water samples, history of symptoms, previously diagnosed diabetes, determination of glucosuria, and blood sugar level after glucose intake.	Rahman et al. (1998)
Neurological disorders	Peripheral neuropathy, and Hearing defects	0.005–0.11 mg kg^{-1} per day	case control study (neurological effects)	56 (10-year-old children residing near a power plant burning	audiometric and clinical examination	Bencko et al. (1977)

				local coal of high arsenic content).		
	Cerebrovascular disease 10–100 μg/L	10–100 $\mu g\ l^{-1}$	ecological study (based on standardized mortality ratio (SMR) analysis	8593 observations for cerebrovascular diseases	total Arsenic in 9251 well water, Michigan resident death files data for 1979- 1997	Meliker et al. (2007)
Haematopoietic system	Disturbed erythropoiesis with anaemia	chronic arsenic intoxication	case report study	1 (47 years patient exposure to a weed spray approximately 2 weeks prior to admission).	arsenic contents of tissues, clinical examination of patient, bone marrow examinations	Westhoff et al. (1975)
Reproductive system	Increased frequency of miscarriages	6-978 $\mu g\ l^{-1}$	prospective cohort study	1,578 mother-infant pairs	Total arsenic in urine collected at around gestational weeks 8 and 30	Rahman et al. (2008)
	Foetal losses	174-319 $\mu g\ l^{-1}$	spatiotemporal analytical study	26,972 pregnancies	spatiotemporal analysis, spatial scan test used to identify unique non-random spatial and spatiotemporal clusters of foetal loss and infant deaths	Sohel et al. (2010)
Genitourinary system	Nephritis and prostate cancer	53-750 $\mu g\ l^{-1}$	cohort (follow-up)	2,203 deceased cases	nephritis (SMR = 1.72; CI, 1.13-2.50), prostate cancer (SMR = 1.45; CI, 1.07-1.91)	Lewis et al. (1999)
	Bladder cancer	18-164 $\mu g\ l^{-1}$	cohort (follow-up) study	312	death certificates from Black Foot Endemic area of Taiwan	Tsai et al. (1999)
	-do-	170-800 $\mu g\ l^{-1}$	ecological study (based on the dose-response relationships between cancer risks and the concentration of inorganic arsenic)		risk estimate of 1/1000 persons	Smith et al. (1992)
	Kidney cancer	60- 860 $\mu g\ l^{-1}$	case-control study	122 kidney cancer cases and 640 population-based controls	total arsenic in water, water consumptions with individual data on exposure and potential confounders during 2007–2010)	Ferreccio et al. (2013)

**1 mg kg^{-1} is equivalent to 1000 μg kg^{-1}*

Table 8: Summary results of methodologies and tools adopted for risk assessment

Technique/ Tool Used	Location	Exposure sources	Risks assessed for form of arsenic	Risk output	Reference
Species sensitivity distribution (SSD) and assessment factor (AF) methods for ecological risks	China	River water and sediments	As^{5+}, As^{3+}, MMA and DMA	Ecological risk from As^{+3} and As^{+5} <1	Du et al. (2015)
Summary Relative Risk Estimate (SRRE)	Taiwan (Southwest)	water	total arsenic	Non-significant (SRREs <1.0) results at low dose *vs.* predicted risk using high-dose extrapolation	Tsuji et al. (2014)
Log-Logistic model	USA	apple juice	Total arsenic	Total cancer rate (per million) at ≥10 μg l^{-1}: 8.0 (0.0, 21.3)	Carrington et al. (2013)
Mantel-Cox Method	Taiwan (Northeastern Coast)	water	Total arsenic	Hazard ratio ranged from 1.0-8.71 for urothelial carcinoma by arsenic exposure at <10-100 μg l^{-1}	Yang et al. (2013)
Generalized estimating equation (GEE) models	Bangladesh	water	Total arsenic	Every $\log_{10}$ decrease in water and toenail arsenic was associated with 22% relative increase in skin lesion recovery	Seow et al. (2012)
Biologically-Based Dose–Response (BBDR) Model	USA	Comparative genomic data from individuals with known exposure from drinking water	inorganic arsenic	*in vitro* dose response is nonlinear for urinary cancer	Clewell et al. (2007)
USEPA one-hit model (1989)	West Bengal, India	water rice	Total arsenic	Median excess lifetime cancer risk above USEPA regulatory threshold target cancer risk level of 10^{-4}–10^{-6}	Mondal et al. (2010)
USEPA Risk Assessment Approach	Pakistan (Kohistan region, northern areas)	water	Total arsenic	Low chronic risk with HQ >1 (Jabba, Dubair) and medium cancer risk with HQ <1	Muhammad et al. (2010)
	Vietnam (Four villages in Ha Nam province)	water	Total arsenic	Potential carcinogenic rate of 5 in 1000 people	Nguyen et al. (2009)
	Thailand (Ronphibun)	water food	Total arsenic	HQ = 6.98 CR = 1.26 x 10^{-3}	Saipan and Ruangwises (2009)
	Turkey (Izmir)	water	Total arsenic	HQ: 41 in 19% of the population Carcinogenic risk of < 10^{-4} in 46% of population Carcinogenic risk >10^{-6} in 90% of population	Kavcar et al. (2009)
	USA	water	As^{5+}, As^{3+}, or DMA^{5+} (without model validation)	**Groundwater:** minimal chronic exposure risk (< 10^{-6}) by DMA^{5+} **Surface water:** lifetime cancer risk (>10^{-4}) of As^{3+}	Markley and Herbert (2009)
Cox's Proportional Hazards Regression Models	Taiwan (North-eastern Coast)	water	Total arsenic	significant dose–response trend (P= 0.001) of lung cancer risk	Chen et al. (2010)
Integration of Weibull dose–response function and a physiologically based pharmacokinetic (PBPK) model	Taiwan (southwestern and northeastern Taiwan)	water	Total arsenic	Positive relationships between arsenic exposures and cumulative incidence ratios of bladder, lung, and urinary-related cancers i.e r^2 = 0.58–0.89.	Liao et al. (2009)
NRC multistage Weibull model	Taiwan vs Chakdha block, West Bengal	water	Total arsenic	Death and DALYs calculations are sensitive to the choice of dose–response model	Mondal et al. (2008)
Cumulative Arsenic exposure Index''(CAI)	Bangladesh	water	Total arsenic	CAI of 1.64–49341.62 mg with arsenic exposure of 0.1–864 mg l^{-1}	Ahsan et al. (2006)
Physiologically Based Toxicokinetic &Toxicodynamic (PBTK/TD) Modeling	Taiwan (southwestern)	Tilapia farm fish	Total arsenic	All predicted 90^{th} percentiles of HQ<1 for city residents and subsistence fishers in the BFD area, indicating small contributions from farmed tilapia consumption	Ling et al. (2005)
Death and Disability Adjusted Life Years (DALYs).	Bangladesh	water	Total arsenic	7930 YLDs lost due to arsenicosis, which accounts for 1908 DALYs	Molla et al. (2004)
Monte Carlo modelling	USA	water air soil food	Inorganic arsenic	Food is more significant for arsenic exposure than water	Meacher et al. (2002)