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Arsenic Exposure in Latin America: Biomarkers, Risk Assessments and Related Health Effects

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Abstract

In Latin America, several regions have a long history of widespread arsenic (As) contamination from both natural and anthropological sources. Yet, relatively little is known about the extent of As exposure from drinking water and its related health consequences in these countries. It has been estimated that at least 4.5 million people in Latin America are chronically exposed to high levels of As (>50μg/L), some to as high as 2000 μg/L - 200 times higher than the World Health Organization (WHO) provisional standard for drinking water. We conducted a systematic review of 82 peer reviewed papers and reports to fully explore the current understanding of As exposure and its health effects, as well as the influence of genetic factors that modulate those effects in the populations of Latin America. Despite some methodological limitations, these studies suggested important links between high levels of chronic As exposure and elevated risks of numerous adverse health outcomes in Latin America - including internal and external cancers, reproductive outcomes, and childhood cognitive function. Several studies demonstrated genetic polymorphisms

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that influence susceptibility to these and other disease states through their modulation of As metabolism, with As methyltransferase (*AS3MT*), glutathione S-transferase (*GST*), and genes of one-carbon metabolism being specifically implicated. While the full extent and nature of the health burden are yet to be known in Latin America, these studies have significantly enriched knowledge of As toxicity and led to subsequent research. Targeted future studies will not only yield a better understanding of the public health impact of As in Latin America populations, but also allow for effective and timely mitigation efforts.

Keywords

Arsenic; water; Latin America; exposure; health; cancer; bladder; lung

1. Introduction

Arsenic (As) exposure has likely been a longstanding problem in Latin America, with mummified bodies in Chile showing signs of As exposure from as long as 7000 years ago (Arriaza et al., 2010). In many Latin American countries, soil and groundwater are highly enriched with As due to its high density in the region's abundant volcanic rock and ash. In some countries, mining operations and copper foundries have unearthed As and enhanced its release into groundwater sources for the past few centuries (Ng et al., 2003). Common features of geography and contamination allow Latin America to be classified into three distinct regions: the Chaco-Pampean plain, Andean range, and Central America. While each of these areas has their own defining characteristics, they share the common burden of having been affected by inorganic As transport into drinking water. High concentrations of As have been found in all sources of drinking water in Latin America, including lake, spring, river and ground water (Castro de Esparza, 2009a; Concha et al., 2010). Though this widespread contamination from both natural and anthropological sources has long been a threat to human health in Latin America, relatively little is known about occurrence, distribution, and exposed populations in countries other than Argentina, Brazil, Chile, and Mexico. Only recently has data begun to emerge from such Central American countries as Nicaragua and El Salvador (Cuevas and Bundschuh, 2010). Despite this relative lack of detailed exposure data, it is estimated that at least 4.5 million people in Latin America are currently drinking As contaminated water (>50μg/L), with some recorded levels as high as 2000 μg/L - roughly 200 times higher than the current World Health Organization (WHO) standard (10μg/L) for drinking water (Farías et al., 2008; WHO, 2003).

Arsenic in drinking water causes a number of adverse health effects, including skin lesions that often appear relatively soon after exposure (within 5–15 years of exposure). Long term As exposure damages several internal organs and has been linked to bladder, lung, and skin cancers. Though evidence of As-related disease in Latin America was first described in the 1920s (Goyenechea, 1917), more systematically gathered data on adverse health effects did not emerge until the mid 1970s. In the mid 1970s, elevated mortality and incidence of respiratory disease from As exposure were observed in the endemic areas of Chile (Borgoño et al., 1977; Rosenberg, 1974; Zaldivar, 1980; Zaldivar and Ghai, 1980). Since the 1990s, research from Chile, Argentina and Mexico has demonstrated malignant and non-malignant effects of As exposure. Though much of the findings were based on retrospective case-control or ecological studies that lacked individual exposure data, consistent association was found between high As concentration and the risk of lung and bladder cancer (Hopenhayn-Rich et al., 1996a; Smith et al., 2006). Recent epidemiologic investigations have found a long latency period for lung cancer and other As-related chronic diseases, even when exposure was limited to a discrete period either during early childhood or *in utero* (Smith et al., 2006). Exposure during these times has also been implicated in adverse reproductive

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outcomes in mothers and impaired cognitive development in children (Hopenhayn-Rich et al., 2000; Hopenhayn et al., 2003a). Recent studies have examined the possible mechanisms of toxicity that bring about these adverse health outcomes, including genotoxicity, oxidative stress, and impaired DNA repair (Dulout et al., 1996; Engstrom et al., 2007; Engstrom et al., 2009; Engstrom et al., 2010).

A number of studies in Latin America have not only helped to establish the link between As exposure and these health outcomes, but also explored the underlying exposure-disease mechanisms and individual susceptibility. Research in Argentina has focused mainly on bladder cancer, describing increased risks and, more recently, exploring how it could be related to susceptibility markers such as Transforming Growth Factor-α (TGF-α) (Valenzuela et al., 2007), polymorphic influences on metabolism (Moore et al., 2004), and exposure-induced chromosomal aberrations (Moore et al., 2002). South American studies related to lung cancer have taken place largely in Chile, reporting an increase in disease risk from discrete childhood exposure (Smith et al., 2006) and exploring the effect of genetic polymorphisms (Steinmaus et al., 2006). Mexico has been a focus for research on As-related skin disease (Valenzuela et al., 2007), including studies on influence of metabolism (Loffredo et al., 2003), DNA damage (Engstrom et al., 2010), and genetic polymorphisms (Sampayo-Reyes et al., 2010).

In addition to drinking water, food is another source of As in Latin American countries. A few studies from As endemic areas in Latin America have indicated that food contributes up to 50% of total As intake (Del Razo et al., 2002; Diaz et al., 2004; Navoni JA et al., 2007; Queirolo et al., 2000). High amount of As has been detected in fish, cow milk, grains and vegetables including potato, onion, beet, pumpkin, radish, cabbage and beans in Bolivia, Brazil, Chile, Ecuador, El Salvador, Honduras, Mexico, Nicaragua and Peru. Cow milk from Argentina and Mexico are shown to have As (Sigrist et al., 2010). At lest two studies from Chile and Brazil have found high amount of As in different species of fish that exceeds FAO/WHO recommended value and current guideline set by Brazil (Lavanchy Dougnac, 1999) (Macedo, 2010). Food preparation with As contaminated water has also found to increase As content in cooked food (Ackerman et al., 2005; Munoz et al., 2002; Navoni JA et al., 2007; Vélez et al., 1997). In order to reduce risk of As exposure and accurately assess As exposure, As contamination from food needs to be given more attention. Please see the paper on As contamination from food in Latin American counties in this issue of the journal (Bundschuh et al., 2011, paper 8). This paper will first describe the historical and current occurrence of As exposure throughout Latin America. That will lead to a review of studies on how As is metabolized in the human body and the various biological markers that exist to measure exposure and metabolism. Based on our review of 82 peer reviewed papers and reports, we then describe specific health outcomes in Latin America, noting the work that has been done to establish general causality, as well as efforts that have been made to understand how these specific diseases are induced. There will be a separate description of studies that investigates general biochemical changes in disease induction, including any modifying effects of genetic variations and biomarkers. This paper closes by placing all prior work in perspective and using it as a context for discussing the future direction of As research in Latin America.

2. Methods

We have conducted an extensive electronic database search from Europe and United States for peer reviewed papers published on As and health related topics from Latin American countries. The following electronic databases have been used for the literature review of this paper: PubMed (1949-July 2010), TOXLINE (1965-July 2010), Biological Abstracts (1969 to July 2010), the Cochrane Library (through July 2010), LILACS (through July 2010),

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SCOPUS (through July 2010), Cumulative Index of Nursing and Allied Health Literature (CINAHL) (1981-July 2010), Electronic Library Online (SciELO) and Secretary of Environment of Argentina (SADS) databases. Each database was systematically searched using the following terms (matching terms in title or abstract fields, if available, or otherwise in "all fields" or similar): 'arsenic' and 'name of the country'(i.e., Argentina, Bolivia, Brazil, Chile, Colombia, Ecuador, Guyana, Paraguay, Peru, Suriname, Uruguay, Venezuela, Guatemala, Honduras, Nicaragua , Panama, Mexico, El Salvador, Costa Rica, French Guiana, Latin America, South America, or Central America). When the results from a particular database included many items unrelated to health effects, additional terms were added (with AND) to narrow search results. These terms were 'health effect,' 'cancer,' 'lung disease,' 'cardiovascular disease,' 'biomarker,' or 'metabolites.' Since the initial search strategy retrieved any item that included the term 'arsenic,' these added terms helped improve the proportion of relevant articles in our search result sets.

Where appropriate—i.e., in PubMed and CINAHL—the searches also included controlled vocabulary terms from PubMed's Medical Subject Headings (MeSH)(i.e., Arsenic Poisoning, South America, Latin America, Central America and CINAHL Headings (Latin America, South America, Central America, or Mexico). We reviewed the titles and abstracts of all identified materials to judge relevance to the topic. For all possibly relevant items, we collected citations and retrieved full text for all the studies where full text was available. Relevance was assessed in terms of whether each study was original research, focused on Latin American human populations, involved with drinking water As exposure, and related to either health outcomes, disease processes, or biomarkers. Of the 1,651 items reviewed (964 unique items), we eventually included 58 reports in this review. An additional 24 reports were added to the review based on authors' knowledge of relevant materials. A total of 82 peer reviewed and published articles either in meeting proceedings or in the format of published articles (indexed) have been included in this review.

3. History, occurrence, distribution and exposed population to arsenic from drinking water in Latin American countries

An estimated four and a half million people in Latin American countries are chronically exposed to high levels of As in drinking water, based on the 50 μg/L value which is still the regulatory limit in many of the Latin American countries (Castro de Esparza, 2009a). In some parts of Latin America, a vast majority of wells (>80%) exceed the World Health Organization (WHO) recommending safe limit for drinking water As (10 μg/L) (Nicolli et al., 1989). This widespread contamination is due primarily to release of As from volcanic rocks and their sediments into drinking and irrigation water, a process that is expedited by gold and silver mining activities. To a lesser extent, As-based pesticides and wood preservation agents also contribute to Latin America's water contamination (Bhattacharya et al., 2006; Bundschuh et al., 2004). Anthropogenic sources of As contamination are of concern in certain countries, including that from the mining and electric reefing industries in Brazil and As-containing pesticides in Mexico (Castro de Esparza, 2009a; Matschullat et al., 2007; Matschullat et al., 2000).

Extremely high As levels have been detected in nearly all possible drinking water sources of many Latin American countries (Argentina, Bolivia, Brazil, Chile, Colombia, Cuba, Ecuador, El Salvador, Guatemala, Honduras, Mexico, Nicaragua, Peru, and Uruguay), seriously minimizing safe water options while increasing the number of people at risk of As exposure. Though high levels of As in drinking water were detected a few centuries ago, very little information on human exposure is available from the majority of these countries.

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Occurrence and distribution of As in Latin America can be clustered according to three geological or geographical regions, as follows (Bundschuh et al., 2010b):

Andes and Chaco-Pampean Plains: *Argentina, Chile and Uruguay, Bolivia, Peru, Colombia, and Ecuador*

In Argentina, about 4 million people are exposed to high levels of As from drinking water (based on the 10 μg/L limit), the largest known As-exposed population in Latin America. Though due mostly to volcanic ash, As-containing pesticides also contribute to the problem (Castro de Esparza, 2009a). In Argentina, elevated levels of As have been detected in the Chaco-Pampean Plains and Cuyo regions of the Andes, located in the central and northwestern and parts of the country, respectively.

High levels of As in drinking water (>1000 μg/L) have been identified in central Argentina, with a high proportion of contaminated wells. For instance, the Córdoba province in the Chaco-Pampean Plain of central Argentina is one of the largest regions with high As (Perez-Carrera and Fernandez-Cirelli, 2005). In the Tucuman province, departments of Leales and Graneros, As concentration in well waters were found to be between 10 and 968 μg/L (Guber et al., 2009). A report published a few decades ago showed that over 82% of water samples exceeded WHO drinking water standard (l0 μg/L) in the Chaco-Pampean region (Nicolli et al., 1989). Another recent study from the south west part of the Pampean Plain identified more than half of the ground water samples as having As levels higher than 50 μg/L, ranging between 60 and 500 μg/L (Paoloni et al., 2005). In La Pampa province, in the central part of Argentina within the Chaco-Pampean Plain, As levels varied from 4 to 5300 μg/L (Smedley et al., 2002) and a recent study observed a range between 3 and 1326 μg/L (O'Reilly et al., 2010). The survey identified a disproportionately large number of water sources with high level of As in rural areas.

Some reports from the Puna area of the Argentinean Andes bordering Chile demonstrated a prevalence of As exposure in different sources of drinking water, and an increased concentration over time. Water As distribution data from the Puna area reports that 61% of the 46 well water contained As more than l0μg/L with a highest concentration of 2,000 μg/L (Farías et al., 2008). A recent survey in 6 different villages in the Puna region found elevated levels of As in tap water, with a range between 3.5 and 220 μg/L (Concha et al., 2010). The study also found that people were drinking spring water with high levels of As (322 μg/L). The river water in Puna area also contains high levels of As (1,000 μg/L). In addition, extremely high levels of As were detected in the Pompeya Hot Spring (10,000 μg/L) that releases As into the river (Concha et al., 2010). Interestingly, significant fluctuation was observed in As levels (from 140 to 220 μg/L) over a 10-year period in the same source in San Antonio de los Cobres of Puna area (Concha et al., 2006). Recent data in the San Juan province of the Cuyo region showed As concentration ranging between 9 and 357 μg/L (O'Reilly et al., 2010).

In Chile, high levels of As were detected in Region II in the northern part the country. People in Antofagasta in Region II were exposed to high As (90–860 μg/L) in their drinking water between 1955 and 1978, with the peak concentration in 1958 (Ferreccio and Sancha, 2006). However, the exposure gradually decreased from 110 μg/L to 40 μg/L from 1970 to 1979 when the first and the second water purifying pumps were intalled in Antofagasta and Calama respectively. Since 2003, As levels have further dropped to 10 μg/L in northern Chile. People from two other cities of northern Chile, Tocopilla and Calama also consumed high As in their driking water between 1958 and 1970 (250 and 150 μg/L, respectively). It is estimated that 400,000 people were exposed to arsenic from these cities during that time period (Ferreccio and Sancha, 2006), and it is currently estimated that 1.8 millon people live in arsenic endemic areas in Chile (Sancha and O'Ryan, 2008). Though the problem of As

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exposure has been addressed in Antofagasta, there are still towns, villages, and isolated households suffering from contaminated water supplies, affecting several thousand people in rural areas of northern Chile, who are drinking As-contaminated water or using it for animal husbandry.

Limited information is available on the As contamination from Uruguay, Bolivia and Peru. Because the Chaco-Pampean plain covering large part of Argentina extends into Uruguay in the aquifer sediments of this country also volcanic ash as primary As source is found. One recent survey has detected As in groundwater in the south of San José in Uruguay an average As concentration between 25 and 50 μg/L in 22 ground water samples and some had more than 50 μg/L (Bundschuh et al., 2008).

In Bolivia, both natural and industrial activities have contributed to high As in ground water. The central and southern parts of Bolivia's Andean highland have high As in water and soil. In Poopó, basin surface water samples from local rivers and from the Poopó lake contained water As ranges between 90 to 140 μg/L, while ground water contained between 10 to 90 μg/L with a seasonal differences in As concentration in the lake water (Bundschuh et al., 2008). A survey from the Rio Pilcomayo region of Bolivia found high levels of As in drinking water (0.2–112 ug/L), irrigation water (0.6–329 ug/L) and very high in river water (0.9–12,805 ug/L), the last range corresponding to sites where mine drainage flows into surface water . Most of the drinking water in the region exceeded the WHO standard for As in drinking water (Archer et al., 2005).

Rocks of the Yucamane volcano area appear to be the main source of As in Peru. The Callazas and the Salado rivers pass though the Yucamane volcano and lift As in river water as high as 640 and 1680 μg/L, respectively (Castro de Esparza, 2009b). Recent studies show the presence of As in groundwater around Puno area and in the departments of Tacna and Moquegua (Castro de Esparza, 2009b).

An estimated 500,000 people in rural Ecuador have been exposed to As from water and food. High levels of As (>10 μg/L) have been been detected in the drinking water of Tumbaco, Guayllabamba, Cumbaya, Yaruqui, El Quinche, Pifo y Puembo, and Pichincha province. Geothermal waters from El Carchi, Imbabura, Pichincha, Cotopaxi, and Tungurahua Provinces show As levels from 113 to 844 μg/L (Bundschuh et al., 2008). El Angel river in the Carchi Province receives thermal waters and shows As in the range of 64 to 113 μg/L (Bundschuh et al., 2008). In the central part of the Andean region, natural As is present in Papallacta Lake. This lagoon is fed by the Tambo river and geothermal residual waters, and shows As concentrations that vary from 104 to 360 μg/L (Bundschuh et al., 2008).

Central America: *Nicaragua, El Salvador and Costa Rica*

In Nicaragua, high levels of As have been identified in ground water (up to 1320 μg/L) in El Zapote and Llano La Tejera (Bundschuh et al., 2008). Between 2002 and 2005, a number of surveys by UNICEF reported a range of As concentrations, from below detection limit to 1320 μg/L in well water of the Llano La Tejera community (Cuevas and Bundschuh, 2010). A survey in 2005 found 87% of the 54 wells had higher As more than 10 μg/L (Cuevas and Bundschuh, 2010). Another survey detected that 36% of 57 groundwater samples had As concentrations more than 10 μg/L, with a range between 10 and 122 μg/L. In addition to these two communities, As in ground water has been detected in several more areas of western Nicaragua (Bundschuh et al., 2010b).

Very little is known about As exposure in El Salvador and Costa Rica. Lake sediment from As-rich volcanic deposits and water in El Salvador both contain high levels of As. Ilopango,

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Coatepeque, and Olomega lake waters in El Salvador all have high As. Arsenic concentrations between 150 and 770 μg/L make this water unsuitable for human consumption (Bundschuh et al., 2008). It is estimated that at least 300,000 people in El Salvador mainly from Ilopango area, may be exposed to high As. Varying amounts of As have been detected in spring water of northwestern Costa Rica, that ranging from 5 μg/L to 11,000 μg/L (Bundschuh et al., 2010a) though drinking water resources seem not be affected.

Arsenic exposure in Brazil and Mexico

Gold and copper mining have contributed to high levels of As in Brazil for over hundreds of years (Matschullat et al., 2007; Matschullat et al., 2000). Very high levels of As have been detected in the soil (50–1000 mg/kg) from the Iron Quardrangle area of the southeastern part of Brazil, where gold and other mining activities have been operating over 250 years (Matschullat et al., 2007). Water from the mining districts Nova Lima and Santa Barbara contain As as high as 350 μg/L (Matschullat et al., 2007).

In Mexico, As is present in the Transmexican Volcanic Belt where As-rich soil-contaminated ground water and As-based pesticides are used. High levels of As in drinking water Mexico was first identified in 1958. Since then, >50 μg/L As had been detected in the other areas in Mexico, including Durango, Coahuila, Zacatecas, Morelos, Agues, Calientes, Chihuahua, Puebla, Nuevo Leon, Guanajuato, Jalisco, Oaxaca, and San Luis Potosi (Armienta and Segovia, 2008) representing 13 out of 31 Mexican states (Bundschuh et al. 2011, this issue). A study in the region of Lagunera found 64% of the wells to have As concentrations higher than 50 μg/L, with a range of 8–624 μg/L (Del Razo et al. 1993). Ground water in the Zimapan and Guanajuato areas contained As between 190 and 650 μg/L (average 380 μg/L) and 280 μg/L (Armienta and Segovia, 2008). As concentrations ranging from 15 to 102 μg/L were seen in a 2002–2003 survey in the Los Altos de Jalisco (LAJ) region of west-central Mexico that included 129 public water systems from 17 municipal capitals. The highest As concentration found in well water samples was 263 μg/L, and high levels of As were detected in Teocaltiche (157 μg/L) and San Juan de los Lagos (113 μg/L) cities of Mexico. Moreover, the mean concentrations in all 17 cities were higher than the World Health Organization guideline value of l0 μg/L of As (Hurtado-Jimenez and Gardea-Torresdey, 2006).

4. Biological markers of arsenic exposure, metabolism, toxicity, and susceptibility

4.1. Biomarkers of Arsenic Exposure

Several biomarkers have been used to assess As exposure in Latin America, namely blood, hair, nail, and urinary As levels. Though As from short-term exposure can be cleared from the bloodstream relatively quickly, blood arsenic (AsB) levels have been proposed as a marker of chronic exposure. AsB levels were used in Latin America in a 1995 study that involved 30 native young women exposed to a variable level of exposure (As in drinking water 2.5–200 μg/L) (Vahter et al., 1995). A wide range of AsB was observed (1.0 to 18.3 μg/L), but the only significant increases of this marker were in those samples that came from the region of the highest exposure As in drinking water (>200 μg/L), with a median AsB of 7.6 μg/L. Samples from regions of lower concentration (As in drinking water from 2.5 to 43.4 μg/L) did not show a proportional increase in AsB level (1.5 μg/L), suggesting that at low levels of exposure this indicator may lack enough sensitivity for exposure assessment (Vahter et al., 1995). High levels of As in hair (range 37–2110 μg/kg, mean ranged from 119 to 617 μg/kg) and in urine (range 11–891 μg/L, and mean ranged from 23 to 64 μg/L) were observed among about 33 study participants in two time points from the four different As-

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exposed to communities. However, the study failed to observe an association between hair and urinary As (Archer et al., 2005).

Because of the sulfhydryl groups in the keratin that comprises hair and nails, As is therefore drawn to these parts of the body more exclusively. As these tissues grow slowly, they can be used as indicators of long-term exposure. In Argentina, hair samples from an area of high As exposure averaged 4.2 μg As/g (range: 0.4 to 20.0 μg/g) compared to the non-exposed population, whose hair As levels ranged from 0.09 to 0.28 μg/g (Astolfi et al., 1982). All the study participants from the exposed area had hair As levels over 1 μg/g (toxicological value considered). Repeating the experiment six years after installation of a treatment plant, the percentage of people with arsenic in hair over 1 μg/g fell to 40% (Borgoño et al., 1977). Such responsiveness to changes in drinking water As suggests that hair could be used as a dependable indicator of exposure.

A pair of studies from Chile illustrated the use of As in fingernails as a marker of exposure (Martinez et al., 2004; Martinez et al., 2005). The population for these studies included 106 individuals from Antofagasta (As in water 3.34 to 1087 μg/L) and 111 from an unexposed area in the southern region (As in water 0.2 μg/L). Though the average level of As in fingernails for the exposed region was proportional to the increase of As in drinking water (2.58 to 18.33 μg/g), those exposed to lower levels of As in drinking water, and the control population, also showed a high level of exposure through this biomarker (3.57μg/g), compared with values from other non endemics arsenicism regions (IPCS, 2001). This was likely due to exposure from other sources of water or contact with As-contaminated soil or dust (Díaz-Barriga et al., 1993).

Urinary As has been used as a maker for As exposure in epidemiological studies throughout Latin America (Astolfi et al., 1982; Biggs et al., 1997; Calderon et al., 2001; Díaz-Barriga et al., 1993; Gonsebatt et al., 1997; Hernández-Zavala et al., 1998; Moore et al., 1997; Navoni et al., 2006; Navoni et al., 2009; Navoni et al., 2010; Pineda-Zavaleta et al., 2004; Yanez et al., 2003). With chronic exposure, urinary As reaches a steady-state level and correlates well with drinking water As concentration. Coupled with the relative ease of non-invasive collection, this makes urinary As a convenient measure of exposure in many settings. The highest urinary As level in Latin America has been recorded in Argentina, at roughly 4000 μg/g creatinine (Navoni et al., 2006). Other reports indicate high urinary As in Chile (2145 μg/L) and Mexico (2058 μg/L) (Biggs et al., 1997; Hernández-Zavala et al., 1998). The degree of exposure is comparable to levels found in other parts of the world (Basu et al., 2005; Samanta et al., 1999) and far exceeds the safe levels (ACGIH, 2009; WHO, 1989). While urinary arsenic does correlate well with the main source of exposure (drinking water), it may be considered as a better metric than water As concentration to assess total exposure in populations where water is not the only path of exposure. This is illustrated by a study of 135 children (aged 3–6 years) from a Mexican mining region, who had also been significantly exposed to As in soil and dust. While urinary As was elevated (69–594 μg/g creatinine), this exposure would have been underestimated if risk had been assessed using the concentration of As in drinking water alone (1.7 to 17.5 μg/L) (Díaz-Barriga et al., 1993).

4.2. Individual Variability in Urinary Arsenic Metabolites Profile

Essential to any discussion of As human toxicity is an understanding of the way in which it is methylated or metabolized, through a series of reduction and oxidative methylation reactions. After entering the bloodstream, inorganic As (InAs) is reduced from arsenate (As^{v}) to arsenite (As^{III}) before being transported to the liver. Once within hepatocytes, arsenite (+III) methyltransferase (AS3MT) facilitates conversion to methylarsonic acid (MMA^{V}). Subsequent reduction produces methylarsonous acid (MMA^{III}), which undergoes

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oxidative methylation to form the dimethylarsinic acid (DMA^V) that is further reduced to dimethylarsinous acid (DMA^{III}) (Loffredo et al., 2003). Because methyl groups needed for these reactions are donated by the S-adenosyl methionine (SAM), which is produced via one-carbon metabolism, activity of this key biochemical pathway is inexorably tied to the balance of As metabolites in the body at any given time (Engstrom et al., 2009).

Much of the susceptibility to As-related health effects is determined by the large interindividual variation observed in As methylation (Loffredo et al., 2003). Of the metabolites, trivalent forms (particularly MMA^{III}) are most associated with adverse health outcomes. With DMA showing the lowest retention and constituting the largest portion of metabolites in urine (60–80%), the excreted proportion of MMA and the ratio of MMA to DMA are likely an accurate reflection of harmful metabolites being retained in body tissue (Del Razo et al., 1997; Vahter et al., 2000). The distributions of urinary As metabolites are determined in large part by genetic variations and is illustrated by the aggregation of methylation patterns within families, as well as the fact that only 30% of metabolic differences (as measured by MMA:DMA) can be explained by factors such as exposure level, smoking status, and gender (Chung et al., 2002; Hopenhayn-Rich et al., 1996b; Hopenhayn-Rich et al., 1996c).

A number of studies from Latin America found that people with skin lesions and high As exposure are likely to have reduced As methylation capacity with high trivalent species MMA in urine (Del Razo et al., 1997; Valenzuela et al., 2005; Valenzuela et al., 2007). Important factors that influence urinary As metabolites include age, smoking, ethnicity, levels of As exposure, and genetic polymorphisms and others (Concha et al., 1998b; Hopenhayn-Rich et al., 1996b; Valenzuela et al., 2007)

4.3. Arsenic-induced genotoxicity, oxidative stress and DNA damage

Arsenic is believed to have a broad array of detrimental effects that contribute to the development of acute and chronic disease states, including genotoxicity, oxidative stress, and altered DNA repair capacity Several studies in Latin America have shown that chromosomal aberrations were more frequent in a Mexican population with high exposure (0.39 mg/L of As in drinking water) compared to those with low exposure (0.019–0.026 mg/L) (Ostrosky-Wegman et al., 1991). Similarly, a significant elevation ($P < 0.001$) in sister chromatid exchange was found in individuals in Argentina whose drinking water contained 0.13 mg/L of As (Lerda, 1994). Genotoxic effects were also observed through evaluation of micronucleus induction in cases of both environmental and occupational exposure in studies from Chile (Martinez et al., 2004; Paiva et al., 2008). Potentially as a result of As-induced DNA damage, levels of tumor suppressor protein p53 were elevated in high-exposure individuals (Salazar et al., 2004). Enhancing any genotoxicity of As would be the impairment of DNA repair capabilities that was observed by Andrew *et al*. in Mexico (Andrew et al., 2006).

Indicators of As-related DNA damage have been studied specifically with respect to the bladder, with initial work characterizing micronuclei in exfoliated cells. Created when parts of the nucleus do not properly migrate during telophase, micronuclei can be used as markers of chromosomal damage. In a population of 125 Chilean males exposed to high and low water As (600 and 15 μg/L), a dose-dependent relationship was found between urinary As levels and micronuclei as As levels increased from 4 to 728.9 μg/L ($p < 0.001$) (Moore et al., 1997). A significant reduction on bladder micronuclei ($p < 0.05$) was observed after 8 weeks of follow-up in an intervention study among a sub-sample of participants in the high exposed group with provision of a drinking water source of lower As content (from 600 μg/L to 45 μg/L). The most significant decline was observed among individuals with previously had urinary As (<700 μg/L) and smokers ($p = 0.002$) (Moore et al., 1997). A 2002 study

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followed these results and described how As exposure affects the genomic stability of bladder tumors, finding a correlation between chromosomal alterations per tumor and As exposure ($p<0.05$). Exposure was, in particular, associated with deletions in chromosome 17p (Moore et al., 2002). A potential early indicator of these bladder tumors was described in a Mexican study of transforming growth factor alpha (TGF-α) concentration in bladder urothelial cells (BUC). TGF-α is a protein that is upregulated in some cancers; hence, high expression in BUC can be used as a marker for early stages of tumor development. It was shown that those in high-exposure areas (mean = 120 μg As/L) had significantly higher TGF-α when compared to individuals with lower exposure ($p<0.05$) (Valenzuela et al., 2007), indicating that TGF-α in BUC could be used as an early indicator of susceptibility to bladder cancer in As-exposed populations.

4.4. Genetic susceptibility to arsenic-related adverse health outcomes

Because As-related health effects are greatly influenced by As metabolism, it is useful to identify genetic variations that dictate the efficiency of this process. Individuals in a genetically favorable position that can better methylate As completely are those with a higher excreted DMA/MMA ratio – achieved either through a high %DMA, a low %MMA, or both. To date, variations in the gene for As (+III) methyltransferase (*AS3MT*) have been shown to be the most influential in the balance of urinary metabolites. Engström *et al*. (2007) identified three variant alleles (G12390C, C14215T, A359916) associated with a low %MMA and a high %DMA ($p < 0.001$), leading to a higher ratio for the second methylation step that converts MMA to DMA (Engstrom et al., 2007). Another study also observed that increased DMA/MMA ratio with *AS3MT* variants was most attributable to low %MMA (Meza et al., 2007). Two single nucleotide polymorphisms (SNPs) (rs3740400, rs7085104) were found to be in strong linkage disequilibrium (LD) with the three aforementioned SNPs. They were similarly associated with a SNP (rs743572) located near the gene *CYP17A1*, 27 kbs upstream of *AS3MT* (Engstrom et al., 2009). Taken together, these results indicate the presence of a large haplotype block (pairwise LD analysis $r^2 = 0.82$) (at least 63 kbs in size, on chromosome 10) that can have a profound effect on health outcomes by altering the methylation of As (Gomez-Rubio et al., 2010). Sampayo-Reyes *et al*. emphasized the impact of variations in this block as carriers of the 287Thr allele were observed to have increased genetic damage, presumably as a result of the increase in MMA (Sampayo-Reyes et al., 2010).

In the biotransformation of electrophilic and hydrophilic xenobiotics, glutathione *S*-transerase (GST) phase II enzymes play a crucial role by catalyzing their conjugation with reduced glutathione (Seidegard and Ekstrom, 1997). In Latin America, four different members of this family have been analyzed for effects of SNPs on As metabolism (*GSTM1*, *GSTO1*, *GSTP1*, *GSTT1*). Three years after it was shown that SNPs in *GSTO1* could account for some of the interindividual metabolic variation (Marnell et al., 2003), the *GSTM1* null polymorphism was found to be associated with a high %MMA ($P = 0.083$) while the *GSTP1* val/val polymorphism was related to a low %DMA ($P = 0.085$) (Marcos et al., 2006). Subsequent studies confirmed these results and additionally noted the effect of *GSTT1* polymorphisms on %MMA and %DMA (Engstrom et al., 2007; Steinmaus et al., 2007). Metabolic effects were also observed in certain *GSTO1* SNPs (Alal40Asp, Glul55del, Glu208Lys, Ala236Val) (Paiva et al., 2008; Sampayo-Reyes et al., 2010).

Noting the significant interplay between As biotransformation and one-carbon metabolism, SNPs involved in this pathway have recently been explored. This includes those in genes for 5,10-methylenetetrahydrofolate reductase (*MTHFR*), 5-methyltetrahydrofolate-homocysteine methyltransferase (*MTR*), choline dehydrogenase (*CHDH*), and 5-methyltetrahydrofolate-homocysteine methyltransferase reductase (*MTRR*). Because the

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MTHFR 222Val allele had previously been associated with lower enzymatic activity and higher plasma homocysteine levels, it was not surprising to find variant *MTHFR* alleles associated with lower DMA/MMA ratios (Engstrom et al., 2007; Steinmaus et al., 2007). Similar results were observed with respect to *MTR* and, to a lesser degree, both *CHDH* and *MTRR* (Engstrom et al., 2007; Engstrom et al., 2009).

With reductive processes also crucial to As metabolism, the genes for glutaredoxin-1 (*GLRX*) and peroxiredoxin-2 (*PRDX2*) were both studied, finding a small impact on metabolite balance (Engstrom et al., 2009). A follow-up study evaluated oxidative DNA damage, as indicated by cellular levels of 8-Oxo-2'-deoxyguanosine (8-oxo-dG). This was shown to correlate positively with %MMA, with an influence seen when measured with respect to variations in APEX nuclease 1 (*APEX1*, a DNA repair enzyme), DNA (cytosine-5)-methyltransferase 1 and 3B (*DNMT1* and *DNMT3B*, DNA methyltransferases), Thioredoxin reductase 1 and 2 (*TXNRD1* and *TXNRD2*, thioredoxin reducers) and Glutaredoxin-1 (*GLRX*, involved in GSH redox reactions) (Engstrom et al., 2010).

The influence of some biomarkers on As metabolism have been shown to specifically affect risk of lung cancer, and could prove valuable in assessing individual or population-specific susceptibility to this disease. Those specifically connected to lung cancer are the null genotype of glutathione S-transferase (*GST*) and the 2A genotype of the Mspl polymorphism in cytochrome P450 1A1 (*CYP1A1*) The combined genotype of 2A and null GSTM1 was related an OR of 2.51 for lung cancer that increases to 2.98 with habitual smoking; in males, the 2A genotype confers an OR of 2.6 (Adonis et al., 2005a; Adonis et al., 2005b). Risks involving *GSTM1* polymorphisms lie in its function in As methylation; the null genotype may hinder this process and cause an overall increase in As retention. Such retention is usually in the form of increased %MMA, which was recently linked to higher lung cancer when caused by variant cystathionine (3-synthase alleles (rs234709 and rs4920037) (Steinmaus et al., 2010). Similar future studies would be useful in understanding a gene-environment in relation to As-related health outcomes.

5. Health effects from arsenic exposure in Latin America

Most studies examining the adverse health effects of drinking water As in Latin America were set in Argentina and Chile, with some limited data also coming from Mexico. As early as the 1970s, studies from Chile's Region II showed As deposits in lung tissue of children with As-induced skin lesions, along with a concurrent increase in the rate of lung disease (Borgoño et al., 1977; Rosenberg, 1974; Zaldivar, 1980; Zaldivar and Ghai, 1980). Since that time, research has continued to describe how As influences the respiratory system, while also beginning to explore its effect on the bladder. Most research on bladder cancer has been conducted in Argentina, while the majority of lung cancer studies have taken place in Chile. Within these mortality studies, consistent association has been observed between As exposure and both lung cancer and bladder cancers - especially among smokers (Hopenhayn-Rich et al., 1996a; Smith et al., 2006). In addition, a few studies have shown disease susceptibility variation due to different levels of As methylation capacity and certain genotype, in particular, higher MMA was associated with an increased risk of bladder and lung cancer (Steinmaus et al., 2006; Steinmaus et al., 2007; Steinmaus et al., 2010). These cancers have shown a long latency period, with clinical presentation coming decades after exposure, even if exposure was limited to early in life (Smith et al., 2006). Recent studies on other non-malignant chronic diseases have been more limited, with inconsistent data having been obtained on such adverse health outcomes as cardiovascular disease, diabetes mellitus, lung disease, and skin lesions (Smith et al., 2006; Yuan et al., 2007).

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Arsenic has been shown to adversely impact reproductive and child health, as it has been shown to cross the placenta and cause anemia, low birth weight, and fetal mortality (Hopenhayn-Rich et al., 2000; Hopenhayn et al., 2003b). *In utero* and early childhood exposure in Mexico has been linked with impaired cognitive development, manifested through lower test scores and slow linguistic abstraction (Calderon et al., 2001; Rocha-Amador et al., 2007). In addition, an ecological study compared liver cancer mortality between 1950 and 2000 in an As endemic area in Chile with an unexposed region. For those exposed as young children, liver cancer mortality between ages 0 and 19 was significantly elevated (RR=10.6; 95% CI: 2.9–39.2) in comparison to those living in the unexposed region (Liaw et al., 2008).

The majority of these studies were based on cross-sectional, case-control, or retrospective designs that relied on past exposure assessment with relatively small sample size and limited data on individual exposure. In many cases, particularly among mortality studies, outcomes were assessed by using death records which may involve misclassification errors. These studies have consistently suggested a link between As exposure and human cancer. Since most of the methodological limitations involve misclassifications of disease or exposure that are non-differential, the true association may be stronger than what has been observed. Though long latency periods of 10 to 35 years have been associated with many As-induced disease states, it is important to note the early life effects in children could include cognitive impairment, low birth weight, and DNA damage. Such effects are indicative of the serious implications of exposure that may manifest in adulthood.

5.1. Bladder cancer

Evidence of bladder cancer mortality from As exposure in Latin American countries mainly comes from a few ecological studies in As endemic areas in Argentina and Chile. An earlier study captured bladder cancer mortality in approximately 2,750,000 inhabitants living in 26 counties of Córdoba province in Argentina between 1986 and 1991. The study found strong association between As exposure and deaths from bladder cancer mortality. Standard mortality ratios (SMRs) were: 0.80 (95% CI: 0.66–0.96), 1.42 (95% CI = 1.14–1.74), and 2.14 (95% CI: 1.78–2.53) for men and 1.21 (95% CI: 0.85–1.64), 1.58 (95% CI :1.01–2.35), and 1.82 (95% CI: 1.19–2.64) for women in relation to low (<=40μg/L), medium (>40–178 μg/L) and high (>178 μg/L) water As (p-for trend, male=0.001 and female=0.04) (Hopenhayn-Rich et al., 1996a). Stronger association was observed in a population of roughly 400,000 living in Chile's Region II, who had been exposed to drinking water averaging 570 μg As/L for over a decade before a treatment plant was installed in 1971 (men: SMR = 6.0 (95% CI: 4.8–7.4); women: SMR = 8.2 (95% CI: 6.3–10.5)) (Smith et al., 1998). Steinmaus et al. (2006) demonstrated that higher MMA in urine was associated with higher risk for bladder cancer (OR=1.33; 95% CI: 0.74–2.39) in population living in the same area (Steinmaus et al., 2006). Another study estimated the rate ratios (RRs) for women to be more than double (RR=13.8; (95% CI: 7.74–24.5) compared to that of men (RR=6.1; 95% CI: 3.97–9.39) for bladder cancer using death records of over half a million from two regions in Chile between 1958 and 2000 (Marshall et al., 2007). Perhaps more importantly, the finding demonstrated that mortality started to increase after 10 years of high exposure the in Chile's Region II in 1958 and continue to rise even after 25 years of reducing the exposure to a low level (Marshall et al., 2007). In a case-control study from Cordoba region, Bates et al. (2004), found elevated risk of bladder cancer only among smokers who were exposed to moderately-to-low levels of As for more than 50 years (OR=2.5; 95% CI: 1.1–5.5) (Bates et al., 2004).

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5.2. Lung cancer

Research on As-related lung cancer in Latin America has been based largely in the As-endemic Region II of Chile. As the world's most important region for copper smelting, the populations of northern Chile (Region II) have a long history of As exposure related to mining activities. Exposed to drinking water As levels that reached an average concentration near 600 μg/L from 1958–1971 before decreasing to under 100 μg/L by 1980, residents were shown to have significantly elevated lung cancer mortality in both men (SMR = 3.8; 95% CI: 3.5–4.1) and women (SMR=3.1; 95% CI2.7–3.7) (Smith et al., 1998). In Argentina, Hopenhayn-Rich *et al*. (1996), reported a dose-response relationship between As exposure and lung cancer: the SMRs (95% CI) for low, medium, and high exposure groups (<=40, 40–178, and >178 μg/L) in men and women, respectively, were 0.92 (0.85–0.98), 1.54 (1.44–1.64), 1.77 (1.63–1.90) and 1.24 (1.06–1.42), 1.34 (1.12–1.58), 2.16 (1.83–2.52) (Hopenhayn-Rich et al., 1996a).

A subsequent case-control study from As endemic area in Chile also found a very strong trend in lung cancer. The OR for lung cancer risk was 1.0, 1.6 (95% CI = 0.5–5.3), 3.9 (95% CI = 1.2–12.3), 5.2 (95% CI: 2.3–11.7), and 8.9 (95% CI = 4.0–19.6), for As concentrations ranging from less than 10 μg/L to a 65-year average concentration of 200–400 μg/L. This association was particularly strong among smokers (OR=32.0; 95% CI: 7.2–198.0) (Ferreccio et al., 2000). Though the large spike in drinking water As concentration occurred in 1958, the overall risk of lung cancer did not peak until the period of 1992–1994 for men (RR=3.61; 95% CI: 3.13–4.16) and in 1989–1991 for women (RR=3.26; 95% CI: 2.50–4.23) suggesting a long latency period for lung cancer over 35 years after the onset of high exposure in Region II (Marshall et al., 2007). Studies from Chile not only showed a long latency period for lung cancer incidence, a recent study also demonstrated that As exposure during a discrete period of exposure *in utero* or during early childhood may have a profound impact on lung cancer later in life (Smith et al., 2006). In one study, lung cancer mortality rate was more than six-fold higher among those who were born during the high-exposure period (SMR=6.1; 95% CI: 3.5–9.9) and seven-fold among those who were exposed *in utero* (SMR=7.0; 95% CI: 5.4–8.9) (Smith et al., 2006). Individual risk to these substantial effects may be largely attributable to metabolic variations, as a recent a case-control study from As-exposed areas in Cordoba, Argentina, showed that lung cancer patients (N=120) had significantly high levels of urinary MMA (OR=3.09; 95% CI: 1.08–8.81) (Steinmaus et al., 2010).

5.3. Kidney, liver, and skin cancers

Among Latin American populations, relatively little has been published on other As-related cancers. However, in a report from Cordoba, kidney cancer mortality was found to be elevated in both men and women (SMR=1.57 and 1.81, respectively) who were exposed to high concentrations of water As (>178 μg/L). This study suggested that the risk of kidney cancer peaked roughly 10 in years and remained elevated for at least 25 years following high-level exposure (Hopenhayn-Rich et al., 1998). A more recent study from Chile demonstrated a peak kidney cancer mortality in 10 years with a long latency period. Interestingly, this study did find significant gender differences, as RR reached a maximum for men at 3.4 (95% CI: 2.2–5.1) in the time period of 1981–1985, but peaked in women (4.4; 95% CI: 3.0 – 6.4) during the span of 1991–1995. Early-life exposure resulted in an increased risk (RR=7.1, 95% CI: 3.1–14) for those born just before or during the high exposure period (Yuan et al., 2010). Hopenhayn et al. (1998) observed a slight increase of liver cancer in As exposed (>178 μg/L) population from Cordoba (SMR 1.80 for men, 1.92 for women).

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However, risk of non-melanoma skin cancer (NMSC) from As exposure was evaluated in a small (N=90) case-control study in the Region Lagunera, Mexico. The effect was observed only among exposed to As and history human papilloma virus (HPV) infection. The study reported a significant increased risk of NMSC was among those exposed to high As and HPV seropositivite (OR=16.5, p< 0.001) (Rosales-Castillo et al., 2004).

5.4. Other chronic health effects

Only a handful of studies have been published on other chronic non-malignant health effects in Latin America, including skin lesion, cardiovascular disease and respiratory illness (Astolfi et al., 1982; Hopenhayn-Rich et al., 1996; Hopenhayn-Rich et al., 1998). The majority of these studies, however, have a number of limitations including small sample size, selection of controls and a lack of reliable exposure data. This has led to inconsistent findings.

A recent study (N=125) from El Zapote in Nicaraguan, identified significantly high risk of skin lesions (OR=4.66, 96% CI: 1.48–14.69) those exposed to As >250 μg/L (Gómez, 2008).

In a small (N=28) ecological study from an endemic area in Chile, Smith et al., (2006) showed a high mortality and incidence of chronic obstructive pulmonary disease (COPD) and bronchiectasis among adults between 1989 and 2000. Strong associations were observed for chronic bronchitis in those who were exposed in their early childhood (SMR:46.2; 95% CI: 21.1–87.7) and in *utero* (SMR: 12.4; 95% CI: 3.3.–31.7) (Smith et al., 2006). However, an earlier study by the same group found no elevation in SMR from COPD (SMR = 1.0, 95% CI: 0.8–1.1) (Smith et al., 1998).

High mortality from acute myocardial infarction (AMI) (RR = 3.23; 95% CI = 2.79–3.75; p < 0.001) was observed among young adult men aged 30–49 who were exposed to As in early childhood or *in utero* during the peak As exposure period in Chile. AMI mortality was found to be the main cause of As-related deaths during and immediately following the high-exposure period (Yuan et al., 2007).

A case-control (N=400) study in Mexico observed effect of As exposure on the type 2 diabetes mellitus in a population exposed to a wide range of As (20 to 400 μg/L). The study observed almost three fold increase in diabetes risk (OR = 2.84; 95% CI = 1.64–4.92) associated with urinary As more than 104 μg/gm creatinine (Coronado-Gonzalez et al., 2007).

5.6. Effects of in utero and early childhood exposure

A few earlier studies from the As endemic area in Chile, showed that high levels of As deposited in the children's lungs (Rosenberg, 1974), leading to abnormal lung tissues (Zaldivar and Ghai, 1980) and lung disease (Rosenberg, 1974; Zaldivar, 1980). Subsequently, papers showed a reduction of respiratory symptoms followed by introduction of As free water the Antafagasta, Chile. For example, autopsies of the five children with arsenical skin lesions who died between 1968 and 1969 from an As endemic areas in Antofagasta reported high levels of As in their lung tissues (Rosenberg, 1974). Abnormal lung tissues were detected in four of these five children and two had interstitial fibrosis (Zaldivar and Ghai, 1980). Relying on survey data between 1968 and 1972 from Antofagasta, a study found a high prevalence of chronic cough among 398 children who were exposed to As from drinking water. The report, though, demonstrated a decline of chronic cough from 38% to 7% (p <0.001) following installation of Antofagasta As removal plant in the area, reinforcing the effects of As among young children (Borgoño et al., 1977).

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Another study showed a 23-fold greater prevalence of bronchiectasis among children living in As endemic area of Antofagasta compared to rest of Chile (Rosenberg, 1974). In 1976, a cross-sectional survey among 144 school children with arsenical skin lesions in Antofagasta showed that children with As skin lesions are 2.5 times more likely to have a pulmonary disease than those with normal skin (Zaldivar, 1980).

Several studies focused on the effects of As and its metabolites on reproductive outcomes in Argentina. An important study among Andean pregnant women in northwest Argentina, showed that As easily crosses into placenta which raised concerns of fetal exposure (Concha et al., 1998b). Interestingly, subsequent studies revealed that methylation of As in the mother seems to increase during pregnancy, passing the more easily excretible DMA on to the fetus (Concha et al., 1998a; Hopenhayn et al., 2003b). Additionally, even at high exposure (>200 μg/L), As concentration was found to be low in breast milk (Concha et al., 1998c). These findings suggest that protective measures occur during pregnancy and postpartum may keep the more sensitive fetus or child from being overwhelmed by As toxicity that could lead to adverse health outcomes.

Such natural safeguards, however, were not adequate to eliminate the possibility of As - induced effects on health during pregnancy and childhood. In Antofagasta, Chile, an area with history of high drinking water As concentration (~860 μg/L, between 1958–1970) was found to elevate late fetal mortality (RR = 1.7; 95% CI: 1.5–1.9), neonatal mortality (RR = 1.53; 95% CI: 1.4–1.7), and postneonatal mortality (RR=1.26; 95% CI: 1.2–1.3) (Hopenhayn-Rich et al., 2000). Even at moderate to low As water concentration (<50 μg/L), a reduction of birth weight was observed (−57g; 95% CI = −123 to 9) (Hopenhayn et al., 2003a). While the mechanism of such changes is not fully understood, anemia in the mother has also been identified as a consequence of As exposure could be a likely explanation. Hopenhayn *et al*. observed that, in the third trimester of pregnancy, there was a significantly high anemia among (49% vs. 17%, $p < 0.0001$) mothers exposed to As 40 compared to < 1 μg/L (Hopenhayn et al., 2006).

Particularly alarming has been the observations that As exposure impairs cognitive development in school children was shown to be impacted by As exposure. Studies from two cities in Mexico where water As was more than 150 μg/L showed an inverse association between intelligence quotient scores and As exposure ($\beta = -5.72$, $P = 0.003$) (Rocha-Amador et al., 2007). Specific detrimental effects were observed in long-term memory and linguistic abstraction (Calderon et al., 2001). A subsequent evaluation using 11 cognitive tests showed that those with high exposure performed significantly poorer in 7 tests ($p < 0.05$). Interestingly, performance on memory evaluations was negatively correlation with urinary As only among girls, while tests of several different cognitive functions were effected in boys (i.e., Visual-Spatial Abilities with Figure Design, Peabody Picture Vocabulary Test, Visual Search, Letter Sequencing Test) (Rosado et al., 2007).

Recent findings from Chile link *in utero* and early life As exposure to cardiovascular, respiratory and lung cancer later in adult life, and were discussed previously in this paper (Smith et al., 2006; Yuan et al., 2007). Some research has begun to discern the specific mechanisms of action for As in children, as well as the extent to which any of these genetic effects are reversible. Research in Mexico found that children with high urinary As displayed severe DNA damage, as evaluated by the Comet assay ($P < 0.05$) (Yanez et al., 2003). Furthermore, a recent study also showed that As exposed children also had an impaired DNA repair response (Mendez-Gomez et al., 2008). A recent study from Mexico indicated an effect of As exposure on immune function among 90 children in relation to urinary As (Vega L et al., 2008). While it is possible that such genetic alterations and

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immunodeficiency are transient, permanent alterations of this nature could be responsible for adverse health effects later in life.

6. Discussion

A large number of individuals from Latin American countries have been drinking As contaminated water for hundreds of years, yet there is still not comprehensive data on the extent of exposure and its health consequences. Latin America has, though, been the focus of importantstudies that have contributed significantly to current knowledge of As effects on human health - specifically with respect to the development of bladder, lung, and skin cancer. While development of and deaths from cancer may take as long 35 years after exposure, deaths from cardiovascular or respiratory diseases in children seem to occur during or soon after a period of high exposure – making shorter-term consequences of exposure a vital area of research (Rosenberg, 1974; Yuan et al., 2007; Zaldivar, 1980). Limited work has been done in these fields in Latin America, with studies of respiratory, cardiovascular, and neurological diseases yielding inconsistent findings. One exception is in the influence of As on pregnancy and childhood health, where substantial research has been conducted on near-term health outcomes. In children, profound effects have been observed, with long-term memory and linguistic abstraction affected by As (Calderon et al., 2001). *In utero* and early childhood exposure has also been linked to consequences such as lung cancer, bronchiectasis, liver cancer, and acute myocardial infraction later in life (Liaw et al., 2008; Steinmaus et al., 2006; Yuan et al., 2007). Though there are innate preventive measures to minimize adverse effects in children (the mother increases methylation during pregnancy and excretes relatively small amounts of As in breast milk), they cannot compensate for high levels or a prolonged period of exposure (Concha et al., 1998c; Hopenhayn et al., 2003b). As a result, studies have observed elevated fetal mortality, neonatal mortality, post neonatal mortality, reduced birth weight, and anemia in the mother (Hopenhayn-Rich et al., 2000; Hopenhayn et al., 2006; Hopenhayn et al., 2003a).

Although many of these As-related studies in Latin America were cross-sectional studies, reverse causation is not likely. The ecologic measure of As exposure, although may not accurately reflect exposure level at the individual level, was useful for assessing disease risk in populations that were exposed to high levels of As for the same period of time. Future studies, however, should consider measuring As exposure level at the individual level to better assess health effects at low-to-moderate levels of exposure in populations with varying levels of As exposure. Since retrospective studies do not allow collection of comprehensive data on host factors, susceptibility factors that may modify health effects of arsenic exposure were often not investigated. Cigarette smoking exemplifies the concept of an influential covariate that should be considered in epidemiological studies such as these. In one bladder cancer study, for example, effects of As were apparent only among smokers (Bates et al., 2004). Smoking was also found to influence risk of bladder cancer due to As, with individuals excreting high %MMA shown to have a quadrupled OR if they were also smokers (Steinmaus et al., 2006). With respect to lung cancer, synergistic effects was observed to among smokers exposed to water As more than 200 μg/L compared to nonsmokers exposed to less than 50 μg/L (Ferreccio et al., 2000). In studies that assessed genetic influences on lung cancer risk, it was found that the 2A genotype of the *CYP1A1* was associated with an increased risk among habitual male smokers. Some *GST* biomarkers that have been shown to influence the distribution of As metabolites have also been implicated to play a role in elevated bladder cancer risks in smokers (Moore et al., 2004). Since individuals with diseases may change lifestyles, it is important to confirm the findings in prospective studies that measure smoking status before disease occurrence. Additional research that aims to identify modifiable susceptibility factors is also needed.

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It should be noted that the literature reviewed in this paper may not represent the entire body of work regarding the health effects of As exposure in Latin America, as there are likely relevant studies that lie outside the scope of this article. Absent from this review are studies not published in English, those whose text were not available online, and those not indexed in searchable databases of medical literature. With the already high number of sources returned by the database searches (964 unique items), though, it was necessary to restrict the literature review to processes that could be conducted in a systematic manner. Even with the number or articles returned through this process, the authors acknowledge that some measure of quality control (such as correspondence with original study authors) was sacrificed in an effort to conduct the most broad and comprehensive review possible.

Though this review was limited to Latin America, As contamination is most certainly a health issue whose effects are felt far beyond the borders of these countries (Nordstrom, 2002). As even in westernized society there remains debate over acceptable levels of As in drinking water, research in Latin America can address local public health issues while also contributing to the current dialogue attempting to safeguard many populations against adverse health outcomes. Based on the studies included in this review, we would like to put forth several suggestions for future research.

First, with respect to childhood exposure, for example, it would be useful to investigate whether observed cognitive effects are reversible to any degree. The entire field of early childhood exposure should receive increased attention, given that children have been identified as more susceptible to arsenic exposure and that profound short-term and chronic health consequences have been found in those with early exposure. Second, conducting follow-up studies would allow a better understanding of the scope and temporality of disease onset. Third, work in other Latin American countries can be replicated to determine any differences in health outcomes that may be unique to Latin America's genetic composition, environmental factors, or multiple routes of As exposure. Related to this suggestion is the need to further explore the influence of nutrition and whether it confers any protective advantage to Latin American populations over some exposed populations in Asia that suffer from malnutrition. This topic was explored in a very limited population (11 families), and warrants a study with more statistical power (Smith et al., 2000). Finally, the wealth of retrospective data provides a unique opportunity to investigate the effects of lower level As exposure on many health outcomes. Such information would be extremely valuable in assessing As exposure and consequences not only in Latin America, but also contribute to a global dialogue on determining safe levels of As in drinking water.

In summary, there is little doubt that the studies performed in Latin America have yielded substantial information on effects of As on the risk of bladder cancer, lung cancer, skin lesions, and other chronic diseases. Such short-term effects such as low birth weight and impaired cognitive development have also been observed. As-induced DNA damage in children may explain the underlying mechanisms of cancer risk at later life and future health risk. The full burden of As exposure in Latin America remains to be seen. With studies indicating that As can account for 7 – 20% of all deaths among exposed populations (Argos et al., 2010; Smith et al., 1998), there is a clear need for research and public health interventions in Latin America.

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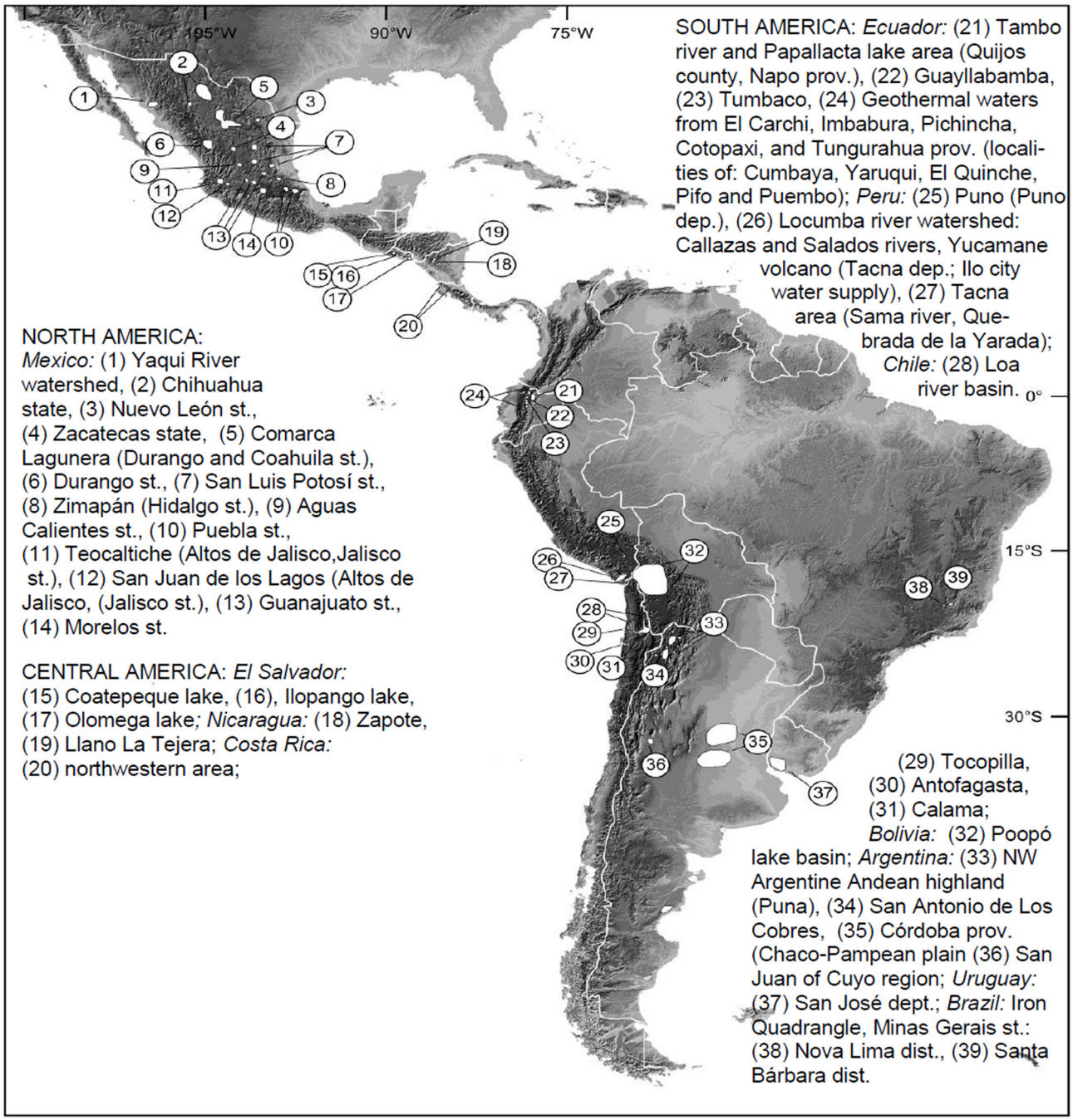

Fig. 1.
Locations of arsenic contamination from different water sources in Latin American countries

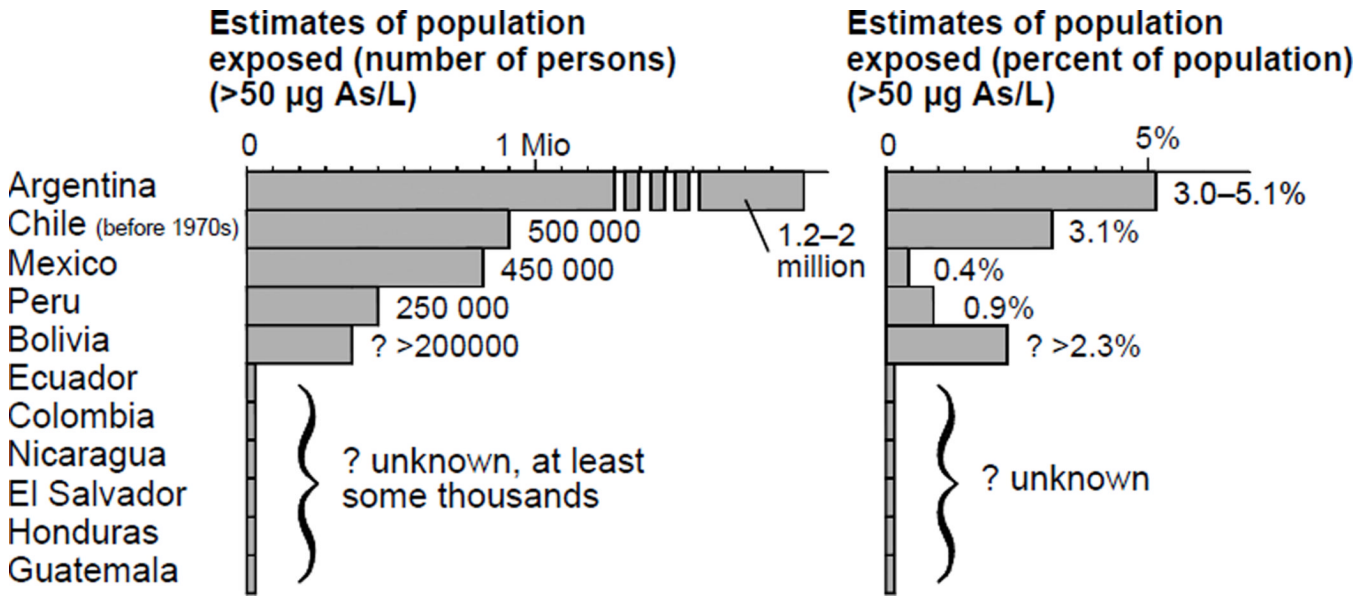

Fig 2.

Estimated population chronically exposed to arsenic (>50 µg/L) from drinking water in Latin American countries

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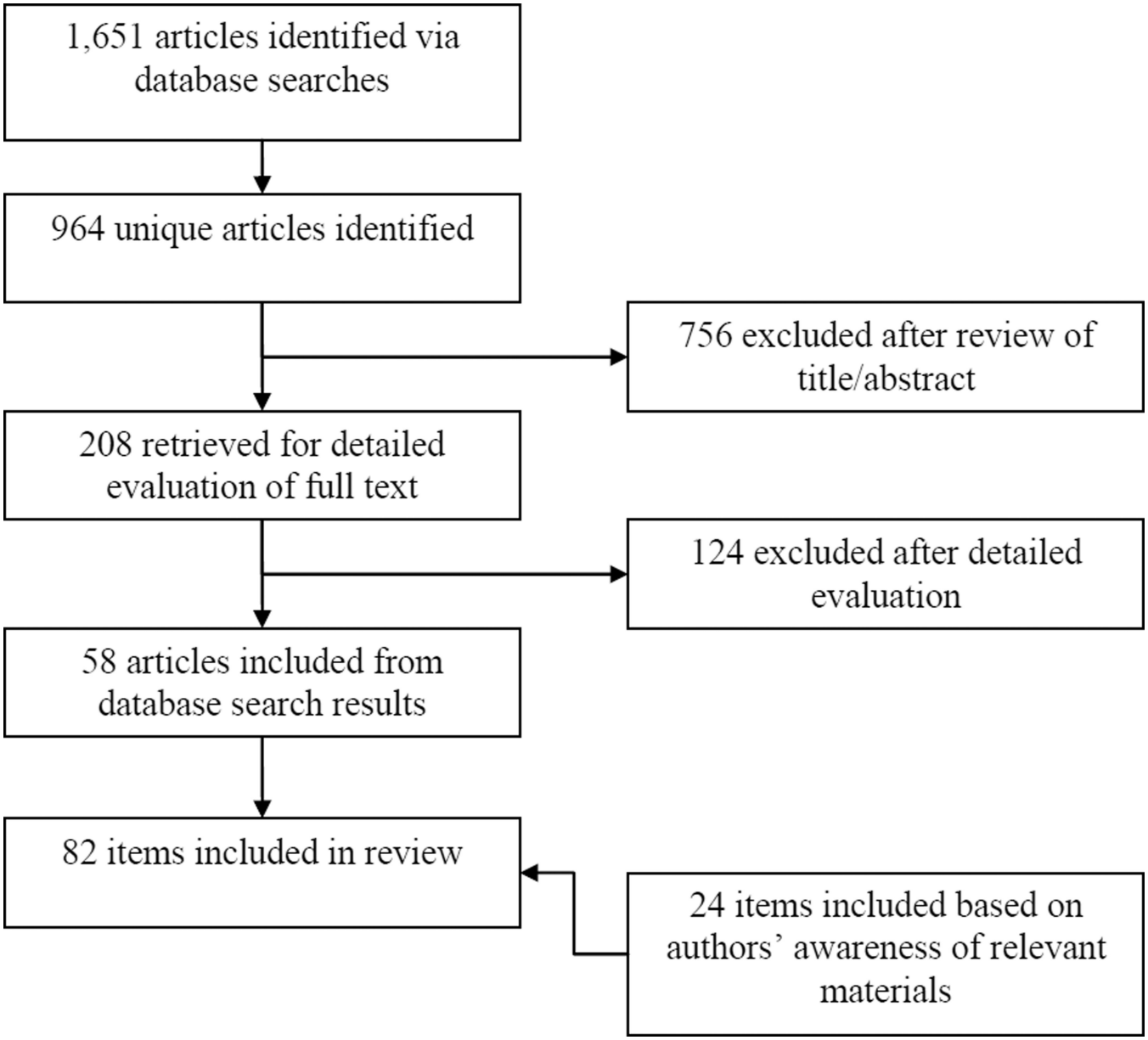

Fig. 3.
Study selection process

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Table 1

Studies from Latin America related to Arsenic-induced genotoxicity, oxidative stress and DNA damage

Reference	County	Design	Characteristics of subjects	Main Findings
Ostrosky-Wegman, et al. (1991)	Mexico	Cross-sectional	11 and 13 individuals drinking water with high and low As (0.39 mg/L and 0.019–0.026 mg/L)	The percentages of chromosomal aberrations and frequencies of sister-chromatid exchanges were similar in both populations, but complex aberrations were more frequent in the highly As exposed group.
Lerda (1994)	Argentina	Cross-sectional	282 and 155 individuals drinking water with high and low As (0.13 mg/L and 0.02 mg/L)	There was a significant elevation in sister-chromatid exchange in high As exposed individuals.
Martinez et al. (2004)	Chile	Cross-sectional	106 and 111 individuals drinking water with and low As (0.750 mg/L and 0.002 mg/L)	In the As exposed group, the overall frequency of binucleated micronucleated cells is higher than in the reference group.
Paiva et al. (2008)	Chile	Cross-sectional	105 smelter workers, 52 administrators, and 50 workers from another copper mine with no significant As exposure	No significant differences in micronuclei frequencies in lymphocytes were detected between the groups.
Salazar et al. (2004)	Mexico	Cross-sectional	19 individuals (12 with skin cancer) from As endemic areas and 44 healthy individuals from outside	A clear relationship was observed between non-melanoma skin cancer and p53 expressionin circulating lymphocytes.
Burgess et al. (2007)	Mexico	Cross-sectional	51 subjects in four communities in Mexico water As ranges from 4.8 to 33.3 μg As/L	Drinking water with As was not associated with increased DNA oxidation as measured by urinary 8-OHdG.
Andrew et al. (2006)	Mexico	Cross-sectional	16 and 37 people with high and low water As (32μg/L and 0.7μg/L),	As exposure increases DNA damage and decreases repair capabilities.

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Table 2

Studies describing genetic susceptibility in relation to arsenic-induced adverse health outcomes

Reference	County	Design	Characteristics of subjects	Main Findings
Loffredo et al. (2003)	Mexico	Cross-sectional	180 and 112 individuals exposed to high and low water As (408 (μg/L and 30 (μg/L)	Gender differences varied by populations. Bimodal distributions were observed in the ratios of DMA to InAs and to MMA. The results of studies among the ethnic groups in this study are consistent with the presence of functional genetic polymorphisms in As methylation leading to measurable differences in toxicity.
Del Razo et al. (1997)	Mexico	Cross-sectional	35 and 34 exposed to high and low water As (0.408 mg/L and 0.031 mg/L)	Significant increases in the relative proportions of InAs and MMA, accompanied by decreases of DMA were found in exposed individuals.
Chung et al. (2002)	Chile	Cross-sectional	11 families with high drinking water As (735–762 μg/L)	Methylation patterns aggregate in families and are correlated in siblings, providing evidence of a genetic basis for the variation in arsenic methylation.
Hopenhayn-Rich et al. (1996)	Chile	Cross-sectional	73 individuals drinking water with As 600 μg/L and intervened with low water As (45 μ/L) for two months	Decrease in As exposure associated with a small decrease in In-As in urine as well as a decrease in the MMA/DMA ratio. Study observed about 20% of the interindividual variability. Genetic polymorphisms in As-methylating enzymes/cofactors likely contribute to a large portion of the remaining variability.
Hopenhayn-Rich et al. (1996)	Chile	Cross-sectional	122 high-exposure individuals (drinking water: 600 μg As/L), 98 low-exposure individuals (drinking water: 15 μg As/L)	MMA:DMA was 1.5 times greater in exposed group. Differences in MMA:DMA were partially (30%) explained through exposure, smoking, and gender.
Engstrom et al. (2007)	Argentina	Cross-sectional	147 women drinking water As 200 μg/L	Polymorphisms in AS3MT - and possibly GSTM1, GSTT1, MTR and MTHFR - are responsible for a large part of the interindividual variation in As metabolism and susceptibility.
Meza et al. (2007)	Mexico	Cross-sectional	135 individuals exposed to water As between 5.5 μg/L and 43.3 μgL	AS3MT individuals may suffer less risk from As exposure than non-variant individuals. Regardless of AS3MT variant status, children tend to have lower %MMA values than adults.
Engstrom et al. (2009)	Argentina	Cross-sectional Cross-sectional	104 women drinking water 200 μg/L As	Polymorphisms in AS3MT and in genes involved in one-carbon metabolism and reduction reactions affects As metabolism.
Gomez-Rubio et al. (2010)	Mexico	Cross-sectional	405 individuals	Genetic association analysis with As metabolism confirmed the previously observed association between AS3MT variats, including a large cluster of linked polymorphisms, and As methylation efficiency.
Paiva et al. (2008)	Chile	Cross-sectional	281 (urinary As: 0–600 mg/L	Heterozygotes inheriting the Val236 variant subunit would likely have a partial deficiency

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Reference	County	Design	Characteristics of subjects	Main Findings
				of GSTOl-1 (glutathione transferase omega 1) activity. Despite their effects on enzyme function, the known variants of GSTOl-1 do not appear to explain the observed variability in the excretion of inorganic arsenic.
Sampayo-Reyes et al. (2010)	Mexico	Cross-sectional	124 high-exposure individuals	A positive association was found between the level of exposure and the genetic damage ($p < 0.001$). AS3MT Met287Thr was found to significantly influence the effect among children carrying the 287Thr variant allele.
Marnell et al. (2003)	Mexico	Cross-sectional	75 individuals living in cities with varying As in drinking water: 9, 17, 52, and 100 μg/L	Polymorphisms in the gene for MM A reductase/hGSTOl may be one of the reasons for the large interindividual variability in the response of humans to chronic As exposure.
Marcos et al. (2006)	Chile	Cross-sectional	105 smelting plant workers, 52 plant administrators, and 50 workers from another copper mine with no significant exposure	High amounts of inorganic As and MMA were observed in the most exposed workers compared to the least-exposed workers who excreted high amounts of DMA. A tendency was observed between GSTM1 null and MMA excretion, as well as between GSTP1 val/val and DMA excretion.
Steinmaus et al. (2007)	Argentina	Cross-sectional	170 individuals from arsenic-exposed region	This study provides evidence that MTHFR and GSTM1 are involved in As metabolism in humans, and polymorphisms in the genes that encode these enzymes may play a role in susceptibility to arsenic-induced cancer.
Engstrom et al. (2010)	Argentina	Cross-sectional	108 women drinking water with 200 μg/L	The strongest association was found between %MMA and 8-oxo-G Inconsistencies between As and 8-oxodG stressed population variations in As metabolism.

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Table 3

Studies from Latin American countries showing association between arsenic exposure and bladder cancer mortality and incidence

Reference	County	Design	Characteristics of subjects and exposure	Measure	Results/Main finding
Hopenhayn-Rich et al. (1996)	Argentina	Ecological	Province of Cordoba (Approximately 2,750,000 inhabitants.	Bladder cancer mortality SMR (95% CI)	Men: 0.80 (0.66–0.96), 1.42 (1.14–1.74), 2.14 (1.78–2.53) and Women: 1.21 (0.85–1.64), 1.58 (1.01–2.35), 1.82 (1.19–2.64) with water As cone. <40, >40–178, and >178 μg/L.
Moore et al. (1997)	Chile	Cohort	70 and 55 males with chronic high and low As exposure (600μg/L and 15μg/L).	Measure of micronuclei cell in urinary As.	Micronuclei in with increased urinary As (53.9 to 728.9 μg/L) p for trend < 0.001
Smith et al. (1998)	Chile	Ecological	Roughly 400,000 residents in Region II (Avg. water As 570 μg/L) from 1955–1969	Bladder cancer mortality SMR (95% CI)	Men: 6.0 (4.8–7.4) and women 8.2(6.3–10.5)
Moore et al. (2002)	Argentina	Case-case	123 bladder cancer patients, exposed to As in drinking water.	Mean chromosomal alterations in tumor with increasing exposure	Changes in chromosomal alterations: 5.7, 5.6, 7.3, and 9.1 compared to As cone. <10, 10–99, 100–299, >299 (p for trend=.02)
Bates et al. (2004)	Argentina	Case-control	114 case-control pairs	Bladder cancer OR (95% CI)	2.5(1.1–5.5)
Steinmaus et al. (2006)	Argentina	Case-control	114 cases-control pairs	Bladder cancer OR (95% CI)	High %MMA in Smokers: 2.17 (1.02–4.63) and Non-smokers: 0.48(0.17–1.33)
Marshall et al. (2007)	Chile	Ecologic	Mortality data on 525,715 from Region II and Region V between 1950 and 2000	Bladder cancer mortality RR (95% CI)	Men: 6.10 (3.97–9.39) Women: 13.8 (7.74–24.5)
Valenzuela et al.(2007)	Mexico	Cross-sectional	51 -person high exposure group, 21 -person low exposure group	TGF-a in exfoliated bladder urothelial cells (BUC) in people living in high vs. low As exposed area and with or without skin lesions.	TGF-α concentration: High vs. low As (128.8 pg/mg vs. 64.4 pg/mg, p<0.05); and With and without skin lesion (157.7pg/mg vs. 64.9 pg/mg, p<0.05)

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Table 4

Studies from Latin American countries showing association between arsenic exposure and lung cancer mortality and incidence

Reference	County	Design	Characteristics of subjects	Measure	Result
Hopenhayn-Rich et al. (1998)	Argentina	Ecological	Population data from Cordoba (~2,750,000)	Lung cancer mortality SMR (95% CI)	Lung cancer: Men 0.92 (0.85–0.98), 1.54 (1.44–1.64), 1.77(1.63–1.90), Women: 1.24 (1.06–1.42), 1.34 (1.12–1.58), 2.16 (1.83–2.52) with increasing water As conc. (<40, 40–178, and >178 ug/L).
Smith et al. (1998)	Chile	Ecological	Roughly 400,000 individuals in Region II (exposure: 570 μg/L from 1955–1969, decreased to less than 100 μg/L by 1980)	Lung cancer mortality SMR (95% CI)	Men: 3.8 (3.5–4.1) Women: 3.1 (2.7–3.7))
Ferreccio et al. (2000)	Chile	Case-Control	152 lung cancer cases and 419 controls	Lung cancer OR (95% CI)	1.6 (0.5–5.3), 3.9 (1.2–12.3), 5.2 (2.3–11.7) and 8.9 (4.0–19.6) with increasing water As conc. (<10, 10–29, 30–49, 50–199 and 200–400 ug/L).
Smith et al. (2006)	Chile	Ecological	Region II compared to the remaining regions of Chile (Region II exposure ~870 μg/L As in drinking water, 1958–1970)	Lung cancer mortality SMR (95% CI)	Early life exposure: 7.0 (5.4–8.9), and *In utero* exposure: 6.1 (3.5–9.9)
Marshall et al. (2007)	Chile	Ecologic	Mortality data on 525,715 from Region II and Region V between 1950 and 2000	Lung cancer mortality RR (95% CI)	Men: 3.61(3.13–4.16) Women: 3.26 (2.50–4.23)
Steinmaus et al. (2010)	Argentina	Case-control	45 lung cancer cases and 75 controls	Lung cancer OR (95% CI)	3.09 (1.08–8.81), upper tertile %MMA compared to the lowest tertile

Effects of arsenic exposure on biomarker and chronic diseases observed in Latin American countries

Reference	County	Design	Characteristics of subjects	Measure	Result
Garcia-Vargas et al. (1991)	Mexico	Cohort	21 and 19 individuals exposed to water As 0.390 mg/L and 0.012 mg/L respectively.	Indicators of heme metabolism	An inversion of the coproporphyrin/uroporphyrin (COPRO/ URO) ratio was observed in most exposed individuals. This was caused by a decrease in coproporphyrin excretion and an increase in uroporphyrin excretion.
Garcia-Vargas et al. (1994)	Mexico	Cohort	36 and 31 individuals exposed to water As: 0.400 mg/L and 0.020 mg/L respectively.	Indicators of heme metabolism	Significant reductions in coproporphyrin III excretion resulting in decreases in the COPRO III/COPROI ratio, and an increases in uroporphyrin excretion in As exposed individuals.
Hernandez-Zavala et al. (1999)	Mexico	Cohort	17 individuals from 3 villages with water As conc: 0.3 mg/L, 0.4 mg/L, 0.014 mg As/L	Indicators of heme metabolism	Significant increases in porphobilinogen deaminase (PBG-D) and uroporphyrinogen decarboxylase (URO- D) activities in peripheral blood erythrocytes; increases in the urinary excretion of total porphyrins, and increases in the COPRO/URO and COPROIII/ COPROI ratios in highly exposed individuals.
Smith et al. (2000)	Chile	Cross-sectional	44 and 31 participants drinking water As 750–800 μg/L, and 10 μg/L respectively	Overall prevalence with more than 20 years residence	Skin lesion prevalence among exposed: 67% (95% CI = 22–96%)

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Effects of arsenic exposure on biomarker and chronic diseases observed in Latin American countries

Reference	County	Design	Characteristics of subjects	Measure	Result
Rosales-Castillo et al. (2004)	Mexico	Case-control	42 cases, 48 controls (previous exposure to drinking water As 416 μg/L and 12 μg/L)	OR non-melanoma skin cancer (NMSC)	16.5 (P = 0.001), high arsenic exposure and HPV seropositivity
Smith et al. (2006)	Chile	Ecological	Region II compared to the remaining regions of Chile (Region II exposure ~870 μg/L As in drinking water, 1958–1970)	Bronchiectasis mortality SMR (95% CI)	Born just before the high-exposure period (1950–1957): 12.4(3.3–31.7). Born during the high-exposure period: 46.2 (21.1–87.7)
Coronado-Gonzalez et al. (2007)	Mexico	Case-control	200 diabetics and 200 controls	Diabetes prevalence OR (95% CI)	2.16 (1.23–3.79) and 2.84 (1.64 −4.92) with increasing urinary As
Yuan et al. (2007)	Chile	Ecological	Mortality from 1950 to 2000 in the As-exposed region II of Chile (population: 477,000 in 2000) in compared to the unexposed region V.	Mortality from acute myocardial infarction (AMI) RR (95% CI)	1.48 (1.37–1.59), p < 0.001), men; 1.26 (1.14–1.40), p < 0.001), women
Valenzuela et al. (2009)	Mexico	Case-control	71 cases with skin lesions and 51 controls	Risk of skin lesions OR (95% CI)	Skin lesion risk: 4.28 (1.0–18.5), carriers of C (TC +CC) allele (Thr)
Yuan et al. (2010)	Chile	Ecological	Arsenic endemic region II compared unexposed region V.	Peak kidney caner mortality in 1981–1985 RR (95% CI)	Male: 3.4 (2.2–5.1) Female: 4.4 (3.0–6.4) Early-life exposure 7.1 (3.1–14)

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Table 5

Effects on arsenic as a consequence of early life and *in utero* exposure

Reference	County	Design	Characteristics of subjects	Measure	Result
Concha et al. (1998)	Argentina	Cross-sectional	11 women in late gestation (exposed to 200 μg/liter drinking water arsenic)	Urinary As metabolite %DMA	In newborns and mothers in late gestation 90% urinary As was DMA compared to 70% in nonpregnant women ($p < 0.001$)
Concha et al. (1998)	Argentina	Cross-sectional	10 lactating women and two nursing babies (drinking water arsenic ~200 μg/1)	Total maternal blood urinary and milk As	10 μg/l, 320 μg/l, 2.3 μg/kg fresh weight
Concha et al. (1998)	Argentina	Cross-sectional	96 women and children, from two villages of high drinking water arsenic exposure (200 μg/l) and one of low exposure (0.65 μg As/1)	Urinary As metabolites	Inorganic As in urine: about 50% in children versus 32% in women. Relative to other studies, there was very little MMA excreted.
Hopenhayn-Rich et al. (2000)	Chile	Ecological	Antofagasta (exposure: ~860 μg/L As in drinking water 1958–1970, abruptly declined to ~110 μg/L in 1971), Valparaiso (reference)	RR (95% CI)	1.7 (1.5–1.9), late fetal mortality; 1.53 (1.4–1.7), neonatal mortality; 1.26 (1.2–1.3), postneonatal mortality
Calderon et al. (2001)	Mexico	Cross-sectional	41 children chronically exposed to arsenic and lead (AsU = 62.9+/−0.03 μgAs/g creatinine), 39 children with low exposure (40.2+/−0.03 μgAs/g creatinine), all 6–9 years of age	Wechsler Intelligence Scale for Children, Revised Version, for Mexico	Higher levels of arsenic were significantly associated with lower performance on WISC-RM factorsexamining long-term memory and linguistic abstraction.
Hopenhayn et al. (2003)	Chile	Prospective cohort	424 infants from a high-exposure town (40 μg As/L drinking water) and 420 from a low-exposure town (<1 μg As/L drinking water)	Birth weight	−57 g; 95% CI = −123 to 9
Hopenhayn et al. (2003)	Chile	Prospective cohort	26 mothers living in a high-exposure city (40 μg As/L drinking water)	Urinary As	Initial mean value of 36.1 to a final value of 54.3 μg/L
Yanez et al. (2003)	Mexico	Cross-sectional	20 children of age 3–6 years from high-exposure community (soil: 100 mg/kg of arsenic), 35 children of age 3–6 years from low-exposure community	Comet assay	PO.05
Hopenhayn et al. (2006)	Chile	Prospective cohort	810 women who gave birth to live singleton infants (drinking water As exposure: 40 μg/L in exposure town, <1 μg/L for control town)	Adjusted percent As	Third trimester: 49.4% vs. 17% ($p< 0.0001$)
Rocha-Amador et al. (2007)	Mexico	Cross-sectional	132 children, age 6–10 years (average exposure in three separate towns: 5.8+/−1.3 μg/L, 169+/−0.9 μg/L, 194+/−1.3 μg/L)	Association between As in drinking water and Performance, Verbal, and Full IQ scores	β= −4.30, −6.40, −6.15
Rosado et al. (2007)	Mexico	Cross-sectional	557 children, 6–8 years of age living within 3.5 km of a metallurgic smelter complex	Visual-Spatial Abilities with Figure Design, the Peabody Picture	Inverse association between U As and performance scores ($p< 0.05$)

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Reference	County	Design	Characteristics of subjects	Measure	Result
				Vocabulary Test, the WISC-RM Digit Span subscale, Visual Search, and Letter Sequencing Tests	
Liaw et al. (2008)	Chile	Ecological	Regions II and V (exposure region: (exposure: ~870 μg/L As in drinking water 1958–1970, abruptly declined to ~110 μg/L in 1971)	Childhood liver cancer mortality RR (95% CI)	10.6(2.9–39.2)
Mendez-Gomez et al. (2008)	Mexico	Cross-sectional	65 children exposed simultaneously to arsenic and lead (93% of children had As in urine above 50 μg/L)	Association of AsU and DNA repair ability	β = −34.43, p = 0.019