

# Arsenic, internal cancers, and issues in inference from studies of low-level exposures in human populations

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## Abstract

Epidemiologic data from regions of the world with very high levels of arsenic in drinking water ( $>150 \mu\text{g/L}$ ) show a strong association between arsenic exposure and risk of several internal cancers. A causal interpretation of the data is warranted based on the strength and consistency of study findings. At lower levels of exposure ( $<100 \mu\text{g/L}$ ), in the absence of unambiguous human data, extrapolation from the high-exposure studies has been used to estimate risk. Misclassification of exposure usually results in depressing observed levels of risk, and studies conducted in populations with exposures below  $100 \mu\text{g/L}$  have been limited by the challenge of estimating past exposures, a critically important aspect of studying relative small increases in risk. Relatively small study size contributes to the variability of findings in most studies and makes interpretation of results all the more challenging. The effects on risk estimates of exposure misclassification and small study size under various scenarios are graphically illustrated. Efforts are underway to improve exposure assessment in a large case–control study of bladder cancer in a region of the United States with moderately elevated levels of arsenic in drinking water.

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## Introduction

Inorganic arsenic is a recognized cause of cancer. Inhalation of high levels of airborne arsenic causes lung cancer, observed primarily among workers exposed in cadmium, lead, and copper smelters (Lubin et al., 2000; Enterline and Marsh, 1982; Lundstrom et al., 2006). Ingestion of high concentrations of arsenic causes cancer of the skin, lung, and urinary bladder and is a suspected cause of kidney and other malignancies (International Agency for Research on Cancer, 2004; Cantor et al., 2006). Arsenic ingestion has also been implicated in many other adverse health effects, including skin lesions, diabetes mellitus, chronic bronchitis, cardiovascular disease, peripheral neuropathy, adverse reproductive outcomes, and hematological effects (National Research Council: Subcommittee on Arsenic in Drinking Water, 1999; National Research Council: Subcommittee to Update the 1999 Arsenic in Drinking

Water Report, 2001). Most evidence linking arsenic in drinking water with elevated cancer risk of internal organs comes from studies of populations in Taiwan, Argentina, and Chile, where historical exposures were very high, generally above  $150\text{--}200 \mu\text{g/L}$ , and where the evidence for risk is strong and highly consistent.

Epidemiologic evidence for risk at lower arsenic concentrations, in the range below  $100 \mu\text{g/L}$ , is more uneven, given the many challenges faced by such research. A major problem is misclassification of exposure arising from uncertainties in assessing exposures during the disease-relevant exposure period, which, for arsenic, may extend to many decades prior to diagnosis. Such misclassification typically leads to underestimation of the true risk. Statistical power may be limited in many previous studies due to relatively small numbers of subjects. The combination of misclassification of exposure and the expected small excess risks minimizes the possibility of drawing clear inferences from currently available data which are based on studies of limited size.

The earliest published case reports of arsenic causing cancer date from the late 19th Century, when Hutchinson (1887) in

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Britain reported unusual skin lesions and skin cancers in patients who had ingested medicinal preparations containing trivalent arsenic (potassium arsenite). In a 1947 review, Neubauer noted 143 cases of skin cancer had been reported in the medical literature since the first report in 1887 (Neubauer, 1947). This extensive review noted that four or five patients with arsenical skin cancers also were diagnosed with lung cancer. Since 1947, dozens of additional case reports of internal cancers after long-term arsenic exposure have appeared, including cancers of the lung, bladder, liver, kidney, prostate, esophagus, colon, and nasopharynx (Sommers and McManus, 1953; Rosset, 1958; Kjeldsberg and Ward, 1972; Jackson and Grainge, 1975; Popper et al., 1978; Prystowsky et al., 1978; Nagy et al., 1980; Reymann et al., 1978). Anecdotal case reports are neither adequate to identify a causal association nor to quantify risk in populations. Epidemiologic studies are conducted to measure risk, to better understand the complex relationships between risk factors and disease, to provide estimates of the disease burden to specific or general populations related to specific risk factors, and to provide data that can guide and support effective preventive actions.

### Ecologic studies in highly exposed populations

Many epidemiologic studies of arsenic have used an ecologic design, in which the geographic distribution of particular diseases, or causes of death, is compared with the geographic distribution of arsenic levels in the drinking water. These investigations analyzed incidence and mortality rates of bladder, lung, kidney, liver, colon, and prostate cancers among populations with different levels of arsenic in their drinking water. As an example of ecologic studies, results for lung, bladder, and kidney cancers and exposure to arsenic in Taiwan, Argentina, and China will be discussed. In addition to findings for skin cancer, these internal sites of cancer show the strongest and most consistent associations with ingested arsenic. Wu et al. (1989) grouped villages in southwest Taiwan into three strata according to the average level of arsenic in their drinking water: <300 µg/L, 300–590 µg/L, and ≥600 µg/L, and found dose-related levels of risk for several cancers. For lung cancer among men, with increasing levels of water arsenic, mortality rates (per hundred thousand per year) were 49.2, 100.7, and 104.1; and among women, 36.7, 70.8, and 122.2. For bladder cancer, the comparable mortality rates among men were 22.6, 61.0, and 92.7 and among women 25.6, 57.0, and 111.3. Kidney cancer rates were 8.4, 18.9, and 25.3 (men) and 3.4, 19.4, and 58.0 (women).

Similar gradients of increasing risks for several types of cancer with increasing arsenic in drinking water were found by Hopenhayn-Rich et al. (1996, 1998) in Cordoba Province, Argentina. Results were expressed as the standardized mortality ratio (SMR), with the comparison group being the general population of the country. The SMR expresses the ratio of the number of observed events (in this case, deaths) to the number expected. The expected number of events is calculated by using rates in a comparison population and applying those rates to the study population, usually with adjustment for differences in age

structure between the study and the comparison population. An SMR of 1.0 denotes that the observed number of disease events (deaths) in the population equals the number expected if the disease rates in the comparison population prevailed. Among men in Cordoba Province, the SMRs for lung cancer mortality were 0.92, 1.54, and 1.77, and for women 1.24, 1.34, and 2.16 for places with “low”, “moderate”, and “high” levels of arsenic in the drinking water. Bladder cancer SMRs were 0.8, 1.4, and 2.1 (men) and 1.2, 1.6, and 1.8 (women). Kidney cancer SMRs were 0.9, 1.3, and 1.6; and 1.0, 1.4, and 1.8, respectively. The average arsenic concentration among the high-level villages was 178 µg/L. In all instances, the statistical test for trend was highly significant ( $p < 0.001$ ).

Another ecologic study was conducted in Region II of northern Chile, where the population was exposed to high levels of arsenic in the drinking water between 1955 and 1969, with population-weighted average levels reaching 570 µg/L over this period. Smith et al. (1998) calculated the SMRs for cancer mortality in the years 1989–1993 in Region II relative to the general Chilean population. Increased mortality was found for lung, bladder, kidney and skin cancer, with all SMRs statistically significant ( $p < 0.05$ ). The SMRs for lung cancer mortality were 3.8 among men and 3.1 among women; for bladder cancer 6.0 and 8.2; and for kidney cancer, 1.6 and 2.7.

The ecologic studies conducted in high-exposure areas are notable for their consistency in showing strong associations and dose–response relationships with arsenic in drinking water for lung, skin, bladder, and kidney cancers (National Research Council: Subcommittee on Arsenic in Drinking Water, 1999; National Research Council: Subcommittee to Update the 1999 Arsenic in Drinking Water Report, 2001; International Agency for Research on Cancer, 2004).

### Studies with individual-level data in highly exposed populations

In contrast to ecologic studies, which use group rates of incident disease or disease-specific mortality as outcomes, and average levels of arsenic in water as the exposure measure, cohort and case–control studies in high-exposure settings have evaluated exposure and disease outcome on an individual level. When individual-level studies are well designed, they can offer greater validity than ecologic studies. Several studies of populations highly exposed to arsenic have been conducted. Cuzick et al. (1992) reported an excess of bladder cancer mortality among 478 patients treated with 1% potassium arsenite (Fowler’s solution) for a variety of conditions (Cuzick et al., 1992). Among subjects exposed to more than 500 mg of arsenic over several years, four deaths due to bladder cancer were observed, whereas less than one was expected (SMR = 5.0). In a prospective cohort of 8102 persons, Chiou et al. (2001) measured arsenic levels in individual household wells and evaluated cancer incidence in a region of Northeast Taiwan where arsenic-contaminated wells had been in use since the 1940s. Relative risks for urinary tract (bladder and kidney) cancer incidence increased in a linear fashion with the level of

long-term exposure to arsenic in drinking water. Relative to subjects with  $\leq 10$   $\mu\text{g/L}$  arsenic in their water, relative risks were 1.6, 2.3, and 4.9 for long-term exposures of 10.1–50.0  $\mu\text{g/L}$ , 50.1–100  $\mu\text{g/L}$ , and  $>100$   $\mu\text{g/L}$ , based on a total of 15 cases. Risks of newly diagnosed lung cancer were also measured in this cohort after combining it with a cohort of 2503 persons from southwest Taiwan (Chen et al., 2004). Compared with subjects having  $<10$   $\mu\text{g/L}$  arsenic in their water, relative risks for lung cancer were 1.1, 2.3, 3.0, and 3.3 for exposures of 10–99, 100–299, 300–699, and  $\geq 700$   $\mu\text{g/L}$ .

A small number of case–control studies of cancer at high-exposure levels have been reported. In a study from northern Chile, 151 incident lung cancer cases and 419 controls were interviewed, and a long-term profile of arsenic exposure was constructed for each subject, merging individual residential histories with historical data on arsenic in drinking water (Ferreccio et al., 2000). Exposures were calculated according to the time-weighted average of arsenic in drinking water over the period 1930–1994. The measure of association from case–control studies is the odds ratio, a close estimate of the relative risk. Relative to persons with average exposure of less than 10  $\mu\text{g/L}$  in 1930–1994, odds ratios were 1.6, 3.9, 5.2, and 8.9 for exposures of 10–29, 30–49, 50–199, and 200–400  $\mu\text{g/L}$ , after adjustment for age, sex, smoking, occupation and other risk factors. In summary, there is consistency in findings among both ecologic and individually based epidemiologic studies. Where populations have been exposed to a range of exposures, risk increases for bladder, lung, and some other cancers in a linear fashion.

### Studies in populations at lower levels of exposure

As noted, characterization of arsenic as a human carcinogen is anchored in data from epidemiologic studies conducted among populations exposed to high levels of arsenic in drinking water – levels above 150 or 200  $\mu\text{g/L}$ . Excess relative risks per unit exposure among different populations are consistent across studies and dose–response relationships are generally linear. Findings from epidemiologic studies among populations exposed at lower levels of exposure are quite mixed, and generally do not reveal risks of bladder, lung, or other cancers that would be expected from linear extrapolation of findings from the high-exposure studies. To illustrate core issues affecting these risk estimates, we will cite data from several studies of bladder cancer and arsenic ingestion, since bladder cancer is the most extensively studied type of cancer with respect to ingested arsenic from drinking water. Data are available from six case–control studies of incident bladder cancer (Bates et al., 1995, 2004; Kurttio et al., 1999; Steinmaus et al., 2003; Karagas et al., 2004; Michaud et al., 2004) and a cohort mortality study that included bladder cancer as one of many outcomes (Lewis et al., 1999). Table 1 shows salient features and summary findings from each study. An effort was made in each investigation to estimate historical levels of drinking water arsenic for each study subject; however, the ability to characterize exposure during long periods of subjects' lifetimes, and to account for past changes

in their exposure, was often very limited. Under even ideal circumstances, characterizing past exposure in detail is challenging, especially in mobile populations in the United States, where four studies were conducted (Bates et al., 1995; Steinmaus et al., 2003; Karagas et al., 2004; Lewis et al., 1999).

It should be noted that the studies from the highly exposed populations cited earlier also included some subjects with exposures lower than 100  $\mu\text{g/L}$ : in particular, the case–control study of incident lung cancer in Chile (Ferreccio et al., 2000), the northeastern Taiwan cohort study of bladder cancer (Chiou et al., 2001), and the combined cohort studies from southwestern and northeastern Taiwan, with lung cancer findings (Chen et al., 2004).

### Sources of bias and variability in low-level studies

The degree to which risk estimates from epidemiologic studies reflect “true” risks depends on the accuracy of the exposure estimates and the appropriate identification of the relevant exposure period. Relatively small errors in assessment of historical exposure to arsenic during relevant exposure periods can have profound effects on the risk that is observed. Some error in estimating past exposures is unavoidable, and when a true risk is present and the misclassification of exposure is non-differential (i.e., similar among cases and non-cases), the risk estimate is typically biased toward the null. Given a “true” relative risk of 2.0 (i.e., an actual 100% increase in risk) the observed relative risk would be decreased to 1.5 (an observed 50% increase in risk) if the correlation coefficient between the actual exposure and the estimated exposure from the study were 0.6, and if the misclassification were non-differentially applied to cases and non-cases (Vineis, 2004). Thus, at this level of exposure misclassification, common in epidemiologic studies of environmental factors, about half of the actual risk increase would be missed. Greater misclassification would result in an even greater diminution of observed risks. In the face of a true link between exposure and effect, a modest level of exposure misclassification, in combination with low initial risk, can result in a null observation. However, in most real situations, a true null association cannot be transformed to a positive finding in the presence of non-differentially misclassified exposure. The bladder cancer studies conducted in populations exposed to arsenic are all limited, to a varying degree, due to this problem. This limitation is of particular concern in low-exposure situations, where expected excess risk is relatively small and the error in exposure estimates can readily be of such magnitude that detection of this small excess risk is problematic. In addition, many of the low-exposure studies are small in size, which limits their statistical power to detect lower levels of risk. In the face of these limitations, there is some consistency among these studies of a positive interaction between arsenic exposure and cigarette smoking on the risk of bladder cancer, raising the possibility that true effects may be much larger than observed (Bates et al., 1995, 2004; Steinmaus et al., 2003; Kurttio et al., 1999).

Table 1  
Studies of bladder cancer in populations with ‘low-level’ exposure to arsenic in drinking water (<100 µg/L)<sup>a</sup>

First author (year)	Study locale	Cases/Controls	Major findings	Comments on exposure assessment and study design
Bates (1995)	Utah, USA	117/266	No association among never smokers. For smokers, OR were elevated for exposures >10 years before interview [e.g., OR=2.92 (CI=1.1–8.0) for ≥13 (mg/L) <sup>a</sup> years in the time window 10–19 years prior compared with <8 (mg/L) <sup>a</sup> years].	Restricted to subjects with long-term residences on public water. Arsenic levels from a cross-sectional sampling of public water systems at time of study.
Kurttio (1999)	Finland	61/275	No association among never smokers. Among smokers, OR was 6.91 (CI=0.8–59.5) for average daily dose ≥1.0 µg/day compared with <0.2 µg/day.	Restricted to subjects with drilled wells used at least from 1967–1980.
Steinmaus (2003)	5 Counties in California and Nevada, USA	181/328	No association among never smokers. Among smokers, highest risk was for exposures >40 years before interview [e.g., for 5-year average >80 µg/day, OR=3.87 (CI=1.4–10.6) compared with <10 µg/day].	Arsenic assessed within study area only, where participants lived an average of 1/3 of their lifetimes. Arsenic was estimated for about 80% of person-time in area.
Bates (2004)	Argentina	114/114	Weak associations among never smokers [e.g., OR=1.83 (CI=0.6–5.9) for >10 µg/L 31–40 years before interview compared with ≤10 µg/L]. No association among smokers.	Water samples from private wells used in last 40 years, when available. Also, nearby ‘proxy’ wells and community water supply records used in estimates.
Karagas (2004)	New Hampshire, USA	383/641	No association among never smokers. Among ever smokers, OR=2.17 (CI=0.9–5.1) for >0.330 µg arsenic/g in toenails compared with <0.060 µg/g.	Toenail arsenic (neutron activation analysis). Toenail arsenic represents inorganic arsenic exposure approximately 1 year prior to sample collection.
Michaud (2004)	Finland	280/280	Only smokers in cohort. No association found. OR=1.14 (CI=0.5–2.5) for >0.757 µg arsenic/g in toenails compared with <0.105 µg/g.	Nested case–control study. Toenail arsenic (neutron activation analysis). Cohort composed of male smokers.
Lewis (1999)	Utah, USA	5 cases observed 9.7 cases expected	SMR=0.36 for <1000 ppb-years; SMR=0.95 for ≥5000 ppb-years. Utah state mortality rates were used for comparison.	Residential histories combined with local water records. High variability in exposure estimates at each place.

<sup>a</sup> All were case–control studies of incident bladder cancer, except that of Lewis (1999), which was a retrospective cohort mortality study.

The consequences of both sample size and exposure misclassification on estimation of odds ratios (OR) in case–control studies (six of the seven studies in Table 1) may be demonstrated using 2000 simulated case–control studies of 100 cases and 100 controls and of 1000 cases and 1000 controls for a binary factor with true exposure probability 0.1 (Fig. 1). In Fig. 1, we specify misclassification in terms of sensitivity, i.e., the probability an exposed individual is observed as exposed, and specificity, i.e., the probability a non-exposed person is observed as non-exposed. Sensitivity and specificity equal to one denotes exposure determined without misclassification. The simulated ORs for a true OR of 1.0 (open bars), i.e., no association of exposure and disease, and for a true OR of 2.0 (shaded bars) represent the random population variation of the estimates. The extent of overlap represents the power to detect a true association. Comparing the upper panels to the lower panels illustrates how increasing sample size enhances the power to identify a true association. It is also evident that increasing misclassification (decreasing sensitivity and specificity from 1.0 to 0.9 to 0.7) increases overlap, i.e., reduces power to identify a true association, biases the observed OR toward the null (i.e., the

mean of the simulated ORs shifts towards one), and the variability of the observed ORs is reduced (i.e., the spread of the estimates is narrowed because the observed proportion exposed increases and exposures in cases and controls become more alike). The same phenomenon is present in cohort studies.

The illustrations in Fig. 1 highlight an important point, namely, in a real life situation, an investigator’s study provides only a single estimate of an association derived from one sample from a larger universe of possible outcome measures. In a typical situation, this concept is represented by the confidence interval, i.e., an interval which includes the presumed “true” measure of effect. For a binary exposure, one can calculate the exact resultant OR for any level of misclassification. However, this “exact OR” represents only the “expected value” (i.e., the mean) of the complete distribution of possible sample values from the larger universe. This expected value is represented by the mean values in Fig. 1. We present the effects of misclassification using the figure, rather than odds ratios and associated confidence intervals, because it illustrates more directly how misclassification influences the OR estimation process.

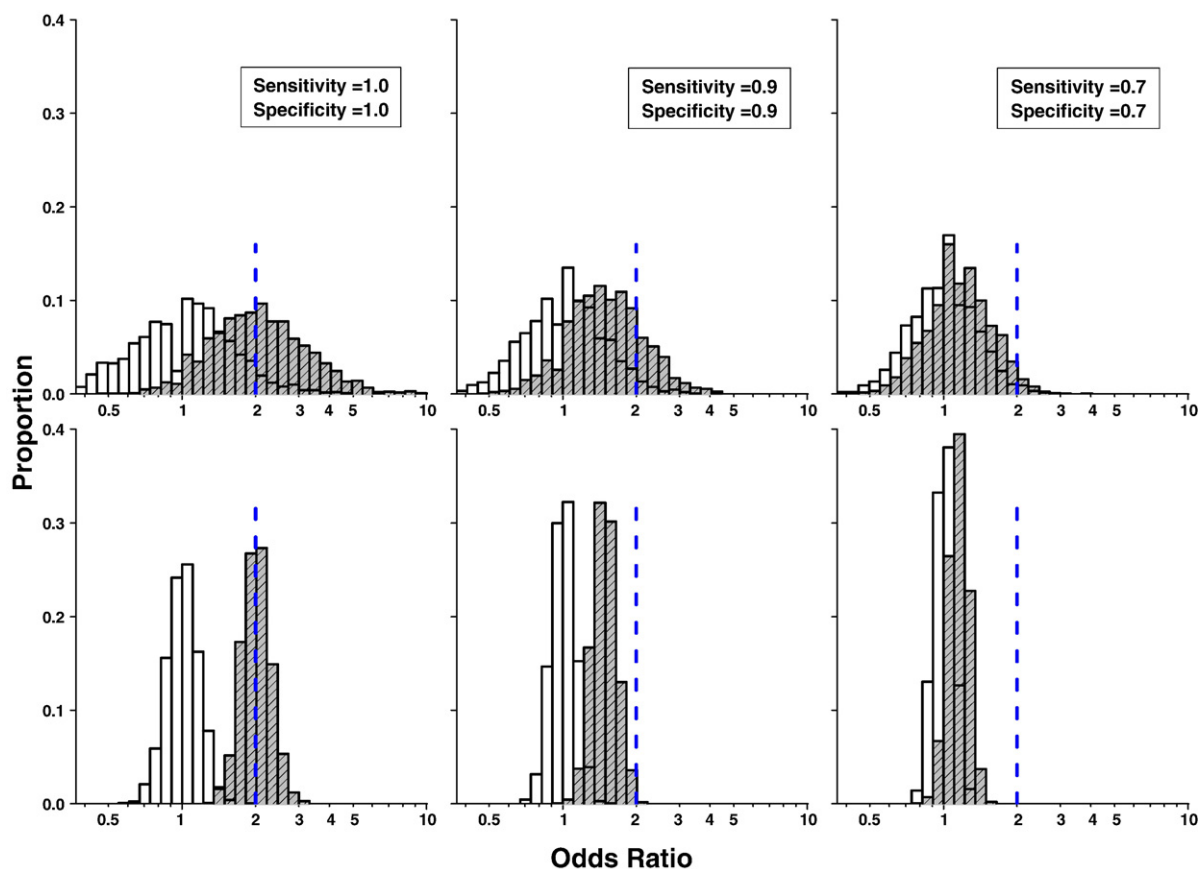


Fig. 1. Estimates of the odds ratio (OR) from 2000 simulated case–control studies with 100 cases and 100 controls (upper panels) or 1000 cases and 1000 controls (lower panels) for a binary exposure with probability of 0.1. The true ORs are 1.0 (open bars) or 2.0 (shaded bars with hatched lines, with true value denoted by vertical dash line). Exposure subject to misclassification as defined by sensitivity (the probability an exposed individual is truly exposed) and specificity (the probability a non-exposed individual is truly non-exposed).

While there is interest in directly using findings from human studies conducted at the lower levels of arsenic exposure for risk assessment, this may not be possible with the currently available data, due to the limitations imposed by small sample size and misclassification of exposure. An extensive effort is required to accurately estimate past arsenic exposure, in the context of very large and statistically robust studies, in order to successfully develop defensible findings. With the knowledge that improvements in this area will enhance detection and quantification of risk, our research group is employing methods to improve the accuracy and precision of exposure assessment in a large population-based case–control study of incident bladder cancer in northern New England that we are conducting collaboratively with Dartmouth Medical School, the United States Geologic Survey, and the state health departments of Vermont, New Hampshire, and Maine (>1200 cases and >1200 controls). Bladder cancer mortality rates in this region, among men and women, have been elevated for many decades, and arsenic levels in drinking water are moderately above the U.S. average (Devesa et al., 1999; Welch et al., 2000; Ayotte et al., 2003). Exposure assessment methods in the study include direct measurement of arsenic in water samples from all current homes and selected past homes of respondents; development and use of predictive multivariate regression models to estimate arsenic levels in past

homes with private wells where samples are not available; and abstracting information from public water systems (Colt et al., 2002; Ayotte et al., 2006). Subject interviews are completed and the data are under initial evaluation.

### Summary

In conclusion, epidemiologic data from areas of the world with very high levels of arsenic in drinking water (>150  $\mu\text{g/L}$ ) show a strong association between arsenic exposure and risk of several internal cancers. A causal interpretation is clearly warranted (International Agency for Research on Cancer, 2004). At lower exposure levels, in the absence of unambiguous human data, extrapolation from the high-exposure studies has been used to estimate risk (Smith et al., 1992; Morales et al., 2000). Misclassification of exposure usually results in depressing observed levels of risk, and many studies conducted in populations with exposures below 100  $\mu\text{g/L}$  are limited by the difficult issue of estimating past exposures. The limited size of most studies contributes to the variability of findings and makes interpretation of results all the more challenging. Efforts are underway to improve exposure assessment in a large case–control study of bladder cancer in a region of the United States with somewhat elevated levels of arsenic in drinking water.

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