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## Arsenic in drinking water and lung cancer: A systematic review

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## ARTICLE INFO

## Article history:

Received 12 November 2007

Received in revised form

18 February 2008

Accepted 9 April 2008

Available online 29 May 2008

## Keywords:

Arsenic

Drinking water

Lung cancer

Mortality

Incidence

Epidemiology

Systematic review

Taiwan

## ABSTRACT

Exposure to inorganic arsenic via drinking water is a growing public health concern. We conducted a systematic review of the literature examining the association between arsenic in drinking water and the risk of lung cancer in humans. Towards this aim, we searched electronic databases for articles published through April 2006. Nine ecological studies, two case–control studies, and six cohort studies were identified. The majority of the studies were conducted in areas of high arsenic exposure (100 µg/L) such as southwestern Taiwan, the Niigata Prefecture, Japan, and Northern Chile. Most of the studies reported markedly higher risks of lung cancer mortality or incidence in high arsenic areas compared to the general population or a low arsenic exposed reference group. The quality assessment showed that, among the studies identified, only four assessed arsenic exposure at the individual level. Further, only one of the ecological studies presented results adjusted for potential confounders other than age; of the cohort and case–control studies, only one-half adjusted for cigarette smoking status in the analysis. Despite these methodologic limitations, the consistent observation of strong, statistically significant associations from different study designs carried out in different regions provide support for a causal association between ingesting drinking water with high concentrations of arsenic and lung cancer. The lung cancer risk at lower exposure concentrations remains uncertain.

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## 1. Introduction

Arsenic is a ubiquitous toxicant and carcinogenic element associated with a wide range of adverse human health effects (Navas-Acien et al., 2005, 2006; Tseng et al., 2002; Chen et al., 1988a; Chiou et al., 1995; International Agency for Research on Cancer, 2004). Exposure to inorganic arsenic via drinking water is a major public health concern (Lubin et al., 2007). Worldwide, more than 100 million people are exposed to arsenic in drinking water at concentrations greater than 50 µg/L (Rahman et al., 2001), levels considered to have harmful health effects. While exposure to such high levels of arsenic is localized to certain

regions of the world, exposure to lower, but still potentially harmful, levels is even more widespread.

A diverse body of epidemiologic evidence has accrued on this topic. As part of a large-scale systematic review of diet and lung cancer, we performed a systematic review of this epidemiological evidence.

## 2. Materials and methods

This work was carried out as a part of a project funded by the World Cancer Research Fund (WCRF) and the American Institute for Cancer Research to develop a report entitled 'Food, Nutrition, Physical Activity and the Prevention of Cancer: a Global Perspective' (World Cancer Research Fund/American Institute for Cancer Research, 2007). All of the work funded under this project was conducted using a standardized protocol developed by WCRF ([http://www.wcrf.org/research/second\\_wcrf\\_aicr\\_report.lasso](http://www.wcrf.org/research/second_wcrf_aicr_report.lasso)). While all work contained in this manuscript was done using the WCRF protocol, the conclusions of this manuscript may differ from those in the WCRF report as the WCRF report includes other data and uses different criteria for judgment.

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## 2.1. Study search

For the WCRF report, we sought all evidence on the associations between dietary intake (including beverage consumption), physical activity, or anthropometric measures and lung cancer that were reported in randomized clinical trials, or cohort, case-control and ecological studies. The search strategy used was similar to one described in a previous publication (Gallicchio et al., 2006), except that the outcome search terms were for lung cancer rather than for nasopharyngeal carcinoma [outcome search terms for this report: lung neoplasm [mh] OR (lung AND (carcinoma × [tiab] OR neoplasm × [tiab] OR tumor × [tiab]))]. Using this search strategy, the following electronic databases were searched: PubMed, Embase, Pascal, ISI Web of Science, NIAAA Alcohol and Alcohol Problems Science, The Cochrane Library, Biological Abstracts, Cumulative Index to Nursing and Allied Health Literature, Index Medicus for WHO Eastern Mediterranean Region, Index Medicus for South East Asian Region, and Latin American and Caribbean Center on Health Sciences Information. The search included all studies published up to April 2006; there were no language restrictions. In addition, the study team hand-searched the references cited in the 1997 WCRF report, in the articles chosen for data abstraction, and in the relevant review articles or meta-analyses identified in the PubMed search.

## 2.2. Study selection

The following exclusion criteria were applied to the abstracts identified in the literature search: (1) no original data (reviews, editorials, meta-analyses); (2) studies not addressing the association between dietary intake, physical activity, or anthropometric measures and lung cancer; (3) studies not in humans; and (4) case reports and case series. The full-text articles of all references selected after applying these criteria were reviewed using the same criteria. After the full-text review, references detailing randomized clinical trials, observational studies (cohort, case-control, cross-sectional studies), or ecological studies on the association between arsenic exposure and lung cancer were selected and examined for inclusion in this analysis. If separate reports from the same study were published, the report with the most updated data was selected for inclusion or, in the case of duplicate publication, only one publication was included. In addition, because only one study identified in the full-text review examined dietary arsenic exposure and the development of lung cancer (Schrauzer et al., 1977), only those studies that investigated the relationship between arsenic in drinking water and lung cancer were included. The eligibility of each abstract or full-text article was assessed independently in a standardized manner by two reviewers.

**Table 1**  
Quality criteria<sup>a</sup>

A. All studies:
1. Was exposure assessed at the individual level?
2. Was exposure assessed using a biomarker?
3. Was the outcome based on objective tests (histological confirmation) in ≥90% of the study participants?
4. Did the authors present internal comparisons within study participants?
5. Did the authors control for potential confounding risk factors in addition to age?
6. Did the authors control for the healthy worker effect?
B. Cohort studies:
1. Was loss to follow-up independent of exposure?
2. Was the intensity of the search of disease independent of exposure status?
C. Case-control studies:
1. Were the data collected in a similar manner for all participants?
2. Were the same exclusion criteria applied to all participants?
3. Was the time period over which cases and non-cases were interviewed the same?
4. Was the interviewer blinded with respect to the case status of the person interviewed?
5. Was the response rate among non-cases at least 70%?
6. Were all cases interviewed within 6 months of diagnosis?
7. Was the study based on incident cases of disease?
8. Were non-cases individuals who, had they developed the disease, been cases?

<sup>a</sup> Adapted from Longnecker et al. (1988).

## 2.3. Data abstraction and quality assessment

Data abstraction for selected articles was performed serially by two reviewers using an electronic abstraction database created by WCRF. Disagreements between reviewers were resolved by consensus. To assess the study quality, we adapted the criteria by Longnecker et al. (1988) for observational studies (Table 1).

## 3. Results

### 3.1. Study selection

The search yielded 22,994 references, of which 21,385 were excluded after abstract review. Of the 1609 articles obtained for full-text review, 22 pertained to arsenic exposure and lung cancer. We excluded four studies that reported data included in other publications (Chen et al., 1988a; Wu et al., 1989; Guo et al., 2004; Ferreccio et al., 1998) and one that examined the association between dietary intake of (but not drinking water exposure to) arsenic and the development of lung cancer (Schrauzer et al., 1977). This left 17 studies conducted in general populations (Fig. 1) that met our inclusion criteria.

### 3.2. Study characteristics

#### 3.2.1. Ecological studies

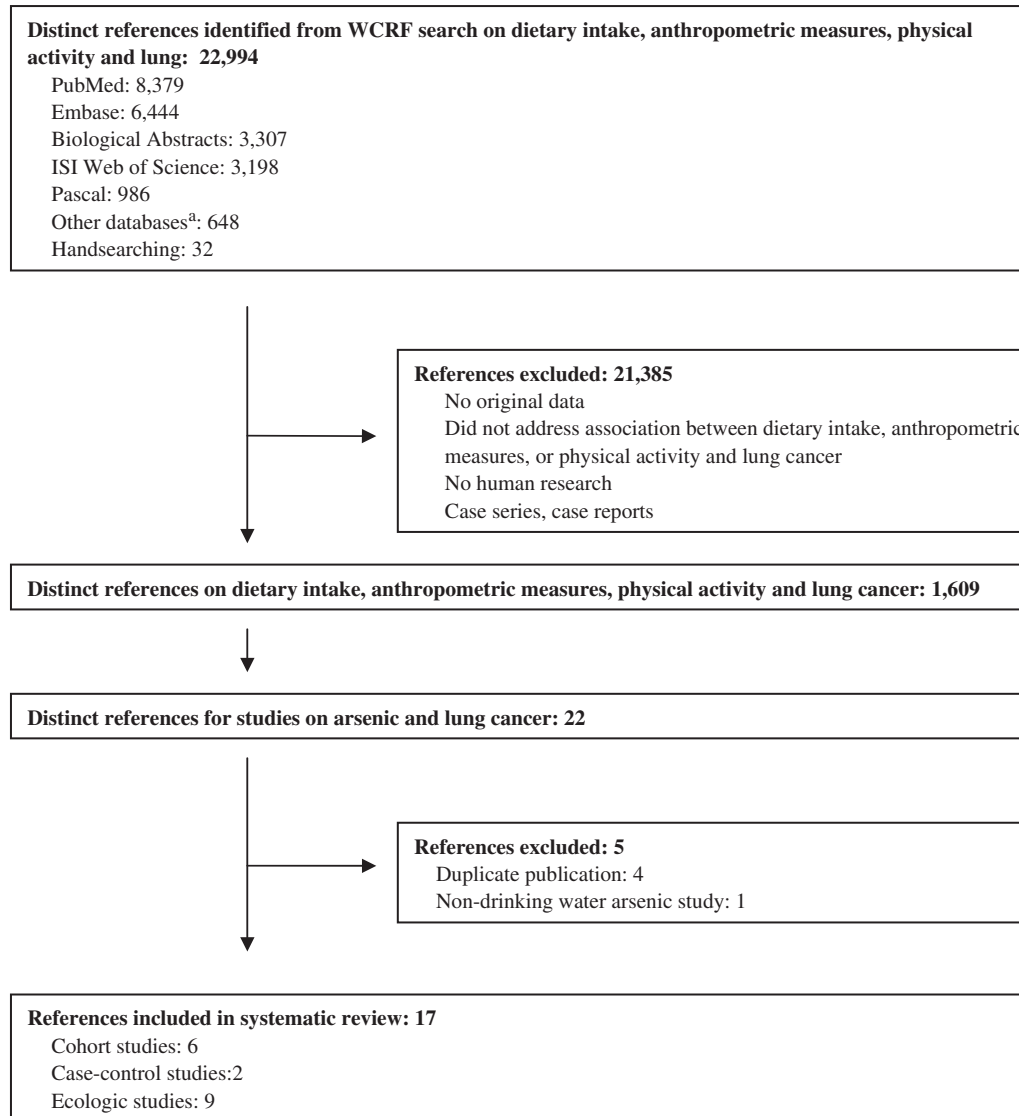
Nine of the 17 studies included in this review were ecological studies (Table 2). Of these, six were carried out in high arsenic areas of Taiwan (Chen et al., 1985, 1992; Guo, 2004; Tsai et al., 1999; Chen and Wang, 1990; Chiu et al., 2004), and one each in Belgium (Buchet and Lison, 1998), in the Cordoba Province, Argentina (Hopenhayn-Rich et al., 1998), and in Northern Chile (Smith et al., 1998). All of the studies assessed arsenic exposure using grouped or ecologic measurements of drinking water (artesian well or tap water) concentrations and compared age-standardized lung mortality rates across geographic regions (Table 2).

#### 3.2.2. Cohort and case-control studies

Eight of the studies included in this review were cohort or case-control studies (Table 3), conducted in southwestern Taiwan ( $n = 4$ ) (Chen et al., 1986, 1988b, 2004; Chiou et al., 1995), in the Niigata Prefecture, Japan ( $n = 3$ ) (Nakadaira et al., 2002; Tsuda et al., 1989, 1995), and in a high arsenic area in Northern Chile ( $n = 1$ ) (Ferreccio et al., 2000). Only two of the studies had more than 100 cancer cases (Chen et al., 2004; Ferreccio et al., 2000). One of the two case-control studies used hospital-based controls (Ferreccio et al., 2000); the other used community-based controls (Chen et al., 2004).

Arsenic drinking water exposure was based on geographic or other grouped or ecologic measurements in most studies. Two studies from Taiwan (Chiou et al., 1995; Chen et al., 2004) created a cumulative arsenic exposure index (mg/liter-year) by multiplying the number of years of living in a specific village/area by the average arsenic level in drinking water in that village/area (usually measured at a single point in time). The study conducted in Northern Chile calculated arsenic exposure histories for each participant by determining the average water arsenic concentration for the county in which he or she resided each year and summing those values over the participant's lifetime (Ferreccio et al., 2000). Other studies assigned exposure on the basis of residence in an area with high arsenic concentrations in water or number of years of drinking artesian well water. None of the studies used biomarkers to assess arsenic exposure.

Two of the cohort studies and one of the case-control studies were based on incident lung cancer cases (Chiou et al., 1995; Chen



**Fig. 1.** Study selection process. <sup>a</sup>Other databases: NIAAA Alcohol and Alcohol Problems Science Database ( $n = 48$ ), Cochrane Library ( $n = 101$ ), CINAHL-EBSCOhost ( $n = 270$ ), Agricola ( $n = 82$ ), Index Medicus for WHO Eastern Mediterranean Region ( $n = 4$ ), Index Medicus for South East Asian Region ( $n = 5$ ), and Latin American and Caribbean Center on Health Sciences Information ( $n = 114$ ).

et al., 2004; Ferreccio et al., 2000). Five of the studies used lung cancer death as the endpoint, ascertained via death certificates and/or national cancer registry databases (Chen et al., 1986, 1988b; Nakadaira et al., 2002; Tsuda et al., 1989, 1995). In both case-control studies, the cases were histopathologically confirmed (Chen et al., 1986; Ferreccio et al., 2000). All cohort and case-control studies were at least adjusted for age. Other adjustment factors included gender in seven studies (Chen et al., 1986, 1988b, 2004; Chiou et al., 1995; Tsuda et al., 1989, 1995; Ferreccio et al., 2000), smoking in four studies (Chiou et al., 1995; Chen et al., 1986, 2004; Ferreccio et al., 2000), presence of other diseases in one study (Chiou et al., 1995), alcohol consumption in one study (Chen et al., 2004), and occupational exposure in one study (Ferreccio et al., 2000).

### 3.3. Quality assessment

When these studies were rated using conventional quality criteria, the overall quality of evidence was not judged to be of the

highest quality. Only four of the studies assessed arsenic exposure at the individual level (Chen et al., 1986, 1988b; Chiou et al., 1995; Ferreccio et al., 2000). All of the ecological studies stratified by gender, but only one presented results adjusted for potential confounders other than age (Chen and Wang, 1990). Of the cohort and case-control studies, only one-half included adjustments for cigarette smoking status.

### 3.4. Associations between arsenic and lung cancer

#### 3.4.1. Ecological studies

The six ecological studies conducted in Taiwan consistently observed markedly higher lung cancer mortality rates in high arsenic areas compared to the general population (Table 2). Three studies comparing an area with high arsenic levels in drinking water (median = 780  $\mu\text{g/L}$ ) to the general population reported age-adjusted SMRs ranging from 2.92 to 4.13 for females and 2.31 to 3.20 for males. Consistent with these findings, Chen et al. (1992) reported significantly elevated rate ratios for lung cancer

**Table 2**  
Ecological studies of the association between drinking water arsenic concentrations and age-adjusted lung cancer mortality rates

Author, year	Population	No. of populations	Time period	Comparison	Risk statistic reported	Estimate (95% CI)
<b>A. Taiwan</b>						
Guo, 2004	10 townships in the southwest coast of Taiwan	6	1971–1990	>0.64 mg/L exposure versus <0.05 mg/L exposure	Unit rate difference (RD): incremental risk increase (per 100,000 person-year) compared to reference group	M: 0.28 (0.06, 0.50) F: 0.18 (0.04, 0.33)
Chiu et al., 2004	4 townships in Taiwan	4	1971–2000	BFD-endemic area (median arsenic concentration in water = 780 µg/L in 1960s) versus general population	Standardized mortality ratio (SMR)	M: 2.31 F: 2.92
Tsai et al., 1999	4 townships in Taiwan	2	1971–1994	BFD-endemic area (median arsenic concentration in water = 780 µg/L) versus general population	SMR	M: 2.64 (2.45, 2.84) F: 3.50 (3.19, 3.84)
Chen et al., 1992	42 villages in the blackfoot disease area of Taiwan	4	1973–1986	≥600 µg/L arsenic versus <100 µg/L	Rate ratio (RR)	M: 2.42 F: 3.90
Chen and Wang, 1990	314 townships in mainland China and Taiwan	1	1972–1983	NA	Age-adjusted regression beta coefficient: increase in age-adjusted mortality/100,000 person-years per 100 µg/L increase in arsenic level	M: 5.3 (0.9) F: 5.3 (0.7)
Chen et al., 1985	4 townships (84 villages) located on the southwest coast of Taiwan	2	1968–1982	BFD-endemic area (median arsenic concentration in water = 780 µg/L) versus general population	SMR	M: 3.20 (2.86, 3.54) F: 4.13 (3.60, 4.66)
<b>B. Other countries</b>						
Buchet and Lison, 1998	Belgium	4	1981–1991	High exposure arsenic area (20–50 µg/L in water) to rural, low exposure area	SMR	M: 1.05 (0.94, 1.18) F: 1.24 (0.83, 1.87)
Hopenhayn-Rich et al., 1998	26 counties in Cordoba Province, Argentina	3	1986–1991	High exposure group (mean = 178 µg/L) versus general population	SMR	M: 1.77 (1.63, 1.90) F: 2.16 (1.83, 2.52)
Smith et al., 1998	Northern Chile	2	1989–1993	High arsenic area (average 43–568 µg/L from 1950 to 1994) versus general population	SMR	M: 3.8 (3.5, 4.1) F: 3.1 (2.7, 3.7)

BFD: blackfoot disease; SMR: standardized mortality ratio; M: males; F: females; NA: not applicable; CI: confidence interval.

mortality associated with high arsenic concentrations ( $\geq 600$  µg/L compared to  $< 100$  µg/L) among both males and females.

In the two Taiwan studies that assessed lung cancer mortality rates according to drinking water arsenic concentration, statistically significant dose–response trends were observed. Guo (2004) reported age-adjusted increases in lung cancer mortality rates of 0.28 and 0.18 cases per 100,000 person years for males and females, respectively, comparing areas with arsenic in drinking water  $> 0.64$  mg/L to areas with  $< 0.05$  mg/L. Similarly, Chen and Wang (1990) found a statistically significant increase in age-adjusted lung cancer mortality rates of 5.3 cases per 100,000 person-years for each 100 µg/L increase in arsenic exposure.

Three ecological studies examined arsenic exposure in drinking water and lung cancer mortality in countries other than Taiwan. In Argentina's Cordoba Province, the age-adjusted SMRs for lung cancer comparing an area with high arsenic levels in the water (mean = 178 µg/L) to the general population were 1.77 (95% CI 1.63–1.90) and 2.16 (95% CI 1.83–2.52) in men and women, respectively (Hopenhayn-Rich et al., 1998). In Chile, compared to the general population, two populations with high drinking water arsenic concentrations (average of 43–568 µg/L) had SMRs for lung cancer mortality of 3.8 (95% CI 3.5–4.1) for men and 3.1 (95% CI 2.7–3.7) for women (Smith et al., 1998).

In a study conducted in Belgium, the highest drinking water arsenic concentrations were considerably lower (50 µg/L) than in the other studies ascertained for this systematic review. When arsenic concentrations of 20–50 µg/L were compared to lower

concentrations, the SMRs for lung cancer mortality were 1.05 (95% CI 0.94–1.18) and 1.24 (95% CI 0.83–1.87) for men and women, respectively (Buchet and Lison, 1998).

#### 3.4.2. Case–control studies

Only two case–control studies have been carried out to assess drinking water arsenic exposure in relation to lung cancer (Chen et al., 1986; Ferreccio et al., 2000) (Table 3). Chen et al. (1986) studied 76 lung cancer deaths and 368 controls in an endemic area for blackfoot disease in Taiwan (blackfoot disease is a severe form of peripheral arterial disease caused by high arsenic exposure). After adjusting for age, sex, cigarette smoking and the intake of other nutrients, foods or supplements, the odds ratio comparing individuals who reported drinking artesian well water for 40 or more years to individuals who reported never drinking artesian well water was 3.01 ( $p < 0.01$ ). In Chile, Ferreccio et al. (2000) compared 152 lung cancer cases and 419 hospital-based controls. The odds ratio comparing individuals consuming water containing 200–400 µg/L arsenic to individuals consuming water containing less than 10 µg/L arsenic was 8.9 (95% CI 4.0–19.6) after adjustment for age, sex and cumulative lifetime cigarette smoking (Ferreccio et al., 2000).

#### 3.4.3. Cohort studies

Three studies in an area endemic for blackfoot disease on the Southwest coast of Taiwan (Chen et al., 1988b, 2004; Chiou et al.,

**Table 3**  
Cohort and case–control studies of the association between drinking water arsenic concentrations and lung cancer risk

Author, year	Design	Population	% Men	Age range (years)	No. of cases/non-cases	Outcome	Comparison (exposed versus reference)	Risk estimate (95% CI)	p-value	Adjustment factors
<b>A. Taiwan<sup>a</sup></b>										
Chen et al., 2004	Cohort	Arseniasis-endemic area	SW: 59.3% NE: 50.1%	SW: mean = 52.9 y NE: mean = 59.1 y	139/10452	Incidence	≥ 700 µg/L arsenic in well water versus < 10 µg/L	RR: 3.29 (1.60, 6.78)		Age, gender, smoking, cohort, education, alcohol
Chiou et al., 1995	Cohort	BFD-endemic areas	NR	NR	27/2256	Incidence	≥ 20 mg/L × year versus 0 mg/L × year cumulative arsenic exposure in drinking water	RR: 4.01 (1.00, 16.12)	< 0.05	Age, gender, smoking, blackfoot disease
Chen et al., 1988a, b	Cohort	BFD-endemic area	55.3%	NR	28/843	Mortality	BFD patients (in region with median arsenic = 780 µg/L) versus general population	SMR: 10.49	< 0.001	Age, gender
Chen et al., 1986	Case-control	BFD-endemic areas	59.2	≥ 60 Mean = 63.4 y	76/368	Mortality	40+ years of use versus no lifetime use of artesian well water in BFD-endemic region (median arsenic = 780 µg/L)	OR: 3.01	< 0.01	Age, gender, smoking, tea drinking, vegetarian, vegetable consumption, bean consumption
<b>B. Japan<sup>b</sup></b>										
Nakadaira et al., 2002	Cohort	Niigata Prefecture: area with endemic arsenic poisoning	48.0	Mean = 27.8 y	8/446	Mortality	Persons with diagnosed arsenic exposure (highest arsenic concentration in 1950s = 3 mg/L) versus general population	SMR: M: 11.01, F: 5.34	M: < 0.001, F: > 0.5	Age
Tsuda et al., 1995	Cohort	Niigata Prefecture: area with endemic arsenic poisoning	NR	NR	8/435	Mortality	High exposure (> 1 mg/L) versus general population	SMR All: 15.69 (7.38, 31.02), M: 19.08 (8.88, 38.76), F: 7.15 (0.36, 4.11)		Age, gender
Tsuda et al., 1989	Cohort	Niigata Prefecture: area with endemic arsenic poisoning	NR (~44.8%)	NR	9/445 (454 sample) 7/274	Mortality	High risk area versus general population High exposure group (≥ 500 µg/L) versus general population	3.57 (1.49, 6.28) SMR: 16.41 (7.15, 36.34)		Age, gender
<b>C. Other countries</b>										
Ferreccio et al., 2000	Case-control	Northern Chile: arsenic-contaminated area	64.0	Mean = 63.2 y	151/419	Incidence	200–400 µg/L average water arsenic exposure versus 0–10 µg/L	OR: 8.9 (4.0, 19.6)		Age, gender, smoking, occupational exposure, SES

NR: not reported; RR: risk ratio; OR: odds ratio; SMR: standardized mortality ratio; BFD: blackfoot disease; SES: socioeconomic status; M: males; F: females.

<sup>a</sup> The studies conducted in Taiwan represent three cohorts and one case–control study. The cohort studied by Chen et al. (2004) included, in part, individuals in the cohort described by Chiou et al. (1995).

<sup>b</sup> Results from Nakadaira et al. (2002) are those from 454 inhabitants of the Niigata Prefecture who underwent medical examinations and who were part of a historical cohort study from 1959 to 1992; results from Tsuda et al. (1995) are based, in part, on the same population; the first comparison, however, includes only the 443 persons for whom arsenic exposures were known—the second comparison presented is of the 454 sample reported on in Nakadaira.

1995) and three studies in a cohort in Nakajo, Japan (Nakadaira et al., 2002; Tsuda et al., 1989, 1995) have presented prospective data on the association between arsenic concentrations in drinking water and lung cancer risk (Table 3). In Taiwan, persons with blackfoot disease had a substantially elevated risk of dying from lung cancer compared to the general population (SMR = 10.49;  $p < 0.001$ ) (Chen et al., 1988b). Within this population, high cumulative arsenic exposure in drinking water [ $\geq 20$  (mg/L × years of exposure)] was associated with a fourfold statistically significant increased risk of developing lung cancer (Chiou et al., 1995). In Japan, drinking arsenic-contaminated well water was associated with an increased risk of dying from lung cancer among both men (SMR = 11.01) and women (SMR = 5.34); only the association in men was statistically significant (Nakadaira et al., 2002; Tsuda et al., 1995). In both the Taiwan and the

Japan populations, a dose–response trend showed that as drinking water arsenic concentrations increased, risk of dying from lung cancer increased (Chen et al., 2004; Tsuda et al., 1989, 1995).

## 4. Discussion

### 4.1. Summary of findings

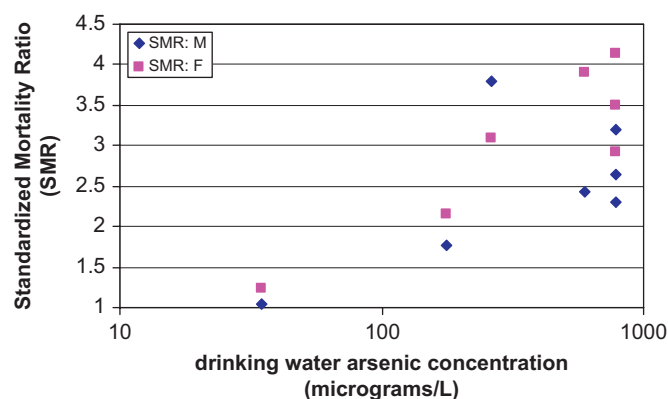
In this systematic review, we ascertained and critically evaluated 17 studies of the association between arsenic in drinking water and lung cancer. These studies were conducted in general populations in different geographic regions, including Taiwan, Japan, Chile, Belgium, and Argentina. The majority of these studies were ecological studies, and, in general, arsenic

exposure was assigned using drinking water (artesian well or tap water) concentrations that were based on geographic or other grouped or ecologic measurements. Despite the limitations of the studies included in this review, the magnitude of the risk estimates from the cohort studies and the consistency of positive and statistically significant associations among studies of different epidemiologic designs indicate that arsenic exposure by ingestion of drinking water at high concentrations is causally associated with an increased risk of lung cancer.

#### 4.2. Arsenic in drinking water and lung cancer

To date, the literature on arsenic in drinking water and lung cancer has primarily been limited to areas with artesian wells contaminated with high levels of arsenic ( $>150\ \mu\text{g/L}$ ). As described in this review, the association between arsenic in drinking water and lung cancer was first observed in southwestern Taiwan, where blackfoot disease, a severe form of peripheral arterial disease caused by high arsenic exposure, is endemic. In a report published in 1962, [Chen et al. \(1962\)](#) noted that in this area, the arsenic content of artesian well water ranged from 350 to 1140  $\mu\text{g/L}$ , with a median concentration of 780  $\mu\text{g/L}$ . Further, estimates indicated that ingested arsenic from drinking water was as high as 1000  $\mu\text{g}$  (1 mg) per day in this area ([Blackwell, 1961](#)). Subsequently, exposure to arsenic in drinking water was strongly linked to lung cancer in the Niigata Prefecture, Japan, an area where a small factory produced 'king's yellow', or arsenic trisulfide, for more than 40 years and disposed waste water into underground gravel. Corroborative findings were also seen in the Cordoba Province, Argentina and Northern Chile. Arsenic concentrations measured in wells in these areas were comparable to those documented in southwestern Taiwan; for example, in Niigata Prefecture, Japan, arsenic concentrations ranged from non-detectable to 3 mg/L, with 32.2% of measured wells having arsenic concentrations of 1 mg/L or greater.

The concentrations of arsenic measured in drinking water were similar in these areas, but substantial heterogeneity in the risk estimates has been observed. Factors that could potentially contribute to this heterogeneity include differences in the (1) patterns of exposure (for example, the type of arsenic species to which the populations were exposed), and (2) characteristics of the populations, such as genetic variation that may contribute to differences in interindividual susceptibility. Further, methodological limitations may have a substantial impact on the magnitude of the associations observed; these limitations include the lack of individual level data on arsenic exposure and the lack of adjustment for potential confounders such as cigarette smoking. For example, among the cohort studies conducted in Taiwan, high arsenic exposure, defined as cumulative arsenic exposure or total reported number of years drinking artesian well water contaminated with arsenic, was associated with smoking-adjusted estimates of a three to fourfold increased risk compared to low or no exposure to arsenic in drinking water. In comparison, the associations were stronger (greater than fivefold) in the studies that did not adjust for cigarette smoking ([Chen et al., 1988b](#); [Nakadaira et al., 2002](#); [Tsuda et al., 1989, 1995](#)). The overall results clearly and consistently indicate that arsenic in drinking water leads to a substantially elevated risk of lung cancer, but the precise magnitude of the excess lung cancer risk from high dose arsenic exposure is difficult to estimate. Given the large increases in risk that persist after the adjustment for cigarette smoking, the association between arsenic in drinking water and lung cancer appears to be independent of cigarette smoking, the principal cause of lung cancer.



**Fig. 2.** Published standardized mortality ratios (SMRs), by gender, for the association between drinking water arsenic concentrations and lung cancer mortality reported in ecological studies. Drinking water arsenic concentration for each study is the average reported in the study area.

Despite the consistent evidence linking arsenic drinking water exposure and lung cancer risk at very high exposure levels, less is known about the risk at lower exposure levels ( $<100\ \mu\text{g/L}$ ) ([Fig. 2](#)). The evidence is sparse: in this systematic review, we identified only one study that examined the association between drinking water arsenic and lung cancer in an area in which arsenic exposure was documented to be  $<100\ \mu\text{g/L}$  ([Buchet and Lison, 1998](#)). In the study of [Buchet and Lison \(1998\)](#), conducted in Belgium, exposure to drinking water containing 20–50  $\mu\text{g/L}$  arsenic was weakly and not significantly associated lung cancer mortality. This evidence concerning the potential risk at lower concentrations is augmented by the studies conducted in high arsenic exposure areas that also included low/intermediate concentrations in their analyses. Specifically, [Chen et al. \(2004\)](#) reported an odds ratio of 1.15 (95% CI 0.69–1.94) for individuals exposed to arsenic levels in well water averaging 10–99  $\mu\text{g/L}$  compared to those exposed to  $<10\ \mu\text{g/L}$  of arsenic. In Chile ([Ferreccio et al., 2000](#)), compared to those whose drinking water arsenic concentrations were 0–10  $\mu\text{g/L}$ , the odds ratio increased from 1.6 (95% CI 0.5–5.3) to 3.9 (95% CI 1.2–12.3) among residents in areas with drinking water arsenic concentrations of 10–29  $\mu\text{g/L}$  and 30–49  $\mu\text{g/L}$ , respectively.

Due to the paucity of studies that have assessed the lung cancer risks at low drinking water arsenic concentrations, the magnitude of the risk remains uncertain. Extrapolating findings from studies conducted in high drinking water arsenic concentration areas to estimate what the lung cancer risks may be at lower concentrations requires the assumption of a linear dose–response relationship. Results from existing retrospective studies that have examined the associations between low level arsenic in drinking water and health outcomes have a strong likelihood of misclassification of arsenic exposure ([Cantor and Lubin, 2007](#)). Assuming this misclassification is non-differential with respect to lung cancer, this would tend to bias the measures of association toward the null. In 2001, the United States Environmental Protection Agency ([US EPA, 2001](#)) set the arsenic drinking water standard of 10  $\mu\text{g/L}$  based on extrapolation of the data from the high arsenic exposure areas in Taiwan ([Chen et al., 1988b, 1992](#); [Wu et al., 1989](#)). Based on the analyses of lung cancer risk at lower levels of exposure described above ([Ferreccio et al., 2000](#); [Buchet and Lison, 1998](#); [Chen et al., 2004](#)), this appears to be a prudent benchmark.

#### 4.3. Biological plausibility

Inorganic arsenic ingested through drinking water is quickly absorbed into the bloodstream and is transported to the liver

where it is metabolized through methylation processes to generate methylarsonic acid (MMA) and dimethylarsinic acid (DMA) metabolites (Aposhian, 1997). Most of the arsenic metabolites are excreted in the urine; however, some are deposited in tissues of the lung, liver, kidney, nails, and hair (Chiou et al., 1995). Arsenic was traditionally considered to be a promoter and not an initiator of carcinogenesis, as no mutagenic potential was shown in experimental models (Goering et al., 1999). However, there has been growing evidence that MMA and DMA are cytotoxic and genotoxic in cell lines (Styblo et al., 2000; Vega et al., 2001). Arsenic-induced carcinogenesis may occur through several biological mechanisms, particularly via the highly biologically active MMA and DMA metabolites (reviewed in Kitchin, 2001). These mechanisms include chromosomal abnormalities, oxidative stress, altered DNA repair, altered DNA methylation patterns, altered growth factors, enhanced cell proliferation, promotion/progression, gene amplification, and suppression of p53 (Kitchin, 2001; Tapio and Grosche, 2006).

Several mechanisms for carcinogenesis with ingested arsenic exposure have been suggested, but exactly how and which of these pathways operate to cause lung cancer is not well understood. One possible explanation is that the high partial pressure of oxygen in the lung creates an environment conducive to oxidative stress (Kitchin, 2001). Under this scenario, first proposed by Yamanaka and Okada (1994), dimethylarsine, a minor metabolite of DMA, reacts with oxygen to produce free radical species which can subsequently cause DNA damage. Because dimethylarsine is a gas, it is excreted in the lungs, where its activity is therefore concentrated (Kitchin, 2001).

#### 4.4. Occupational exposure to arsenic and lung cancer

An additional body of epidemiologic evidence supports the carcinogenic nature of arsenic; these studies show that occupational exposure to inorganic arsenic is associated with an increased risk of developing lung cancer (Lundstrom et al., 2006; Chen and Chen, 2002; Lubin et al., 2000; Jarup and Pershagen, 1991; Enterline et al., 1987; International Agency for Research on Cancer, 1987). These studies have been conducted primarily among miners exposed to inorganic arsenic through the inhalation of dust particles (Tapio and Grosche, 2006). For example, in a study of 2802 men who worked 1 year or more during the period of 1940–1967 at a copper smelter in Tacoma, Washington, Enterline et al. (1987) found that men with a cumulative air arsenic exposure of  $\geq 45,000 \mu\text{g arsenic}/\text{m}^3\text{-years}$  had a respiratory cancer SMR of 338.5 compared to the general population. Similarly, in a cohort of 8346 tin miners in Yunnan, China, Qiao et al. (1997) reported that exposures of  $\geq 16,093 \text{ mg As}/\text{mg arsenic}/\text{m}^3 \times \text{months}$  were associated with an approximate fourfold increase in lung cancer risk compared to exposures of  $0.062\text{--}1.731 \text{ mg As}/\text{mg arsenic}/\text{m}^3 \times \text{months}$ . In both cohort and case-control studies, a consistent dose-response pattern has been observed between cumulative arsenic exposure and lung cancer risk (International Agency for Research on Cancer, 1987). In contrast to the drinking water studies which suggest a linear dose-response relationship between arsenic exposure and lung cancer mortality, the occupational studies indicate a supra-linear dose-response relationship (Hertz-Picciotto and Smith, 1993).

Unlike ingested arsenic, which is usually metabolized and excreted in the urine within days, arsenic particles have low solubility and are, therefore, less rapidly eliminated from the body (Tapio and Grosche, 2006). Using electron-probe microanalysis, Liu and Chen (1996) showed that the content of arsenic in the lung was 17 times higher among patients diagnosed with lung

cancer compared to unexposed, disease-free individuals. Inhaled arsenic may cause lung cancer in part through mechanical inhalation, contributing to inflammation of the lung tissue (Tapio and Grosche, 2006). Inhaled arsenic may also contribute to lung carcinogenesis through mechanisms similar to ingested arsenic (described above), including oxidative stress, increases in cellular proliferation, altered DNA repair, altered DNA methylation patterns, and suppression of p53 (Kitchin, 2001; Tapio and Grosche, 2006). Evidence from studies of occupational exposure supports the principle that arsenic acts as a lung carcinogen. The mechanistic pathways through which exposure to arsenic via the respiratory route in occupational settings causes lung cancer likely differs from the pathways through which arsenic ingested via drinking water causes lung cancer. Thus, the occupational studies provide only indirect evidence to support the plausibility that arsenic exposure from ingested drinking water could cause lung cancer.

#### 4.5. Conclusion

Different review groups are in agreement that the evidence supports an association between high drinking water arsenic concentrations and lung cancer, but there are differing opinions about drawing causal inferences. There have been few previous reviews of this topic, and none that we are aware of are based on a transparent, pre-specified systematic review protocol. This systematic review was carried out in support of the World Cancer Research Fund's report (World Cancer Research Fund/American Institute for Cancer Research, 2007), which rated the evidence that drinking water arsenic is associated with lung cancer as 'probable' but not 'convincing'. A conclusion of causality is consistent with a 2004 report of the International Agency for Research on Cancer (IARC), which found the evidence is sufficient that arsenic in drinking water is a cause of lung cancer (International Agency for Research on Cancer, 2004). The present report, based on a complete review of the world's epidemiologic evidence on this topic, is based on a more current literature search and on an a priori systematic review protocol.

On the basis of the evidence reviewed in the present report, we assert that the totality of the epidemiologic evidence supports the presence of a causal association between exposure to elevated arsenic concentrations in drinking water and the risk of developing or dying from lung cancer. Uncertainty persists about the lung cancer risks at lower levels of exposure, which have yet to be fully characterized (Fig. 2). However, at high concentrations, the evidence is clear (Fig. 2). Strong associations, including dose-response trends, have been consistently observed in studies of this topic. The conclusion of a causal association is further supported by data from biological models of arsenic-induced carcinogenesis and by the fact that arsenic through another route of exposure has been shown to be a cause of lung cancer. The association between arsenic in drinking water and lung cancer likely cannot be attributed to chance or confounding, and findings point to a significant increase in the risk of lung cancer with exposure to arsenic in drinking water in populations exposed to high concentrations.

#### Funding source

This study was funded by the World Cancer Research Fund.

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