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Arsenic speciation and transformation pathways in ground water system.

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Abstract

Arsenic (atomic number, 33; relative atomic mass, 74.92) has chemical and physical properties intermediate between a metal and a non-metal, and is often referred to as a metalloid or semi-metal. It belongs to Group VA of the Periodic Table, and can exist in four oxidation states: -3, 0, +3, and +5. Arsenite, AsIII, and arsenate, AsV, are the predominant oxidation states under, respectively, reducing and oxygenated conditions (WHO, 2001; IARC, 2004). Arsenic is the 20th most common element in the earth's crust, and is emitted to the environment as a result of volcanic activity and industrial activities. AsIII, MMAIII, and DMAIII can induce chromosomal aberrations in vitro (Oya-Ohta et al., 1996; Kligerman et al., 2003). Statistically significant increases in chromosomal aberrations occur only at toxic doses (Klein et al., 2007), except as a secondary effect of genomic instability in long-term, low-dose treatment protocols (Sciandrello et al., 2004). In the human body, inorganic arsenic compounds are converted to AsIII and AsV. AsV is rapidly converted to AsIII. AsIII species are more toxic and bioactive than are AsV species, both because of the greater chemical reactivity of AsIII, and because AsIII enters cells more easily. Many of these effects depend on altered gene expression that can result from genetic and epigenetic effects . Changes in gene expression by AsIII can also be mediated by the alteration of miRNA patterns (Marsit et al., 2006). Some short-term changes in gene expression (e.g. changes in the expression of DNA-repair proteins or DNA methyltransferases) can result in long-term changes. Genome-wide changes in gene expression and signal transduction induced by arsenicals have been reported in several publications (Su et al., 2006; Kumagai & Sumi, 2007; Ghosh et al., 2008). An analysis of micronuclei induced by AsIII in human fibroblasts shows that at lower (relatively non-toxic) doses, AsIII acts as an aneugen by interfering with spindle function and causing micronuclei with centromeres, but at high (toxic) doses, it acts as a clastogen, inducing micronuclei without centromeres (Yih & Lee, 1999). Aneuploidy is seen after treatment with AsIII concentrations lower than those that cause chromosomal aberrations (Yih & Lee, 1999; Ochi et al., 2004; Sciandrello et al., 2002, 2004).

1.INTRODUCTION

Arsenic (atomic number, 33; relative atomic mass, 74.92) has chemical and physical properties intermediate between a metal and a non-metal, and is often referred to as a metalloid or semi-metal. It belongs to Group VA of the Periodic Table, and can exist in four oxidation states: -3, 0, +3, and +5. Arsenite, As^{III}, and arsenate, As^{V}, are the predominant oxidation states under, respectively, reducing and oxygenated conditions (WHO, 2001; IARC, 2004). From a biological and toxicological perspective, there are three major groups of arsenic compounds 1-inorganic arsenic compounds, 2-organic arsenic compounds, and 3-arsine gas. The inorganic arsenic compounds, arsenic trioxide, sodium arsenite and arsenic trichloride are the most common trivalent compounds, and arsenic pentoxide, arsenic acid and arsenates (e.g. lead arsenate and calcium arsenate) are the most common pentavalent compounds. Common organic arsenic compounds include arsanilic acid, methylarsonic acid, dimethylarsinic acid (cacodylic acid), and arsenobetaine (WHO, 2000). Arsenic is an elusive element, with a mysterious ability to change color, behavior, reactivity, and toxicity. For example, two arsenic sulfide minerals, red-colored realgar (As_4S_4) and bright yellow orpiment (As_2S_3), were described by the ancient Greeks, but they considered them to be two entirely different substances (Irgolic 1992). As noted in the lead article in this issue, arsenic has a long history with humans, having been used as both a poison and a curative, in metallurgy, for decoration and pigmentation, and in pyrotechnics and warfare (Miller et al. 2002; Nriagu 2002). Arsenic trioxide (As_2O_3), for example, is a tasteless, odorless, white powder. It is the form of arsenic favored historically for eliminating enemies and aged relatives, while Schweinfurt green (copper acetoarsenite) is a bright

green, very toxic powder that was formerly used extensively as a pigment in wallpaper (National Research Council 1977; Cullen and Reimer 1989). Today, elevated levels of arsenic in groundwater aquifers threaten human health in widespread areas worldwide, but the spatial unpredictability of dissolved arsenic concentrations leaves scientists at a loss to explain contamination at one site and clean water in the neighbor's well next door (see Charlet and Polya this issue). The chemical variability of arsenic stems from its electronic structure and bonding properties, which give rise to a variety of forms in the solid, aqueous, and gas states. As a metalloid, third-row, group V element, arsenic is seated beneath nitrogen and phosphorus in the periodic table and thus has an excess of electrons and unfilled orbitals that stabilize formal oxidation states from +5 to –3. The electron configuration for neutral arsenic is $[Ar]3d^{10}4s^24p_x1p_y1p_z1$, a state that supplies up to five valence electrons for participation in chemical bonding and empty p orbitals for electron occupation. Although the electronegativity of arsenic is greater than that of nitrogen and similar to that of phosphorus by most measures (Allred and Hensley 1961), arsenic has a greater oxidation potential (i.e. the ability to lose electrons) than nitrogen and phosphorus, which increases its cationic character. However, the assignment of formal oxidation states to arsenic is not very meaningful from a chemical standpoint because arsenic bonding overall is essentially covalent (Cotton and Wilkinson 1988). Arsenic bonds readily to a variety of ligands, which strongly influences its chemical behavior. Compared to nitrogen and phosphorus, the potential participation of lone pair electrons and outer d orbitals in arsenic bonding stabilizes some different types of molecular configurations than are found in the lighter group elements. While arsenic can combine with many other elements to form covalent compounds, it most commonly bonds to oxygen and sulfur in nature. The ability of arsenic to shift from an electropositive state, such as in oxo-anions, to an electronegative state, as in metal arsenides, is a consequence of electron occupation of bonding and antibonding orbitals of arsenic and its myriad of ligands. This facile chemistry has led to extensive investigation of synthetic compounds of arsenic, both inorganic and organic. This article, however, focuses primarily on natural forms of arsenic and presents a brief survey of its speciation and occurrence in solid, aqueous, and biological compounds in environments at and near the Earth's surface.

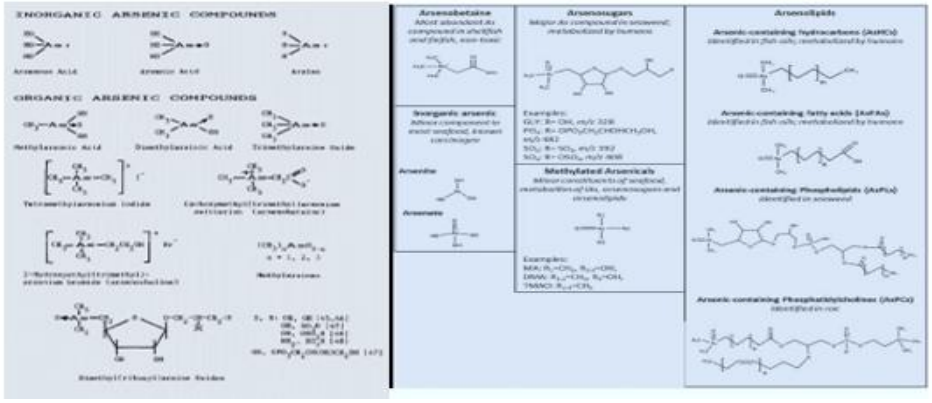
OBJECTIVE OF STUDY

1. Study of different chemical forms of Arsenic.
2. Analyze the transformation pathways of arsenic and understand the geochemical and environment factors.
3. Explain the sources and contamination pathways and evaluate the health impact
4. Suggest possible control and remediation strategies.

CHEMISTRY OF ARSENIC

In aqueous solutions, arsenic forms the oxo-anions arsenite, $H_3As_3+O_3$ [or commonly written $As^{3+}(OH)3$] and arsenate, $H_3As_5+O_4$. From the pKa's (acid dissociation constant) shown in FIGURE 1, aqueous arsenic species in most natural waters (pH ~4–10) are the neutral species H_3AsO_3 for As^{3+}, and H_2AsO^{4-} and $HAsO_4^{2-}$ for As^{5+} (National Research Coun cil 1977; Cullen and Reimer 1989). The redox potential of arsenic oxo-anions is such that arsenite is expected to be the stable aqueous form under moderately reducing condi tions, roughly from oxidation potentials (Eh) of about +300 mV at pH 4 to –200 mV at pH 9, while arsenate is stable in oxidized aqueous solutions (Inskeep et al. 2002 also has similarities to phosphoric acid (H_3PO_4), with the important exception of the greater oxidizing potential of arsenate compared to phosphate (Cotton and Wilkinson 1988). The second and third acid dissociation constants for arsenate (pKa2 = 6.97; pKa3 = 11.53) are only slightly more acidic than the corresponding constants for phosphate (pKa2 = 7.21; pKa3 = 12.32) (Butler 1998). As such, under equilibrium oxidized conditions, dis solved arsenate and phosphate will be present as aqueous species of similar charge and chemical structure over the pH range of natural waters, with only slight offsets in speciation as a function of pH. This similarity points out the importance of competitive chemical behavior between arsenate and phosphate in natural systems if arsenate reduction does not come into play. Low levels of inorganic and organic arsenic have been measured in most foodstuffs (typical concentrations are less than 0.25 mg/kg). Factors influencing the total concentration of arsenic in food include: food type (e.g. seafood versus meat or dairy), growing conditions (e.g. soil type, water, use of arsenic-containing pesticides), and food-processing techniques. The highest concentrations of arsenic have been found in seafood (2.4–16.7 mg/kg in marine fish, 3.5 mg/kg in mussels, and more than 100 mg/kg in certain crustaceans), followed by meats, cereals, vegetables, fruit, and dairy products. Inorganic arsenic is the predominant form found in meats, poultry, dairy products and cereal, and organic arsenic (e.g. arsenobetaine) predominates in seafood, fruit, and vegetables (WHO, 2000, 2001).

Regional differences are seen in the daily intake of total arsenic through food, and are mainly attributable to variations in the quantity of seafood consumed. For example, the daily dietary intake of total arsenic in Japan is higher than that in Europe and the USA (WHO, 2000). Based on the limited data available, it is estimated that approximately 25% of daily dietary arsenic intake is from inorganic sources. Arsenic intake is typically higher in men than it is in women and children, with estimated levels ranging from 1.3 µg/day for infants under 1 year of age, 4.4 µg/day for 2-year olds, 9.9 µg/day for 25–30-year-old men, 10 µg/day for 60–65-year-old women, and 13 µg/day for 60–65-year-old men (WHO, 2001).



(A)-Arsenic Oxides- The affinity of arsenic to bond with other elements and species means that it is rarely found as a native element, with the occasional exception in hydrothermal ores. The simple As^{3+}oxides, arsenolite and claudetite (both As_2O_3), are polymorphs with similar thermodynamic stability, with claudetite thought to be slightly more stable at standard conditions (Nordstrom and Archer 2003). These minerals form naturally as secondary weathering products of arsenic sulfides but are more commonly found as the oxidation products of the roasting of arsenic-bearing ore minerals or coal. Condensation of combustion vapors makes "white arsenic" powder characteristic of arsenic trioxide (National Research Council 1977). The arsenolite structure is some what unusual, consisting of $[As_4O_6]$ cages linked by bridg ing oxygen atoms

(B)-Arsenic Sulfides-Arsenopyrite, orpiment, and realgar are the most common arsenic sulfide minerals occurring primarily in hydrothermal and magmatic ore deposits. As a pigment and dye, orpiment was sought in ancient times for its golden color (from Latin auri pigmentum). Realgar (from Arabic rahj al ghar, "powder of the mine") was a common red pigment for paints and dyes in paintings and manuscripts. It is unstable in air, however, and alters to pararealgar, a yellow orange powder, which is seen now in old, unrestored paint ings or manuscripts that have a yellow or orange hue over the original red (Clark 1999). Other transition metals, such as Co, Ni, and Cu, also combine with arsenic and sulfur to form a variety of minor sulfides and sulfosalts, often with extensive solid solution. More recently, spectroscopic meth ods have verified the formation of orpiment- and realgar type structures in low-temperature, sulfate-reducing envi ronments, probably related to microbiological sulfur and arsenic reduction (O'Day et al. 2004).

(C)-Metal Arsenides- A large number of metal arsenides are known and can be considered as alloys of metals, generally with the form MeAsn, where n = 1, 2, or 3 and Me is a metallic element. Electron counting would indicate a negative formal oxida tion state for arsenic in these compounds. However, bond ing is strongly covalent in these semiconducting solids, and they are better described by band gap formalism (Partik and Lutz 1999). The well-known industrial semiconductor GeAs is a typical example. In nature, the most common arsenides form with Fe, Co, Ni, and Cu (TABLE 1), but are typically rare, occurring in hydrothermal and magmatic ore deposits in association with a variety of sulfide minerals. They often form solid solutions with each other and with sulfide min erals in structural arrangements of common sulfides (e.g. pyrite, pyrrhotite, marcasite, galena).

ARSENICIFEROUS IN GROUND WATER

(A) Taiwan (China)-Exposure to arsenic was endemic in two areas of Taiwan (China): The south-western coastal area (Chen *et al.*, 1985), and the north-eastern Lanyang Basin (Chiou *et al.*, 2001). Residents in the south-western areas drank artesian well-water with high concentrations of arsenic from the early 1910s to the late 1970s, with levels mostly above 100 µg/L (Kuo, 1968; Tseng *et al.*, 1968). In the Lanyang Basin, residents used arsenic-contaminated water from household tube wells starting in the late 1940s. Arsenic in the water of 3901 wells, tested in 1991–94 ranged from undetectable (< 0.15 µg/L) to 3.59 mg/L (median = 27.3 µg/L) (Chiou *et al.*, 2001).

(B) Northern Chile-The population-weighted average concentration of arsenic in drinking-water in Region II, an arid region of northern Chile, was about 570 µg/L over 15 years (1955–69) (Smith *et al.*, 1998). With the introduction of a water-treatment plant in 1970, levels decreased. By the late 1980s, arsenic levels in drinking-water had decreased to less than 100 µg/L in most places. With minor exceptions, water sources elsewhere in Chile have had low concentrations of arsenic (less than 10 µg/L) (Marshall *et al.*, 2007).

(C) Cordoba Province, Argentina-Of the 24 counties in Cordoba Province, two have been characterized as having elevated exposure to arsenic in drinking-water (average level, 178 µg/L), six as having medium exposure, and the remaining 16 rural counties as having low exposure (Hopenhayn-Rich *et al.*, 1996, 1998).

(D) Bangladesh, West Bengal (India), and other locations in the Ganga plain-Millions of tube wells were installed in West Bengal (India), Bangladesh, and other regions in the Ganga plain of India and Nepal starting in the late 1970s to prevent morbidity and mortality from gastrointestinal disease (Smith *et al.*, 2000). Elevated arsenic in wells in Bangladesh was confirmed in 1993 (Khan *et al.*, 1997). In a Bangladesh survey by the British Geological Survey of 2022 water samples in 41 districts, 35% were found to have arsenic levels above 50 µg/L, and 8.4% were above 300 µg/L, with an estimate of about 21 million persons exposed to arsenic concentrations above 50 µg/L (Smith *et al.*, 2000).

TRANSFORMATION PATHWAY OF ARSENIC

ENVIRONMENTAL EXPOSURE

A. Air
B. Water
C. Soil and sediments

(A)-Air-Arsenic is emitted to the atmosphere from both natural and anthropogenic sources. Approximately one-third of the global atmospheric flux of arsenic is estimated to be from natural sources (7900 tonnes per year). Volcanic activity is the most important natural contributor, followed by low-

temperature volatilization, exudates from vegetation, and windblown dusts. Anthropogenic sources are estimated to account for nearly 24000 tonnes of arsenic emitted to the global atmosphere per year. These emissions arise from the mining and smelting of base metals, fuel combustion (e.g. waste and low-grade brown coal), and the use of arsenic-based pesticides (WHO, 2000, 2001). Arsenic is present in the air of suburban, urban, and industrial areas mainly as inorganic particulate (a variable mixture of As^{III} and As^{V}, with the pentavalent form predominating). Methylated arsenic is assumed to be a minor component of atmospheric arsenic (WHO, 2000). Mean total arsenic concentrations in air range from 0.02–4 ng/m^3 in remote and rural areas, and from 3–200 ng/m^3 in urban areas. Much higher concentrations (> 1000 ng/m^3) have been measured in the vicinity of industrial sources, such as non-ferrous metal smelters, and arsenic-rich coal-burning power plants (WHO, 2001).

(B)-Water-Arsenic, from both natural and anthropogenic sources, is mainly transported in the environment by water. The form and concentration of arsenic depends on several factors, including whether the water is oxygenated (for example, arsenites predominate under reducing conditions such as those found in deep well-waters), the degree of biological activity (which is associated with the conversion of inorganic arsenic to methylated arsenic acids), the type of water source (for example, open ocean seawater versus surface freshwater versus groundwater), and the proximity of the water source to arsenic-rich geological formations and other anthropogenic sources (WHO, 2000, 2001). The concentration of arsenic in surface freshwater sources, like rivers and lakes, is typically less than 10 µg/L, although it can be as high as 5 mg/L near anthropogenic sources. Concentrations of arsenic in open ocean seawater and groundwater average 1–2 µg/L, although groundwater concentrations can be up to 3 mg/L in areas with volcanic rock and sulfide mineral deposits (WHO, 2001). Exposure to high levels of arsenic in drinking-water has been recognized for many decades in some regions of the world, notably in the People's Republic of China, Taiwan (China), and some countries in Central and South America. More recently, several other regions have reported having drinking-water that is highly contaminated with arsenic. In most of these regions, the drinking-water source is groundwater, naturally contaminated from arsenic-rich geological formations. The primary regions where high concentrations of arsenic have been measured in drinking-water include large areas of Bangladesh, China, West Bengal (India), and smaller areas of Argentina, Australia, Chile, Mexico, Taiwan (China), the USA, and Viet Nam. In some areas of Japan, Mexico, Thailand, Brazil, Australia, and the USA, mining, smelting and other industrial activities have contributed to elevated concentrations of arsenic in local water sources (IARC, 2004). Levels of arsenic in affected areas may range from tens to hundreds or even thousands of micrograms per litre, whereas in unaffected areas, levels are typically only a few micrograms per litre. Arsenic occurs in drinking-water primarily as As^{V}, although in reducing environments significant concentrations of As^{III} have also been reported. Trace amounts of methylated arsenic species are typically found in drinking-water, and higher levels are found in biological systems. More complete data on arsenic in water may be found in the previous *IARC Monograph* (IARC, 2004).

(C)- Soil and sediments- Natural and anthropogenic sources contribute to the levels of arsenic found in soil and sediments. Mean background concentrations in soil are often around 5 mg/kg, but can range from as low as 1 mg/kg to as high as 40 mg/kg. This variation in levels of naturally occurring arsenic in soils is associated with the presence of geological formations (e.g. sulfide ores, mineral sediments beneath peat bogs). Soils contaminated with arsenic from anthropogenic sources (e.g. mine/smelter wastes, agricultural land treated with arsenical pesticides) can have concentrations of arsenic up to several grams per kilogram. Mean sediment arsenic concentrations range from 5–3000 mg/kg, with the higher levels occurring in areas of anthropogenic contamination (WHO, 2001).

HUMAN EXPOSURE

A. Exposure of the general population
B. Occupational exposure
C. Dietary exposure

(A)-Exposure of the general population-The primary route of arsenic exposure for the general population is via the ingestion of contaminated food or water. The daily intake of total arsenic from food and beverages is generally in the range of 20–300 µg/day. Inhalation of arsenic from ambient air is generally a minor exposure route for the general population. Assuming a breathing rate of 20 m^3/day, the estimated daily intake may amount to about 20–200 ng in rural areas, 400–600 ng in cities without substantial industrial emission of arsenic, about 1 µg/day in a non-smoker and more in polluted areas, and up to approximately 10 µg/day in a smoker (WHO, 2000, 2001).

(B)-Occupational exposure-Inhalation of arsenic-containing particulates is the primary route of occupational exposure, but ingestion and dermal exposure may be significant in particular situations (e.g. during preparation of timber treated with chromated copper arsenate). Historically, the greatest occupational exposure to arsenic occurred in the smelting of non-ferrous metal, in which arseniferous ores are commonly used. Other industries or industrial activities where workers are or were exposed to arsenic include: coal-fired power plants, battery assembly, preparation of or work with pressure-treated wood, glass-manufacturing, and the electronics industry. Estimates of the number of workers potentially exposed to arsenic and arsenic compounds have been developed by the NIOSH in the USA and by CAREX in Europe. Based on the National Occupation Exposure Survey (NOES), conducted during 1981–83, NIOSH estimated that 70000 workers, including approximately 16000 female workers, were potentially exposed to arsenic and arsenic compounds in the workplace (NIOSH, 1990). Based on occupational exposure to known and suspected carcinogens collected during 1990–93, the CAREX (CARcinogen EXposure) database estimated that 147569 workers were exposed to arsenic and arsenic compounds in the European Union, with over 50% of workers employed in the non-ferrous base metal industries (*n* = 40426), manufacture of wood and wood and cork products except furniture (*n* = 33959), and construction (*n* = 14740). CAREX Canada estimates that 25000 Canadians are exposed to arsenic in their workplaces (CAREX Canada, 2011). These industries include: sawmills and wood preservation, construction, farms, non-ferrous metal (except aluminium) production and processing, iron and steel mills and ferro-alloy manufacturing, oil and gas extraction, metal ore mining, glass and glass-product manufacturing, semiconductor manufacturing, and basic chemical manufacturing.

(C)-Dietary exposure- Low levels of inorganic and organic arsenic have been measured in most foodstuffs (typical concentrations are less than 0.25 mg/kg). Factors influencing the total concentration of arsenic in food include: food type (e.g. seafood versus meat or dairy), growing conditions (e.g. soil type, water, use of arsenic-containing pesticides), and food-processing techniques. The highest concentrations of arsenic have been found in seafood (2.4–16.7 mg/kg in marine fish, 3.5 mg/kg in mussels, and more than 100 mg/kg in certain crustaceans), followed by meats, cereals, vegetables, fruit, and dairy products. Inorganic arsenic is the predominant form found in meats, poultry, dairy products and cereal, and organic arsenic

(e.g. arsenobetaine) predominates in seafood, fruit, and vegetables (WHO, 2000, 2001). Regional differences are seen in the daily intake of total arsenic through food, and are mainly attributable to variations in the quantity of seafood consumed. For example, the daily dietary intake of total arsenic in Japan is higher than that in Europe and the USA (WHO, 2000). Based on the limited data available, it is estimated that approximately 25% of daily dietary arsenic intake is from inorganic sources. Arsenic intake is typically higher in men than it is in women and children, with estimated levels ranging from 1.3 µg/day for infants under 1 year of age, 4.4 µg/day for 2-year olds, 9.9 µg/day for 25–30-year-old men, 10 µg/day for 60–65-year-old women, and 13 µg/day for 60–65-year-old men (WHO, 2001).

A summary of the findings of epidemiological studies on arsenic in drinking-water and risk for lung cancer are shown in Table 2.6 (water exposures) available at http://monographs.iarc.fr/ENG/Monographs/vol100C/100C-01-Table2.6.pdf, and online Tables 2.1 to 2.4 (air exposures).

EXPOUSRE via IGNETION

A. Ecological studies
B. Case–control and cohort studies

(A) Ecological studies-Ecological studies, based on mortality records, were conducted in the arseniasis endemic area of south-western Taiwan (China) (Chen *et al.*, 1985, 1988a; Wu *et al.*, 1989; Chen & Wang, 1990; Tsai *et al.*, 1999). All studies found elevated risks for lung cancer mortality associated with levels of arsenic in drinking-water, or surrogate measurements. In Chile, Rivara *et al.* (1997) found an elevated relative risk (RR) for mortality from lung cancer in 1976–92 in Region II compared with Region VIII, a low-exposure area. Smith *et al.* (1998) found an elevated standardized mortality ratio (SMR) of approximately 3 for lung cancer for both sexes in Region II, using the national rate as standard. In Cordoba Province, Argentina, significant increases in lung cancer mortality were associated with increasing exposure to arsenic (Hopenhayn-Rich *et al.*, 1998). Smith *et al.* (2006) found an elevated lung cancer mortality (RR, 7.0; 95%CI: 5.4–8.9) among the 30–49-year-old residents of Antofagasta and Mejillones born in the period 1950–57, just before the period of exposure to high arsenic levels (1958–70). They were exposed in early childhood to high levels of arsenic through the drinking-water. The temporal pattern of lung cancer mortality rate ratios in Region II compared with that in Region V (a low-exposure area) from 1950 to 2000, showed an increase about 10 years after the onset of high arsenic exposure, and peaked in 1986–87, with relative risks of 3.61 (95%CI: 3.13–4.16) and 3.26 (95%CI: 2.50–4.23) for men and women, respectively (Marshall *et al.*, 2007).

(B)- Case–control and cohort studies-In northern Chile, a case-control study of 151 cases and 419 controls reported significantly increasing risks with increasing levels of arsenic during the 1958–70 high-exposure period, with an odds ratio increasing to 7.1 (95%CI: 3.4–14.8) (Ferreccio *et al.*, 2000). In a cohort from south-western Taiwan (China), Chen *et al.* (1986) observed a dose–response relationship between the duration of consumption of artesian well-water containing high levels of arsenic and lung cancer mortality risk, showing the highest age- and gender-adjusted odds ratio among those who consumed artesian well-water for more than 40 years compared with those who never consumed artesian well-water. Another cohort study from south-western Taiwan (China) endemic for arsenic found a smoking-adjusted increased risk for lung cancer in relation to increasing average concentrations of arsenic and increasing cumulative exposure to arsenic (Chiou *et al.*, 1995). A further study of combined cohorts in south-western (*n* = 2503) and north-eastern (*n* = 8088) Taiwan (China) found a synergistic interaction between arsenic in drinking-water and cigarette smoking (Chen *et al.*, 2004). A case-control study from Bangladesh, conducted in 2003–06, found an elevated risk (odds ratio [OR], 1.65; 95%CI: 1.25–2.18) for male smokers consuming tube well-water with arsenic levels of 101–400 µg/L (Mostafa *et al.*, 2008). In non-smokers, the study did not report an increased risk with increasing arsenic exposure.

HEALTH IMPACT

A. Cancer of the urinary bladder and of the kidney
B. Genetic and related effects
C. Co-carcinogenic and *in utero* carcinogenic effects

(A)- Cancer of the urinary bladder and of the kidney-The results of the epidemiological studies on arsenic in drinking-water and the risk for cancers of the urinary bladder and of the kidney are in south-western and north-eastern Taiwan (China), the relation between cancer of the urinary bladder and of the kidney and drinking-water containing arsenic was evaluated in many of the studies cited above (Chen *et al.*, 1985, 1988a; Wu *et al.*, 1989; Chen & Wang, 1990; Tsai *et al.*, 1999). Each reported an elevation in mortality from these cancers during various time periods in 1971–94 associated with levels of arsenic in well-water from rural artesian wells, with many reporting a dose–response relationship among both men and women. An additional study, based on incidence records, found comparable risks for bladder cancer (Chiang *et al.*, 1993).In Region II of Chile, two studies found markedly high SMRs for cancer of the urinary bladder and of the kidney in 1950–92 (Rivara *et al.*, 1997) and in 1989–93 (Smith *et al.*, 1998). In the latter study, mortality from chronic obstructive pulmonary disease was at the expected level, suggesting that smoking was not involved. The temporal pattern of bladder cancer mortality in Region II from 1950–2000 was compared with that in Region V (Marshall *et al.*, 2007). Increased relative risks were reported about 10 years after the start of exposure to high arsenic levels, with peak relative risks of 6.10 (95%CI: 3.97–9.39) for men, and 13.8 (95%CI: 7.74–24.5) for women in the period 1986–94. In Cordoba Province, Argentina, positive trends in SMRs were reported for bladder and kidney cancers associated with estimates of exposure to arsenic in drinking-water (Hopenhayn-Rich *et al.*, 1996, 1998), again with no findings for chronic obstructive pulmonary disease.

(B)- Genetic and related effects-Arsenicals do not react directly with DNA, but cells treated with low concentrations of trivalent arsenicals show increased oxidative DNA damage (Wang *et al.*, 2002; Schwerdtle *et al.*, 2003; Shi *et al.*, 2004; Ding *et al.*, 2005; Wang *et al.*, 2007a). As^{III} and MMA^{III} are equally potent inducers of oxidative DNA damage in human urothelial cells, where they are equally toxic (Wang *et al.*, 2007a). Cytotoxic concentrations of trivalent arsenicals also cause DNA strand breaks and/or alkali-labile sites (Kligerman *et al.*, 2003; Klein *et al.*, 2007). In mice, DMA^{V} causes lung-specific DNA damage attributed to the DMA peroxy radical $(CH_3)_2AsOO$ (Yamanaka & Okada, 1994), which can also induce DNA strand breaks and DNA-protein crosslinks in cultured cells (Tezuka *et al.*, 1993). Gallium arsenide and other arsenicals are not mutagenic in the Ames test (NTP, 2000; IARC, 2004). There was no increase in frequency of micronucleated erythrocytes in mice exposed to gallium arsenide by inhalation for 14 weeks (NTP, 2000). Despite the fact that low (non-toxic) concentrations of trivalent arsenicals cause oxidative DNA damage such as 8-hydroxy-2′-deoxyguanosine, which is expected to cause G→T transversions, neither As^{III}, MMA^{III} nor DMA^{III} are significant point mutagens (Rossman, 2003; Klein *et al.*, 2007). This may be due to the efficient removal of oxidative DNA lesions (Fung *et al.*, 2007; Pu *et al.*, 2007b). At toxic concentrations, As^{III} increased large-deletion

mutations in human/hamster hybrid cells through a mechanism mediated by reactive oxygen species (Hei *et al.*, 1998). MMA^{III} and DMA^{III} are weakly mutagenic in mouse lymphoma L5178Y cells, but only at toxic concentrations, and yield mostly deletions (Moore *et al.*, 1997; Kligerman *et al.*, 2003). Using a transgenic cell line that readily detects deletions as well as point mutations, statistically significant mutagenesis was never observed for DMA^{III}, and was only seen for As^{III} or MMA^{III} at toxic concentrations. MMA^{III} yielded a mutant fraction about 4-fold over background at 11% survival, and 79% of these mutants were deletions (Klein *et al.*, 2007). As^{III}, MMA^{III}, and DMA^{III} can induce chromosomal aberrations *in vitro* (Oya-Ohta *et al.*, 1996; Kligerman *et al.*, 2003). Statistically significant increases in chromosomal aberrations occur only at toxic doses (Klein *et al.*, 2007), except as a secondary effect of genomic instability in long-term, low-dose treatment protocols (Sciandrello *et al.*, 2004). An analysis of micronuclei induced by As^{III} in human fibroblasts shows that at lower (relatively non-toxic) doses, As^{III} acts as an aneugen by interfering with spindle function and causing micronuclei with centromeres, but at high (toxic) doses, it acts as a clastogen, inducing micronuclei without centromeres (Yih & Lee, 1999). Aneuploidy is seen after treatment with As^{III} concentrations lower than those that cause chromosomal aberrations (Yih & Lee, 1999; Ochi *et al.*, 2004; Sciandrello *et al.*, 2002, 2004). Aneuploidy associated with disruption of spindle tubulin has been reported in other cells treated with arsenicals (Huang & Lee, 1998; Kligerman & Tennant, 2007; Ramírez *et al.*, 2007). Disrupted mitotic spindles and induced persistent aneuploidy were maintained even 5 days after As^{III} removal (Sciandrello *et al.*, 2002). Humans exposed to high concentrations of inorganic arsenic in drinking-water also show increased micronuclei in lymphocytes, exfoliated bladder epithelial cells and buccal mucosa cells, and sometimes chromosomal aberrations and sister chromatid exchange in whole-blood lymphocyte cultures (Basu *et al.*, 2001). Micronuclei and chromosomal aberrations are also induced in mice after intraperitoneal treatment with As^{III} (IARC, 2004).

(C)-Co-carcinogenic and *in utero* carcinogenic effects-There are several non-genotoxic actions of As^{III} (sometimes demonstrated also for its trivalent metabolites) that may contribute to arsenic-induced carcinogenesis. The effects of As^{III} on preventing blockage of the cell cycle after genotoxic insult by a second agent were discussed above. In addition, low concentrations of As^{III} in the absence of a second agent can also stimulate cell proliferation *in vitro* (Germolec *et al.*, 1997; Trouba *et al.*, 2000; Vogt & Rossman, 2001; Benbrahim-Tallaa *et al.*, 2005b; Komissarova *et al.*, 2005), and *in vivo* (Germolec *et al.*, 1998; Burns *et al.*, 2004; Luster & Simeonova, 2004). The concentration-dependent increase in proliferation of human keratinocytes after 24 hours of treatment with arsenicals followed the potency trend: $DMA^{III} > MMA^{III} > As^{III}$ (Mudipalli *et al.*, 2005). As^{III} upregulates pro-growth proteins such as cyclin D1, c-myc, and E2F-1 (Trouba *et al.*, 2000; Vogt & Rossman, 2001; Ouyang *et al.*, 2007). The increased proliferation in mouse skin by As^{III} alone (in drinking-water) is not sufficient to induce skin cancer (Burns *et al.*, 2004), but may contribute to its co-carcinogenesis with solar ultraviolet. As^{III} was found to block the differentiation of skin cells, resulting in increased numbers of keratinocyte stem cells, the cells that proliferate (Patterson & Rice, 2007; Waalkes *et al.*, 2008). Because tumours may arise from stem cells, this would increase the pool of target cells for cancer of the skin. Another mechanism for arsenic-related carcinogenesis might be acquired resistance to apoptosis. Long-term growth of human skin cells (HaCaT) in the presence of low concentrations of As^{III} resulted in cells with a generalized resistance to apoptosis (Pi *et al.*, 2005). This may allow the survival of cells with DNA damage, thus facilitating tumorigenesis. Even short-term exposure to As^{III} affected the apoptotic response to solar UV in a mouse keratinocyte cell line (Wu *et al.*, 2005) or to UVB in normal human keratinocytes (Chen *et al.*, 2005b). It is possible that the loss of the P53 function partially mediates the reduction in apoptotic response (Chen *et al.*, 2005b). Numerous studies report increased inflammation after As^{III} exposure (NRC, 1999; Straub *et al.*, 2007). The transcription factor NF-κB is involved in the inflammatory response, and As^{III} causes oxidant-dependent activation of NF-κB (Barchowsky *et al.*, 1999). Activation of the NF-κB inflammatory signalling pathway was seen in infants born to As^{III}-exposed mothers in Bangladesh (Fry *et al.*, 2007).

As^{III} can disrupt the signalling of the estrogen receptor, glucocorticoid receptor, and of other steroids *in vivo* and *in vitro* (Benbrahim-Tallaa *et al.*, 2005b, 2007; Liu *et al.*, 2007; Davey *et al.*, 2008). Submicromolar concentrations of As^{III} stimulate the transcription of several steroid receptors, but slightly higher concentrations (1–3 μM) are inhibitory (Bodwell *et al.*, 2006). Exposure of mice *in utero* to As^{III} in a protocol leading to hepatocarcinogenesis resulted in altered expression of numerous genes involved in estrogen signalling or steroid metabolism, as well as hypomethylation of estrogen receptor α (Liu & Waalkes, 2008).

Angiogenesis, which provides a blood supply to developing tumours, is stimulated by very low concentrations of As^{III} (Mousa *et al.*, 2007; Straub *et al.*, 2007). This activity can be blocked by selenium compounds (Mousa *et al.*, 2007), which also blocks As^{III}-induced co-carcinogenesis with UV and delays mutagenesis (Uddin *et al.*, 2005). Many of these effects depend on altered gene expression that can result from genetic and epigenetic effects discussed above. Changes in gene expression by As^{III} can also be mediated by the alteration of miRNA patterns (Marsit *et al.*, 2006). Some short-term changes in gene expression (e.g. changes in the expression of DNA-repair proteins or DNA methyltransferases) can result in long-term changes. Genome-wide changes in gene expression and signal transduction induced by arsenicals have been reported in several publications (Su *et al.*, 2006; Kumagai & Sumi, 2007; Ghosh *et al.*, 2008).

CONTROL AND REMEDIATION STRATEGIES

Arsenic contamination in groundwater can be effectively controlled and remediated through integrated scientific, technological, and policy-based approaches. Preventive strategies include continuous monitoring of aquifer quality, regulation of excessive groundwater extraction, and minimizing anthropogenic sources such as industrial effluents, mining activities, and arsenic-based agrochemicals. Sustainable alternatives like rainwater harvesting, artificial recharge, and the utilization of treated surface water can significantly reduce dependency on contaminated aquifers. Remediation techniques primarily involve advanced arsenic removal methods such as adsorption using activated alumina and iron-oxide media, coagulation-flocculation, ion exchange, membrane filtration, and reverse osmosis. In addition, innovative approaches including bioremediation with arsenic-transforming microorganisms and phytoremediation using hyperaccumulator plants have shown promising environmental benefits. Effective implementation of public health awareness programs, strict environmental regulations, and community-based water management systems is crucial for mitigating arsenic mobility pathways and ensuring the long-term sustainability of safe groundwater resources.

SUMMARY

Much of the behavior of arsenic in the environment is determined by what it bonds to in different abiotic and biotic compartments. In

oxidized settings, the stronger elec tronegativity of oxygen shifts arsenic to a more cationic state and stabilizes the As3+ and As5+ oxo-anion groups that form the basis of the major arsenic oxide mineral classes, aqueous species, and adsorbed complexes. The stability of As–S and As–As dimeric units in reduced conditions, a con sequence of the similar electronegativity of these elements and strong covalent bonding, comprises the structural basis for the generation of a variety of sulfide and arsenide min erals and synthetic compounds. The biomethylation of arsenic by living organisms dominates its organic chemistry in the environment, and its chemical similarities to nitro gen and phosphorus help explain the diversity of natural and synthetic organic compounds. Perhaps increased understanding of the subtleties of bonding and rates of exchange between arsenic and its ligands in cells and bio logical fluids will further elucidate mechanisms associated with both the detrimental and beneficial effects of arsenic on living systems.

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