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# Health Effects of Arsenic and Chromium in Drinking Water: Recent Human Findings

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## Key Words

early life exposure, skin lesions, childhood cancer, methylation

## Abstract

Even at high concentrations, arsenic-contaminated water is translucent, tasteless, and odorless. Yet almost every day, studies report a continually increasing plethora of toxic effects that have manifested in exposed populations throughout the world. In this article we focus on recent findings, in particular those associated with major contributions since 2006. Early life exposure, both in utero and in childhood, has been receiving increased attention, and remarkable increases in consequent mortality in young adults have been reported. New studies address the dose-response relationship between drinking-water arsenic concentrations and skin lesions, and new findings have emerged concerning arsenic and cardiovascular disease. We also review the increasing epidemiological evidence that the first step of methylation of inorganic arsenic to monomethylated arsenic (MMA) is actually an activation step rather than the first step in detoxification, as once thought. Hexavalent chromium differs from arsenic in that it discolors water, turning the water yellow at high concentrations. A controversial issue is whether chromium causes cancer when ingested. A recent publication supports the original findings in China of increased cancer mortality in a population where well water turned yellow with chromium.

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## INTRODUCTION

Arsenic is classified as a metalloid and chromium a metal, but they do have some properties in common. Inhalation of inorganic arsenic and inhalation of hexavalent chromium each cause lung cancer in smelter workers (21, 39). They also share a peculiar property in that each may cause lung cancer following ingestion via drinking water. However, they differ in that the evidence regarding inorganic arsenic in drinking water is extensive and sufficient for it to be established by the International Agency for Research on Cancer (IARC) as a Group 1 carcinogen. In contrast, the human evidence for hexavalent chromium is limited largely to one population study in China.

Arsenic and chromium have another feature in common. Entering each into PubMed retrieves more than 6000 publications in the past 10 years, which is daunting when trying to write a review on even one of them. We have therefore limited our review to topics in which there have been important new health findings presented in epidemiological studies published since 2006. Even with this restriction, an exhaustive assessment was not possible, so we have further restricted ourselves to selected major topics concerning arsenic in drinking water and one important topic concerning hexavalent chromium in drinking water. We identified new studies published since 2006 on each of these topics and review earlier publications when they are on the same topic.

## ARSENIC

### Effects of Early Life Exposure to Arsenic

The potential for arsenic in drinking water to cause effects in utero and for early life exposures to affect child development, child health, and adult disease has been a topic of increasing attention in recent years (77). **Table 1** presents the findings from epidemiological studies contributing information on these topics.

### Pregnancy Outcomes

The main findings concerning pregnancy outcomes relate to spontaneous abortion, stillbirths, reduced birth weight, and infant mortality (**Table 1**). Studies have produced mixed findings.

### Fetal Loss

Fetal loss includes spontaneous abortions (loss up to 28 weeks of pregnancy) and stillbirths (loss after 28 weeks). Increased fetal loss was reported in some studies but not others (**Table 1**). Differences are apparent in studies of the affected populations in Bangladesh and adjacent West Bengal, India. Ahmad et al. (2) present data for 96 exposed women (>50 μg/L) compared with 96 nonexposed women (<20 μg/L). The relative risk (RR) can be estimated at 2.9 ($p = 0.008$) for spontaneous abortion and 2.2 ($p = 0.046$) for stillbirths. Similar estimates were found in a study by Milton et al. (51) involving 533 women: spontaneous abortion RR = 2.5 (95% CI 1.5–4.3) and stillbirth RR = 2.5 (95% CI 1.3–4.9). In contrast, von Ehrenstein et al. (79), who studied 202 pregnancies, did not find increased risks of spontaneous abortion (RR = 1.0, CI: 0.4–2.7), but reported increased stillbirths above 200 μg/L (RR = 6.1, CI: 1.5–24), especially for 12 women who had arsenic skin lesions (RR = 13.1, CI: 3.2–54). Kwok et al. (37) studied outcomes for 2006 pregnant women and found no increase in stillbirths (they did not investigate spontaneous abortions). One can estimate from data they present that, among 732 women with arsenic exposure above 200 μg/L, there were 20 stillbirths, whereas among 556 low-exposure women (<50 μg/L) there were 13 stillbirths (RR = 1.17, $p = 0.33$).

By far the largest study, which also had the advantage of being a population-based cohort study, reported outcomes of 29,134 pregnancies in Matlab, Bangladesh (60). Results were not separated by spontaneous abortions and stillbirths, but the RR estimate for fetal loss was

**Table 1 Studies concerning the health consequences of early life exposure to arsenic in drinking water**

| Study/author | Publication year | Population Studied | Arsenic concentration[a] | Findings |
|---|---|---|---|---|
| **Pregnancy outcomes** | | | | |
| Borzsonyi et al. (7) | 1992 | Hungary | 170–330 μg/L | Increase in stillbirths and spontaneous abortion |
| Hopenhayn-Rich et al. (29) | 2000 | Chile | 860 μg/L | Increase in stillbirths and infant mortality |
| Ahmad et al. (2) | 2001 | Bangladesh | 100+ μg/L | Increase in spontaneous abortions, stillbirths, and preterm births |
| Hopenhayn et al. (28) | 2003 | Chile | Up to 50 μg/L | Reduced birth weight |
| Yang et al. (87) | 2003 | Taiwan | Up to 3590 μg/L | Reduced birth weight |
| Milton et al. (51) | 2005 | Bangladesh | Average 279 μg/L | Increase in spontaneous abortion and stillbirths |
| Kwok et al. (37) | 2006 | Bangladesh | 300+ μg/L | No increase in stillbirth or low birth weight |
| von Ehrenstein et al. (79) | 2006 | India | 200+ μg/L | Increase in stillbirths not in spontaneous abortions |
| Huyck et al. (34) | 2007 | Bangladesh | Up to 734 μg/L | Reduced birth weight |
| Rahman et al. (60) | 2007 | Bangladesh | 500+ μg/L | Minor increase in fetal loss and infant mortality |
| **Child cognitive function** | | | | |
| Siripitayakunkit et al. (63) | 2001 | Thailand | Not clear[b] | Impaired visual perception |
| Tsai et al. (73) | 2003 | Taiwan | Average 185 μg/L | Reduced pattern memory and switching attention |
| Wasserman et al. (84) | 2004 | Bangladesh | Up to 790 μg/L | Reduction in some performance and full-scale scores tests |
| von Ehrenstein et al. (80) | 2007 | India | 100+ μg/L | Reduction in vocabulary, object assembly, and picture completion scores |
| **Child cancer** | | | | |
| Moore et al. (52) | 2002 | United States | 35–90 μg/L | Leukemia not increased, slight increase in some other cancers |
| Liaw et al. (40) | 2008 | Chile | Up to 860 μg/L | Increased liver cancer mortality for ages 10–19 |
| **Adult diseases following early life exposure** | | | | |
| Smith et al. (65) | 1998 | Chile | Up to 860 μg/L | Increased lung cancer and chronic obstructive pulmonary disease (COPD) deaths aged 30–39 |
| Smith et al. (66) | 2006 | Chile | Up to 860 μg/L | Lung cancer/bronchiectasis deaths after in utero/child exposure |
| Yuan et al. (89) | 2007 | Chile | Up to 860 μg/L | Increased acute myocardial infarction deaths after in utero/child exposure |
| Lindberg et al. (41) | 2008 | Bangladesh | Average lifetime 181+ μg/L | Lower skin lesion risk if exposed in infancy |

[a]Where possible, the highest arsenic exposure category is given.
[b]Arsenic measurements in hair were obtained, and the high exposure group had hair concentrations above 5 μg/g.

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1.14 (95% CI 1.04–1.25) for exposure above 50 μg/L. The fetal loss relative risk estimate for the 5607 pregnancies in the highest exposure category (>409 μg/L during pregnancy) was only 1.10 (95% CI 0.97–1.25). In summary, these studies have yielded conflicting findings. The Matlab study involving 29,134 pregnancies is 10 times larger than any other study and found negligible evidence of increased risk. Coupled with a lack of increased risk demonstrated in the second largest study (37), the evidence that arsenic in drinking water increases the risk of fetal loss is limited. The conflicting findings from the smaller studies are thus puzzling, although smaller studies may have better exposure data.

## Reduced Birth Weight and Infant Mortality

Reductions in birth weight have been found in a low-arsenic-exposure study in Chile (<50 μg/L) (28), and in higher-exposure studies in Taiwan (87) and in Bangladesh (34). In the low-exposure study in Chile, the reduction in average birth weight estimate was 57 g, in Taiwan 30 g, and in Bangladesh one can derive from the regression coefficients that an increase in 1 μg/g in hair arsenic was associated with a 193.5-g reduction in birth weight.

Infant mortality was reported by Hopenhayn et al. 2000, Rahman et al. 2007, and von Ehrenstein et al. 2006 (29, 60, 79). The largest study (60) involved 29,134 pregnancies and reported a relative risk estimate of 1.17 (CI: 1.02–1.32) for infant mortality.

## Child Cognitive Function

The first study that reported effects of arsenic in drinking water on cognitive function was conducted in Thailand (63). Data were collected from 529 children ages 6–9 years, and arsenic exposure (based on hair concentrations) was associated with reduced visual perception test rescores ($p = 0.01$). A study of 49 exposed children and 60 unexposed children in Taiwan reported reduced pattern memory and switching attention scores ($p < 0.01$) with arsenic concentrations in water that averaged 185 μg/L in the high-exposure group (73). This result was followed by a study of 201 children in Bangladesh, which reported reduced intellectual function tests for exposures above 50 μg/L of arsenic in water, particularly in performance and full-scale scores ($p < 0.01$) (84). The associations were stronger for well-water arsenic concentrations than for urinary arsenic concentrations. Finally, in a study of 351 children in India, von Ehrenstein et al. (80) reported reduced vocabulary test scores, reduced object assembly scores, and reduced picture completion scores ($p = 0.02$) associated with urine concentrations of arsenic but not with the histories of arsenic water concentrations.

These studies of cognitive function in children each suggest some effects related to arsenic. The findings are difficult to compare because of differences in test instruments used or differences in assembling and reporting findings. The two most recent studies are distinctly different in that one finds an association with arsenic water concentrations but not with urine arsenic concentrations (84), whereas the other study found a relationship only with urine arsenic concentrations (80). In summary, although these studies suggest that arsenic does produce some effects on intellectual development in children, the inconsistencies in the findings suggest that further studies are needed to confirm and clarify the effects.

## Childhood Cancer

Limited information has been documented on arsenic exposure in drinking water and the incidence of childhood cancer. Infant-Rivard et al. (35) reported a relative risk estimate for lymphoblastic leukemia of 1.39 (CI: 0.7–2.76); however, the arsenic concentrations in drinking water were very low, so no increase could be expected. Moore et al. (52) studied childhood cancer incidence rates in Nevada at higher water concentrations, up to concentrations in the range of 35–90 μg/L. For all childhood cancer combined, the RR estimate in the high-exposure category was 1.25 (CI 0.91–1.69), and 1.37 (CI: 0.92–1.83) for leukemia.



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Childhood cancer and much higher water arsenic concentrations in Northern Chile, up to 860 μg/L, were studied by Liaw et al. (40). No increases were detected for all cancers combined. However, childhood liver cancer mortality under age 20, which is normally extremely rare, was markedly increased for those who were young children when they would have experienced high water arsenic concentrations (RR = 10.6, 95% CI 2.9–39.2, $p < 0.001$). These children all died before 1980 and medical records could not be located for histological confirmation, nor could individual exposure be confirmed. In summary, the evidence to date does not support an overall increase in mortality from childhood cancers, but one study has found high relative risks for liver cancer associated with high water arsenic concentrations.

## Adult Disease Following Early Life Exposure

Smith et al. (65) reported that 10 individuals ages 30–39 (0.8 expected) died in northern Chile from chronic obstructive pulmonary disease (COPD) in the years 1989–1993, and these individuals would have been young children during the peak arsenic exposure period. Lung cancer relative risk estimates were also elevated in this age range (14 men observed, 1.2 expected; 5 women observed, 1.2 expected). Mortality in the same population in northern Chile was further studied up to the year 2000, and investigators found that the cause of the increased COPD mortality rate was bronchiectasis. For the birth cohort born just before the high-exposure period (1950–1957), and exposed in early childhood, the standardized mortality ratio (SMR) for lung cancer was 7.0 (CI 5.4–8.9, $p < 0.001$) and the SMR for bronchiectasis was 12.4 (CI 3.3–31.7, $p < 0.001$). For those born during the high-exposure period (1958–1971), with probable exposure in utero and in early childhood, the corresponding SMRs were 6.1 (CI 3.5–9.9, $p < 0.001$) for lung cancer, and 46.2 (CI 21.1–87.7, $p < 0.001$) for bronchiectasis. They noted that the magnitude of the effects found on lung cancer and bronchiectasis mortality has no parallel when compared with effects of other environmental exposures occurring in utero and/or in early childhood.

Biological plausibility for the cancer findings can be found in experiments conducted in mice (81, 82). The offspring of pregnant mice who were given high doses of arsenic in their drinking water developed tumors at multiple sites, including the lung in female offspring, with incidence of lung carcinoma increased to 5/24 (21%) compared with 0/25 (0%) in the unexposed controls.

Mortality from acute myocardial infarction was also assessed in northern Chile, and studies showed that mortality increased soon after high exposures started (89). Of particular interest was the fact that the highest relative risk estimates were for young adult men ages 30–49 who were born in the high-exposure period, with probable exposure in utero and in early childhood (RR = 3.2, 95% CI: 2.79–3.75, $p < 0.001$). Atherosclerosis has been induced in mice by in utero exposure (67).

In contrast to these marked increased mortality risks following early life exposure to arsenic in drinking water, Rahman et al. 2006 (61) and Lindberg et al. 2008 (41) reported reduced risks of arsenic-induced skin lesions in Bangladesh in those exposed since infancy, compared with those exposed only later in life. For example, the relative risk estimate for those starting to drink tubewell water at ages 1–17, compared with those who started the year they were born, was 4.0 (CI: 2.5–6.2) (41). For a variety of reasons, assessing exposures many years in the past (i.e., exposures in infancy) is difficult, and misclassification of past exposure is likely. If misclassification was greater for exposures in the distant past (i.e., those in infancy) than exposures that were more recent (i.e., those later in life), risks could spuriously appear to be greater in those who have experienced only later life exposure compared with those exposed early in life. No information is provided in these studies to assess the accuracy of distant past or infant exposures.

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In summary, studies in one exposed population in Chile provide evidence for marked increase in adult mortality from lung cancer, bronchiectasis, and myocardial infarction following early life exposure. These findings need to be confirmed in other populations. One study reports lower risk of skin lesions with arsenic exposure in infancy compared with those whose exposure started later.

## Concentrations of Arsenic in Drinking Water and Skin Alterations

Arsenic ingestion causes characteristic pigmentation changes in the skin of the trunk and limbs and nodular keratosis on the palms and soles. In most populations with arsenic water problems, lesions are the first sign to indicate the problem. Skin lesions were identified in connection with arsenic in drinking water in Taiwan in the 1960s (75) and in West Bengal, India, in the 1980s (10). An important current issue is whether skin lesions occur soon after exposure first begins and are caused by relatively low arsenic exposures. If they are, then skin lesions could perhaps serve as a sentinel event for arsenic problems that require public health intervention. However, if they are not, then priority would need to be given to performing extensive arsenic testing in all groundwater sources used for drinking, even in populations where arsenic-caused skin lesions are not evident.

**Table 2** presents the findings from studies that identify the prevalence of skin lesions in relation to concentrations of arsenic in drinking water. As shown in this table, several studies have reported skin lesions in subjects in whom the highest known arsenic exposure was below 50 μg/L. A superficial reading of these data could suggest to the unwary that skin lesions occur at very low water arsenic concentrations. Most of these studies, however, involved cross-sectional ascertainment of exposure, and no data are given concerning missing exposure information, including the possibility of high exposures in the distant past. In India and Bangladesh (where all the studies linking low exposures to skin lesions have been done), individuals generally obtain water from multiple sources over their lifetimes, and incomplete or missing data are inevitable. In addition, even when past water source histories are obtained, previously used tubewells may be closed or broken at the time of cross-sectional study investigations. So far, only one study has focused on participants investigators thought had

**Table 2 Studies of arsenic concentrations in drinking water and skin lesion prevalence[a]**

| Author | Publication Year | Population Studied | Number of cases with skin lesions | Range of As concentration μg/L | Number of skin lesion cases with exposure <50 μg/L | Percentage of cases with skin lesions with exposure <50 μg/L |
|---|---|---|---|---|---|---|
| Guha Mazumder (25) | 1998 | India | 517 | 0–3400 | 12 | 2.3% |
| Tondel (72) | 1999 | Bangladesh | 430 | 10–2040 | 37[b] | 8.6% |
| Ahsan (5) | 2000 | Bangladesh | 36 | <29–991 | 13 | 36.1% |
| Haque (26) | 2003 | India | 192 | 0–500 | 6 | 3.1% |
| Maharjan (42) | 2005 | Nepal | 93 | 3–1072 | Not given | Not given |
| Ahsan (4) | 2006 | Bangladesh | 714 | 8–864 | 147[c] | 20.6% |
| Rahman (61, 62) | 2006 | Bangladesh | 504 | 0–3644 | 78 | 15.5% |
| Ghosh (24) | 2007 | India | 373 | 50–1188 | Not given | Not given |
| McDonald (49) | 2007 | Bangladesh | 155 | 0–166 | 138 | 89.0% |

[a]Cases reported to have been consuming water containing less than 50 μg/L of arsenic.
[b]As exposure <150 μg/L.
[c]Time-weighted well arsenic concentration <40 μg/L.

provided complete exposure data for the previous 20 years (26). This study, in West Bengal, India, originally began as a cross-sectional survey of 7683 participants, including 361 with pigmentation changes and 156 with keratosis (25). In the original report, 12 with skin lesions had been consuming water containing less than 50 μg/L of arsenic. At the time, however, the authors noted that "more detailed exposure assessment and measurement of all past and present water arsenic levels may show that those thought to be consuming low arsenic water may actually have been more heavily exposed from other sources" (25). After completing such an investigation, producing detailed information on past exposure for more than 20+ years, the same group found that all individuals confirmed to have had skin lesions as well as complete water source histories had consumed water containing arsenic at concentrations higher than 100 μg/L at some point in time, and the large majority had consumed water containing arsenic concentrations higher than 200 μg/L (26). In addition, this study also reported that the average latency for skin lesions was 23 years from first exposure. The data from this study suggests that arsenic exposures well above 100 μg/L (and most likely above 200 μg/L) are needed to cause skin lesions. These data also highlight the need for investigators to focus on those subjects with complete information on past water sources and past exposure. Many, if not all, of the studies in **Table 2** likely included subjects with incomplete past exposure information. These studies could have missed past periods of high exposure in some skin lesion subjects and therefore could have reported incorrect evidence linking skin lesions with low arsenic exposure. In summary, the Haque et al. study, the only one focusing on subjects with complete past exposure information, provides evidence that cases of skin lesions caused by arsenic rarely occur when arsenic water concentrations are lower than 200 μg/L. Implementation of drinking water standards should be based on the risks of other more serious diseases or diseases that may occur at exposures below 200 μg/L.

## Cardiovascular Disease

A large number of studies have considered cardiovascular effects of arsenic in drinking water, especially in Taiwan (20, 57, 83). Here we focus our attention on publications appearing in the literature since 2006. The major epidemiological studies are listed in **Table 3**. Ahmad et al. (1) in Bangladesh and Mumford et al. (54) in a study in China reported similar electrocardiogram changes in exposed populations, which included changes associated with increased risk of arrhythmia and mortality. Chen et al. (11) in Bangladesh and Kwok et al. (38) in China reported blood pressure changes, suggesting potential increased risk for both cardiovascular and cerebrovascular disease.

A report of increased carotid atherosclerosis correlating with arsenic exposure in Taiwan further supported evidence linking cerebrovascular disease and arsenic exposure (86), and some evidence, also in Taiwan, documented that small increases in intracerebral hemorrhage mortality decreased after reducing arsenic exposure (50). A clear latency pattern was found between myocardial infarction mortality and exposure to arsenic in drinking water in Chile (89), supplementing the latency findings concerning lung cancer and bladder cancer (46). However, there was no evidence of increased cerebrovascular mortality despite high arsenic exposures affecting a large population living in northern Chile (89).

In summary, mounting evidence supports that arsenic in drinking water causes increased risks of coronary artery disease, including increased mortality, but the evidence concerning cerebrovascular disease is mixed.

## Evidence that Arsenic Methylation Increases Disease Risks

Susceptibility to the health effects of arsenic appears to vary from person to person, and a wide variety of factors including age of exposure, genetics, diet, and concurrent exposures such as smoking can impact the degree of severity of those effects. The results of several previous

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**Table 3 Studies concerning cardiovascular consequences of early life exposure to arsenic in drinking water published since 2006**

| Study/author | Publication year | Population studied | Arsenic concentration | Findings |
|---|---|---|---|---|
| Ahmad et al. (1) | 2006 | Bangladesh | Average about 500 μg/L | Electrocardiogram abnormalities related to arsenic-induced skin lesions |
| Chen et al. (12) | 2006 | Bangladesh | Up to 864 μg/L | Increased pulse pressure with arsenic exposure |
| Wu et al. (86) | 2006 | Taiwan | Up to 3590 μg/L | Increased prevalence of carotid atherosclerosis |
| Chen et al. (11) | 2007 | Bangladesh | Up to 864 μg/L | Increased vascular inflammation |
| Chiu et al. (15) | 2007 | Taiwan | Up to 1140 μg/L | Intracerebral hemorrhage mortality reduced after exposure was reduced |
| Kwok et al. (38) | 2007 | China | 100+ μg/L | Increased blood pressure |
| Meliker (50) | 2007 | USA | Average 11 μg/L | Cerebrovascular disease; both men and women, SMR = 1.19 |
| Mumford et al. (54) | 2007 | China | 430–690 μg/L | Electrocardiogram abnormalities related to arsenic water concentrations |
| Yuan et al. (89) | 2007 | Chile | Up to 860 μg/L | Increased myocardial infarction but not cerebrovascular mortality |
| Heck et al. (27) | 2008 | Bangladesh | 200+ μg/L | Increased anemia with high arsenic exposure |

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studies have shown that interindividual differences in arsenic metabolism may be responsible for a substantial portion of these susceptibility differences. The primary metabolic pathway of ingested inorganic arsenic in humans is methylation (76). Once ingested, InAs is methylated to monomethylarsonic acid (MMA5), which is reduced to monomethylarsonous acid (MMA3). MMA3 is then methylated to dimethylarsinic acid (DMA5), which is reduced to dimethylarsinous acid (DMA3). In humans, this process is not complete, and some arsenic remains as InAs and MMA. In humans, arsenic is eliminated primarily via urinary excretion, and the relative distribution of InAs, MMA, and DMA in urine reflects internal metabolism (44, 45). As such, the proportions of InAs, MMA, and DMA excreted in urine have been commonly used as biomarkers of the degree to which individuals methylate ingested InAs (56). Ingested InAs is typically excreted as 10%–20% InAs, 10%–15% MMA, and 60%–75% DMA, although large interindividual variations exist (30).

Until recently, methylation of InAs was thought to be primarily a detoxification pathway because the methylated species most commonly measured in human urine samples, MMA and DMA, are more readily excreted and thought to be less toxic than InAs (9, 23, 53). MMA3 and DMA3 are highly unstable in human urine and therefore have been measured in only a few human studies. However, MMA3 is generally much more toxic *in vitro* than is its pentavalent form, and it is even more toxic than trivalent InAs (18, 47, 58, 71). These findings have led to the hypothesis that MMA3 may be the primary toxic species of ingested arsenic.

Several studies have investigated the relationship between interindividual differences in arsenic metabolism and risks of arsenic-related disease. These studies have investigated risks in subjects who excrete high or low proportions of each of the three major arsenic species (InAs, MMA, DMA) in their urine. **Figure 1** and **Table 4** show the results of studies comparing the risks of various arsenic-related disease end points in those who excrete high and low proportions of arsenic as MMA [MMA/(InAs + MMA + DMA) or %MMA]. In most studies, adjustments were made for total arsenic intake, typically either by adjusting for cumulative arsenic exposure (CAE) in the analysis or by stratifying subjects into high and low CAE groups. In several of the Taiwan studies, results

**MMA3:** monomethylarsonous acid

**DMA3:** dimethylarsinous acid

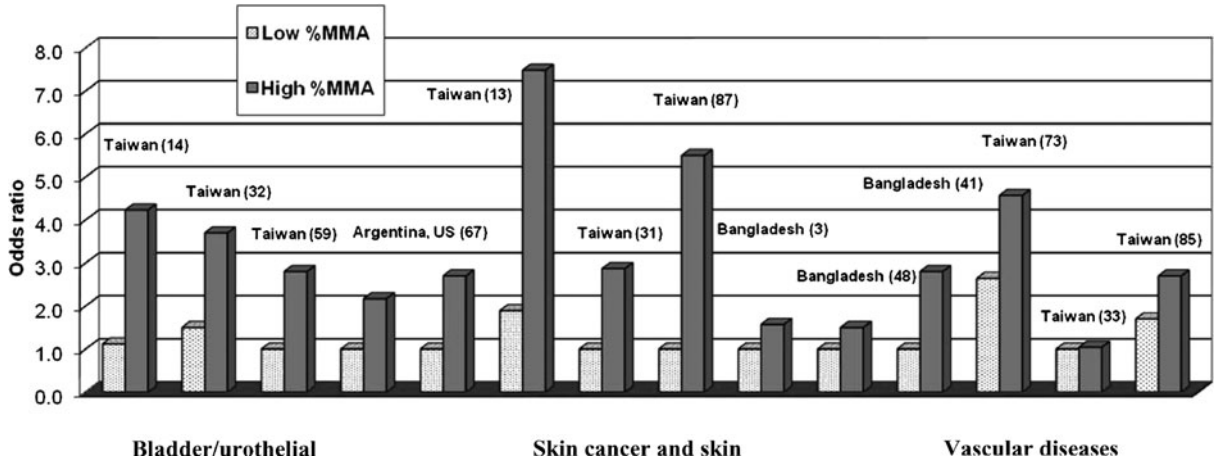


**Figure 1**

Odds ratios of various arsenic-related health effects in people who excrete high and low proportions of arsenic in their urine as (%MMA).

are for the MMA/DMA ratio rather than for the %MMA. Because 60%–75% of arsenic in urine is in the form of DMA, the ratio MMA/DMA is closely related to %MMA. In some of the study results shown in **Figure 1**, the reference group (OR = 1.0) is the group with low %MMA. In other studies, data were stratified by CAE, and the reference groups are those subjects with low CAE and low %MMA. For these studies, only data from the high-CAE strata are shown.

As a whole, the studies in **Figure 1** and **Table 4** provide a consistent body of evidence that interindividual differences in arsenic metabolism, specifically the proportion of arsenic excreted as MMA, is associated with susceptibility to arsenic-related disease. In all but one study, odds ratios for the various diseases are ~1.5–4 times greater in subjects with higher %MMA compared with those with lower %MMA. The one exception is the study of hypertension by Huang et al., where adjusted odds ratios in the low and high %MMA group were essentially no different (1.00 and 1.04, respectively).

Several biases could have affected the studies shown in **Figure 1**, but are unlikely to have caused the positive differences identified. In most of the studies, only a single urine sample was collected from each subject, and this sample was collected at or near the time of disease diagnosis. The latency period of several arsenic-caused diseases such as cancer may be several decades or more, which calls to question the validity of using a recent assessment of methylation to estimate past methylation patterns. Methylation patterns remain fairly stable over periods of time of up to a year (17, 70), but intraindividual variability over time does exist and could have led to some misclassification of %MMA. However, because samples were collected, stored, and analyzed independently of disease status, these factors would most likely have had nondifferential effects and biased results toward the null, not toward the positive effects identified in **Figure 1**. The assessment of methylation near or after disease diagnosis also raises concerns about the temporal relationship between disease and methylation capacity. That is, the effects seen in these studies might not be due to the impact of methylation patterns on disease, but rather to the impact of disease or disease treatment on methylation patterns. However, five of the studies presented in **Figure 1** involved nonmelanoma skin cancer or skin lesions. Another study has reported an association between %MMA and the presence of chromosomal aberrations in lymphocytes (43). These conditions are generally

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**Table 4 Study descriptions and odds ratios of arsenic-related health effects comparing people with high and low %MMA[a]**

| | | | | Low %MMA | | High %MMA | | |
|---|---|---|---|---|---|---|---|---|
| Author | Year | Country | Outcome | Odds ratio | Confidence interval | Odds ratio | Confidence interval | Definition of high %MMA |
| Hsueh et al. (31) | 1997 | Taiwan | Skin cancer | 1.00 | Ref | 2.87 | Not available | %MMA > 26.7% |
| Yu et al. (88) | 2000 | Taiwan | Skin cancer | 1.00 | Ref | 5.50 | 1.22–24.81 | %MMA > 15.5% |
| Chen et al. (13) | 2003 | Taiwan | Skin cancer | 1.89 | 0.60–6.01 | 7.48 | 1.65–33.99 | MMA/DMA > 0.20 |
| Chen et al. (14) | 2003 | Taiwan | Bladder cancer | 1.12 | 0.26–4.7 | 4.23 | 1.12–16.01 | MMA/DMA > 0.21 |
| Tseng et al. (74) | 2005 | Taiwan | PVD | 2.64 | 0.56–12.45 | 4.57 | 1.01–20.61 | %MMA > 11.42% |
| Steinmaus et al. (68) | 2006 | Argentina | Bladder cancer | 1.00 | Ref | 2.17 | 1.02–4.63 | %MMA > = 16.7% |
| Steinmaus et al. (68) | 2006 | United States | Bladder cancer | 1.00 | Ref | 2.70 | 0.39–18.6 | %MMA > = 14.8% |
| Wu et al. (86) | 2006 | Taiwan | Atherosclerosis | 1.7 | 0.6–4.5 | 2.7 | 1.0–7.8 | %MMA > = 13.4% |
| Ahsan et al. (3) | 2007 | Bangladesh | Skin lesions | 1.00 | Ref | 1.57 | 1.10–2.26 | %MMA > 16.4% |
| Huang et al. (33) | 2007 | Taiwan | Hypertension | 1.00 | Ref | 1.04 | 0.66–1.62 | %MMA > = 15.55% |
| McCarty et al. (48) | 2007 | Bangladesh | Skin lesions | 1.00 | Ref | 1.50 | 1.00–2.26 | 10X MMA/InAs |
| Pu et al. (59) | 2007 | Taiwan | Bladder cancer | 1.0 | Ref | 2.8 | 1.6–4.8 | %MMA > 9.2% |
| Huang et al. (32) | 2008 | Taiwan | Bladder cancer | 1.5 | 0.4–5.9 | 3.7 | 1.2–11.6 | %MMA > = 11.40% |
| Lindberg et al. (41) | 2008 | Bangladesh | Skin lesions | 1.0 | Ref | 2.8 | 1.9–4.2 | %MMA > 12% |

[a]Abbreviations: 10X MMA/InAs, tenfold increase in MMA/InAs ratio; CAE, cumulative arsenic exposure; PVD, peripheral vascular disease; Ref, reference group.

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benign and would not be expected to cause the major systemic metabolic changes that can be caused by more fatal diseases. Identifying associations in studies involving these relatively benign conditions suggests that the results shown in **Figure 1** were not due to the impact of disease on methylation capacity.

As discussed above, evidence increasingly demonstrates that MMA3 is much more toxic than its pentavalent form and is more toxic than InAs or DMA. All the studies given in **Figure 1** involve both valence forms of MMA combined (MMA3 + MMA5). Because MMA3 is highly unstable in urine and rapidly oxidized to MMA5, isolating MMA3 and separating its effects from those of MMA5 are very difficult in field investigations. Only one study has assessed the role of MMA3 in an arsenic-related disease in humans. (This study did not present odds ratios so was not included in **Figure 1**.) In this study, in an arsenic-exposed region in Mexico, %MMA3 levels were higher in subjects with arsenic-caused skin lesions (mean %MMA3 = 7.7%, $n = 55$) than in exposed subjects without skin lesions (mean %MMA3 = 5.9%, $n = 21$, $p = 0.072$) (78). Using *in vitro* assays, it

is plausible that MMA3 is the primary toxic species responsible for the effects seen in **Figure 1**, and the total MMA (MMA3 + MMA5) measured in these studies is simply a marker for MMA3. Investigators do not currently know how well total MMA accurately reflects MMA3. However, total MMA is likely not a perfect measure of MMA3, and a less-than-perfect correlation would result in nondifferential misclassification of %MMA3. This misclassification would bias odds ratios truly related to %MMA3 toward the null. Thus, if MMA3 really is the primary toxic agent, the difference in odds ratios due to interindividual differences in methylation capacity would likely be even greater than the 1.5 to 4-fold differences shown in **Figure 1**.

In summary, almost all studies of arsenic metabolism and arsenic-related health effects have shown that people who excrete elevated proportions of MMA have higher risks of arsenic-caused cancer and other arsenic-related health effects than do those who excrete lower proportions. Although some studies involve relatively small numbers of subjects, the consistency of these findings—across different studies, different health effects, different countries, different researchers, and different study populations—supports the hypothesis that individual differences in arsenic methylation patterns may play an important role in susceptibility to arsenic-related disease. Future research is also needed to ascertain which factors control %MMA in humans. Several demographic (e.g., gender and age), dietary (e.g., folate and selenium), and genetic factors have been linked to arsenic metabolism in humans, but these have generally accounted for only a small amount of the total interindividual variability in the metabolic process (16, 22, 56, 69).

## CHROMIUM

In contrast with arsenic, not much that is new has appeared in the epidemiological literature since 2006. An important exception to this are findings concerning chromium ingestion and cancer. Like arsenic, it has long been established that inhalation of chromium, in particular hexavalent chromium (CrVI), can cause human lung cancer (36). But could chromium also cause cancer following ingestion like arsenic can? The answer to this is not so clear, but a recent publication by Beaumont et al. (6) concerning a study in the Liaoning Province in China documents increased cancer risks following ingestion of CrVI in drinking water: In particular, increased stomach cancer risks were demonstrated, but some evidence also indicated increased lung cancer risks. The cancer evidence from the population exposed in China first appeared more than 25 years ago.

In 1959, production of ferrochromium commenced in a factory in Liaoning Province, China (6, 64, 85). In 1964, residents living near the factory reported a yellow coloration in nearby wells used for drinking water, and in 1965, high concentrations of CrVI were confirmed and remediation work commenced; declines in concentrations of chromium in ground water were documented in 1967. Twenty years later, in 1987, Zhang & Li (91) published a paper in the *Chinese Journal of Preventive Medicine*, reporting increased stomach and lung cancer rates in the exposed villages. An unfortunate sequence of events followed, including publication by the same authors of an article in the *Journal of Occupational and Environmental Medicine* (*JOEM*) concluding that the results did not indicate an association of cancer mortality with exposure (90). Evidence emerged later that this paper involved a U.S. consulting firm that had been hired by industry clients with liability for chromium pollution in the United States (19). In 2006, nine years after the article had been published, the editor of *JOEM* retracted the paper, stating that "financial and intellectual input to the paper by outside parties was not disclosed" (8).

The recent publication by Beaumont et al. (6) presents findings from the same chromium-exposed population in China (6). They found that stomach cancer mortality in the exposed population was elevated compared with regions without contaminated water (RR = 1.82; CI 1.11–2.91) and compared with the whole

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province (RR = 1.69; CI 1.12–2.44). Lung cancer was not much increased in comparison with the unexposed regions (RR = 1.15; CI 0.62–2.07) but was increased in comparison with the whole province (RR = 1.78; CI 1.03–2.87). The study had some rather severe limitations described by the authors; these limitations included lack of information on mortality year by year so trends could be examined and lack of knowledge as to how the original authors had determined the deceaseds' places of residence (6). Perhaps the greatest weakness of the evidence was the short latency from exposure to increased mortality risks (64). The exposures may have started as early as 1960, but mortality was assessed for 1970–1978, concerning only 10–18 years from the time of first exposure. Yet the findings concerning stomach cancer at least seem consistent with the indication of increased risk. This study is important because the world may have no other population large enough in which to study high exposures of CrVI in water (64). It provides human evidence on its own but with serious limitations. It is noteworthy, however, that animal ingestion studies also find carcinogenic effects of CrVI in water.

In summary, new epidemiological studies concerning chromium are lacking. However, the mortality study in China provides fascinating evidence that human ingestion of CrVI may increase the risk of stomach cancer.

## DISCLOSURE STATEMENT

The authors are not aware of any biases that might be perceived as affecting the objectivity of this review.

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