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Low-Dose Risk Assessment for Arsenic: A Meta-Analysis Approach

Munni Begum, DrPh[1], John Horowitz, PhD[1], and Md. Irfan Hossain, MA[2]

Abstract

We conducted a meta-analysis to explore dose–response relationships for bladder and lung cancers when people are chronically exposed to low doses of arsenic. We searched electronic databases for articles published through 2010. Ten studies on bladder cancer and ingested arsenic exposure and five studies on lung cancer and ingested arsenic exposure fit our selection criteria. We also investigate the sensitivity of the absolute risk of lung and bladder cancer under different underlying prevalence measures. Males have a higher risk of bladder cancer than do females at all maximum contamination levels. The absolute risk of bladder cancer and lung cancer from ingested arsenic correlates highly with smoking rates. For a maximum contamination level of 10 μg/L, we estimate that there are about 2.91 additional bladder cancer cases per 100 000 people and, considering studies since 2000, we estimate that there are about 4.51 additional lung cancer cases per 100 000 people.

Keywords

arsenic, bladder cancer, lung cancer, risk assessment, meta-analysis

Introduction

At high doses, epidemiological studies provide solid evidence in favor of carcinogenic risk of ingested arsenic.[1] However, there is no adequate scientific evidence on carcinogenicity of arsenic at low doses. The concern is that long-term chronic exposure to arsenic at low doses is associated with several internal cancers (such as lung and bladder cancer) and other negative health effects. Because of the lack of scientific evidence of carcinogenicity of arsenic at lower levels, there is some disagreement about what the appropriate maximum contamination level (MCL) should be. Wildavsky[2] argued that epidemiological studies only find clear evidence of arsenic carcinogenicity at doses >250 to 300 μg/L per day. However, Chiou et al[3] and Chiou et al[4] find evidence of arsenic carcinogenicity at doses >50 μg/L per day.

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Determining the appropriate MCL is important. If the MCL is too low, then some consumption or production activities will be thought to create negative effects when actually they do not. On the other hand, if the MCL is too high, then some consumption or production activities that are thought to be safe may have negative health effects. In 1993, the World Health Organization suggested that for arsenic in potable water, the MCL should be set at 10 μg/L. The United State Environmental Protection Agency (US EPA) had an MCL of 50 μg/L prior to 2001.[5] In 2001, the US EPA lowered the MCL for arsenic to 10 μg/L. Currently, the USEPA is considering whether to lower the MCL even further.

Because of the lack of consistent results on the risk of arsenic carcinogenicity from animal models, observational studies in epidemiology form the basis for arsenic risk assessment. Although the use of human data from epidemiological studies provides direct evidence of carcinogenicity in humans, results from these studies are highly variable and often times are conflicting. Meta-analysis is a common statistical method to combine results from multiple studies that address the same hypothesis.[6,7] Other methods include incorporating biological information by using pharmacokinetic and pharmacodynamic modeling. A meta-analysis of systematically selected studies can reduce the variability and bias of the parameter estimates. Because of its simplicity and intuitiveness, we use a meta-analysis approach to determine the health implications of low-dose chronic exposure to arsenic.

This study has 3 objectives. The first is to develop a dose–response relationship for bladder and lung cancer when people are chronically exposed to low doses of arsenic. The second objective is to obtain a synthesis of the results from studies on bladder and lung cancer due to chronic low-dose exposure to arsenic. The third objective is to investigate the sensitivity of the absolute risk of lung and bladder cancer under different underlying prevalence measures.

Background

Evidence on the association of ingested arsenic and the occurrence of internal cancer, such as bladder and lung cancer, are available from epidemiological studies conducted world-wide. Because of the lack of consistency in study results, statistical meta-analysis can be a powerful tool to combine and synthesize research findings in a meaningful way for risk assessment. Because of conflicting results from animal studies, epidemiological data provide the best sources of evidence for arsenic risk assessment. A quantitative meta-analysis (systematic review) is implemented to combine results across studies and to provide an aggregate measure of carcinogenic risk from ingested arsenic exposure. Chuand and Crawford-Brown[8] and Mink et al[9] conducted meta-analyses on the association between bladder cancer and ingested arsenic. We updated their studies with more recent studies on bladder cancer and compare our results with their results. We also conducted a meta-analysis for lung cancer. We estimate absolute risks for bladder and lung cancer from the low-dose exposure of ingested arsenic. We also investigate the sensitivity of the absolute risk of lung and bladder cancer under different underlying prevalence measures.

Study Selection Process

The epidemiological studies are included from all over the world, ranging from low-concentration regions (such as the United States) to high-concentration regions (such as Taiwan, Bangladesh, West Bengal, Inner Mongolia, and China). Bangladesh and other low-income countries tend to have an MCL of 50 μg/L whereas higher income countries such as Western Europe and the United States have MCL of 10 μg/L. The inclusion criteria for the studies to be considered in the meta-analysis are as follows:

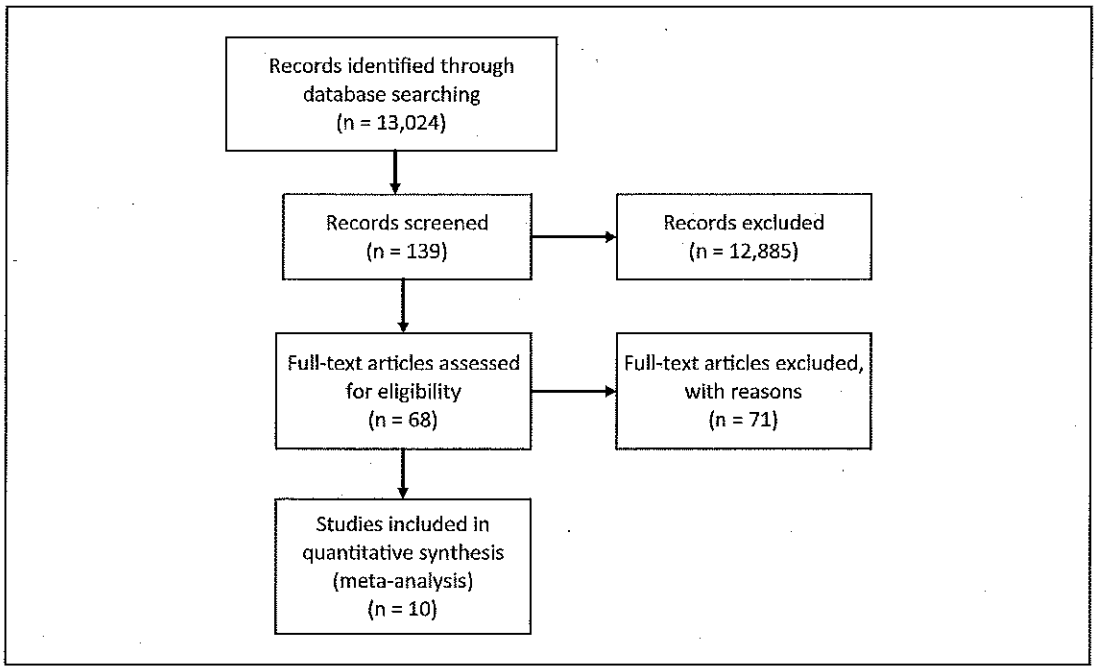

Figure 1. Flow diagram for bladder cancer study selection

1. Internal cancer, such as lung, bladder, and urinary tract, as the endpoint or health outcome.
2. Long-term exposure at low levels of arsenic in drinking water or bio-markers reflective of such exposure.
3. Well-defined epidemiological study designs (prospective cohort or retrospective case–control) and ecologic studies conducted at low exposure levels (proper averaging out of relevant extraneous factors).
4. Relative risk estimates (eg, rate ratios or odds ratios) with measures of variability (or data that allowed for such calculations) and availability of covariate information or stratified analysis.

We used electronic library database search engines such as Google Scholar, PubMed, and other relevant search engines with keywords arsenic, arsenite, arsenate, arsenicals, bladder cancer, transitional cell carcinoma of the bladder, urothelial cancer, transitional cell carcinoma of the bladder, urinary tract cancer, bladder neoplasm or urinary bladder neoplasm or urinary bladder cancer. As shown in Figure 1, using these terms, we identified 13 024 studies with publication dates through 2010.

We then combined the terms arsenic, arsenite, arsenate, arsenicals with any of the terms bladder cancer, transitional cell carcinoma of the bladder, urothelial cancer, transitional cell carcinoma of the bladder, urinary tract cancer, bladder neoplasm, urinary bladder neoplasm, and urinary bladder cancer. We screened 139 studies. Of these 139 studies, we accessed full text articles for 68 studies. Of these 68 studies, 10 bladder cancer studies met all 4 inclusion criteria.

For lung cancer, we used the same electronic data base search engines described above using keywords arsenic, arsenite, arsenate, arsenicals, and lung cancer, lung neoplasm, small cell lung carcinoma, non–small cell lung carcinoma, bronchioloalveolar carcinoma, bronchiectasis, and

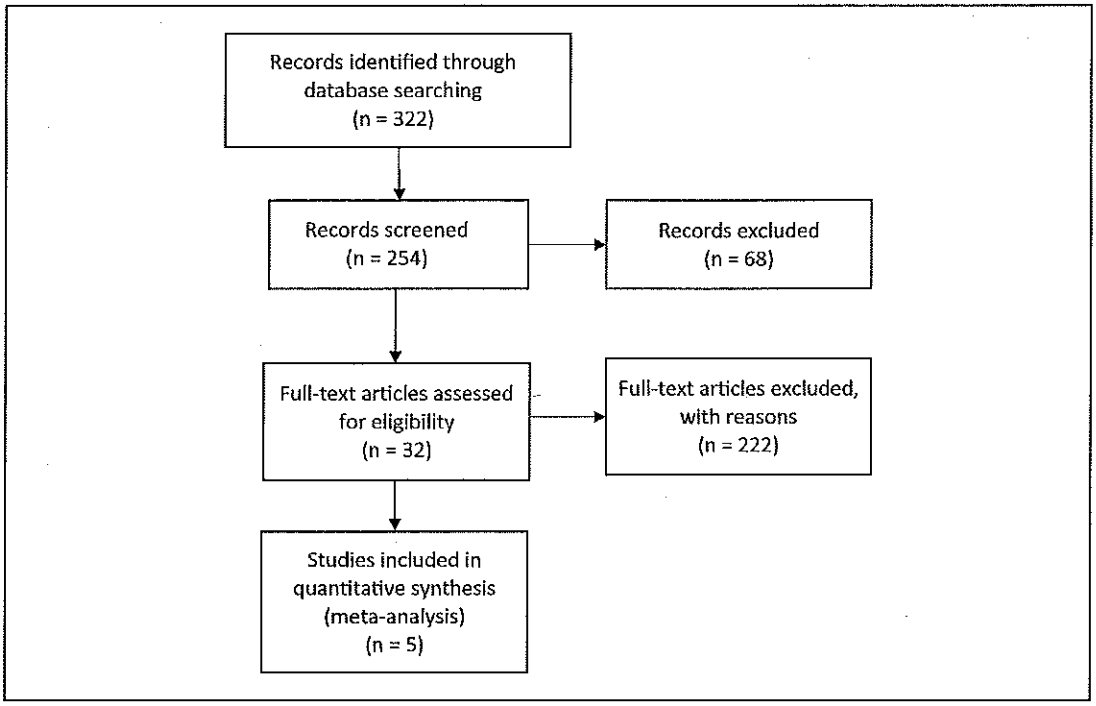

Figure 2. Flow diagram for lung cancer study selection

bronchorrhea. As shown in Figure 2, using these terms, we identified 322 studies with publication dates through 2010.

We then combined the terms arsenic, arsenite, arsenate, arsenicals with any of the terms lung cancer, lung neoplasm, small cell lung carcinoma, non–small cell lung carcinoma, bronchioloalveolar carcinoma, bronchiectasis, and bronchorrhea. We screened 254 studies. Of these 254 studies, we accessed full text articles for 32 studies. Of these 32 studies, 5 lung cancer studies met all 4 inclusion criteria.

A brief summary of each of these 10 bladder cancer studies and 5 lung cancer studies are presented in Tables 1 and 2, respectively. The tables contain information about each study's authors, publication year, study design, outcome measure, exposure measure, and whether adjustments of covariates are made in the analysis. Meta-analyses are conducted separately on these 2 sets of studies to create a dose–response relationship for bladder cancer studies and another dose–response relationship for lung cancer studies.

For both bladder and lung cancer outcomes, ingestion of arsenic through drinking water was considered as the exposure route. The studies included in the meta-analysis reported exposure levels in various ranges. The dose–response curves are constructed for the relative risk measures and exposure midpoints. For an open-ended lower limit, we assume that the lower limit is zero. For an open-ended upper limit, for example, greater than 100, we assume that the upper limit is 100. Using these assumptions, exposure midpoints are calculated by taking the average of the lower and upper limits of each range. Karagas et al,[10] Michaud et al,[11] and Heck et al[18] reported toenail arsenic concentration as exposure levels, which was converted to equivalent drinking water exposure measures as 0.05 μg/L toenail concentration = 1 μg/L drinking water concentration.

Methodology

In summarizing a dose–response relationships across studies, we estimate the slope parameter β, which measures the change in the natural logarithm of the relative risk (ln RR) per unit change

Table 1. Bladder Cancer Studies Description

Study (Publication Year)	Type of Study	Study Population	Outcome Measure	Exposure Measure	Analysis Adjusted for Covariates?
Karagas et al (2004)[10]	Case–control	A total of 459 bladder cancer cases and a total of 665 controls were considered.	Odds ratio	Exposure to arsenic was determined by analyzing toenail clipping samples using instrumental neuron activation analysis. Toenail arsenic concentration ranged from 0.009 to 1.007 μg/g among controls and from 0.014 to 2.484 μg/g among bladder cancer cases.	Adjustments were made for smoking and other relevant covariates.
Michaud et al (2004)[11]	Case–control	331 bladder cancer cases and same number of controls were considered.	Odds ratio	Individual exposure to arsenic was determined using toenail concentrations that served as a biomarker of arsenic concentration.	Logistic regression analysis is adjusted for smoking and other relevant covariates.
Steinmaus et al (2003)[12]	Case–control	181 bladder cancer cases and 328 controls were considered.	Odds ratio	The highest single year cumulative arsenic concentrations to which the subjects were exposed were estimated.	Statistical analysis was adjusted for smoking and duration of exposure to arsenic.
Chiou et al (2001)[4]	Prospective (cohort) study	A cohort of 8102 subjects was considered.	Relative risk	Well water samples were assayed to estimate arsenic concentrations to which study subjects were exposed.	Multivariate analysis was adjusted for smoking and other covariates.
Kurttio et al (1999)[13]	Case–cohort	61 bladder cancer cases, 49 kidney cancer cases, and 275 subjects in the reference cohort were considered.	Relative risk	Arsenic exposure was estimated for short and long latency periods and daily dose of arsenic was calculated from reported consumption of drinking water from wells.	Statistical analysis was adjusted for smoking and other covariates.
Bates et al (2004)[14]	Case–control	A total of 114 case control pairs were considered.	Odds ratio	Exposure to arsenic was estimated from water samples collected from subjects' current residence.	Statistical analysis was adjusted for covariates.
Bates et al (1995)[15]	Case–control	117 cases and 266 controls were considered.	Odds ratio	Two arsenic exposure indices (total cumulative exposure) and intake concentration were used as exposure measures.	Statistical analysis was adjusted for smoking.
Moore et al (2003)[16]	Case–case	147 bladder tumor patients were considered.	Odds ratio	Exposure to arsenic was determined from water samples.	Statistical analysis was adjusted for smoking and other covariates.
Chiou et al (1995)[3]	Follow-up study	263 patients with black foot disease and 2293 healthy residents in the arseniasis-endemic area of Taiwan were considered.	Relative risk	A cumulative arsenic exposure was estimated as the arsenic concentration in the artesian well multiplied by the duration of drinking artesian well water.	Statistical analysis was adjusted for covariates.
Meliker et al (2010)[17]	Case–control	411 bladder cancer cases and 566 controls were considered.	Odds ratio	A lifetime exposure to arsenic was predicted using geostatistical modeling.	Statistical analysis was adjusted for smoking and other relevant covariates.

in the exposure level within each study and combines these estimates of $\hat{\beta}$ across studies.[22] A dose–response model for each study is fitted using the functional relationship $\ln RR = \hat{\beta}(X\text{-}X_0)$, where ln RR is the natural logarithm of relative risk, X is the exposure midpoint, X_0 is the exposure concentration of the reference category, and $\hat{\beta}$ is the fitted slope coefficient of the dose–response model. Although the procedure is logically simple, it is important to identify sources of variation within and across studies before combining any summary statistic $\hat{\beta}$. The studies on arsenic exposure and internal cancers (bladder and lung) vary in terms of sample size, geographic

Table 2. Lung Cancer Studies Description

Study (Publication Year)	Type of Study	Study Population	Outcome Measure	Exposure Measure	Analysis Adjusted for Covariates?
Heck et al (2009)[18]	Case–control	A total 223 lung cancer cases and 238 controls were considered.	Odds ratio	Arsenic exposure measures were estimated from toenail concentrations.	Relationship of smoking in addition to arsenic ingestion was investigated.
Smith et al (2009)[19]	Case–control	152 lung cancer cases and 419 controls were considered.	Odds ratio	Exposure to arsenic was estimated as the lifetime average arsenic water concentrations in the counties of residence.	Statistical analysis was adjusted for smoking, working at a copper smelter, and other covariates
Chen et al (2010)[20]	Follow-up study	8086 subjects were followed for 11 years, out of whom 6888 were included in the final analysis.	Relative risk	Arsenic concentration was estimated using water samples collected from the wells used by the subjects.	Statistical analysis was adjusted for smoking and other covariates.
Chen et al (2004)[21]	Follow-up study	A total of 2503 residents and 8088 residents in 2 arseniasis-endemic areas in Taiwan.	Relative risk	Arsenic exposure was estimated as lifetime cumulative exposure taking arsenic concentration in well water and duration of drinking water into account.	Statistical analysis was adjusted for smoking and other covariates.
Chiou et al (1995)[3]	Follow-up study	263 patients with black foot disease and 2293 healthy residents in the arseniasis-endemic area of Taiwan.	Relative risk	A cumulative arsenic exposure was estimated as the arsenic concentration in the artesian well water multiplied by the duration of drinking artesian well water.	Statistical analysis was adjusted for covariates.

location, and inclusion of other predictor variables. We set the selection criteria carefully to include as many homogeneous studies as possible.

To check if the slope parameters of the dose–response relationship from each study are similar, we use a test of homogeneity on the study specific slopes. Although this test is not very powerful against the alternative hypothesis, rejection of the null hypothesis implies that the studies are not homogeneous in terms of the summary measures. The bladder cancer studies are found to be homogeneous with respect to the slope parameter by the test of homogeneity. However, the lung cancer studies are found not to be homogeneous by the test. Thus, we considered a fixed-effects model for the bladder cancer studies and a random-effects model for the lung cancer studies to combine the estimates of study specific slope parameters. The combined estimate under a fixed-effects model is calculated as

$$\hat{\beta} = \frac{\sum_{i=1}^{k} w_i \overline{\beta}_i}{\sum_{i=1}^{k} w_i} \quad \text{with } w_i = \frac{1}{s_i^2},$$

where s_i^2 measures within-study variation. The statistical software package SAS version 9.2 is used to conduct the meta-analysis using the MIXED procedure.

Dose–Response Relationships

Dose–Response Relationship for 10 Selected Studies on Bladder Cancer and Arsenic Exposure

In the 10 bladder cancer studies, the exposure levels of arsenic range from <5 μg/L to <300 μg/L. However, except for Moore et al,[16] the studies have exposure levels <100 μg/L. The studies report predicted odds ratios within various ranges of exposure levels. To explore if there is any

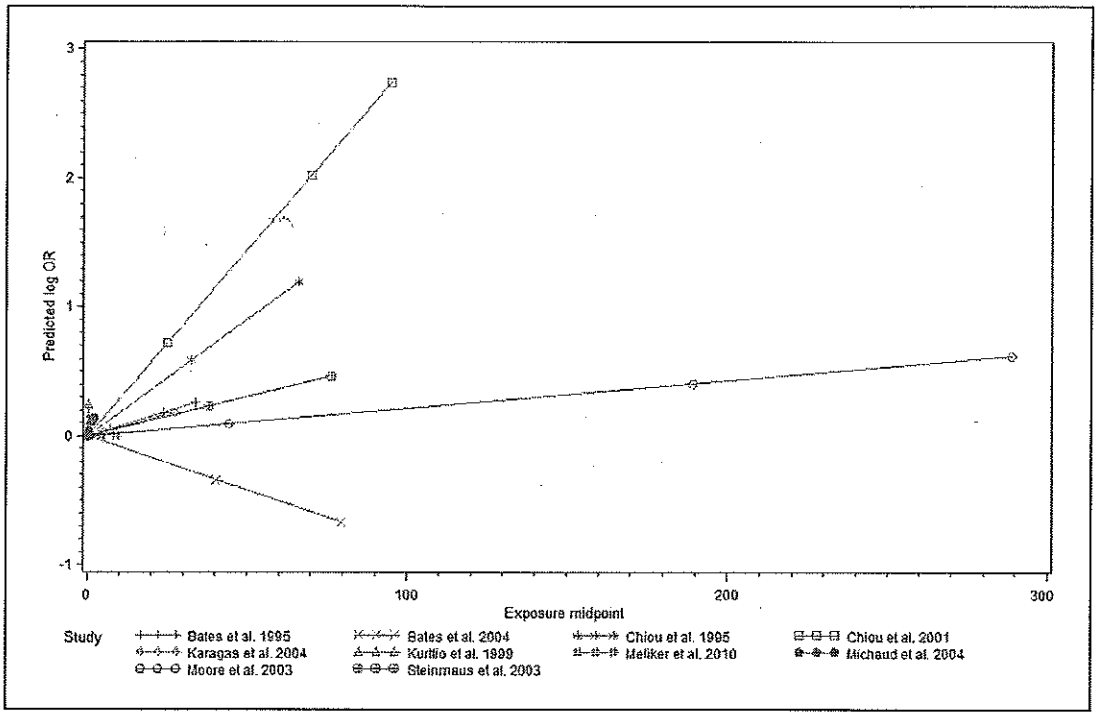

Figure 3. Bladder cancer predicted log odds ratio (OR) versus exposure plot from 10 studies

dose–response relationship among arsenic exposure and bladder cancer, we constructed simple dose–response relationships (Figure 3) by plotting available exposure midpoints and respective predicted logarithm of odds ratios (log ORs) for each study.

A predicted log OR of 0 means no risk. Negative numbers imply beneficial effects and positive numbers imply adverse health effects. A predicted log OR of 1 implies a predicted OR of 2.73. This means that the risk of developing bladder cancer is 2.73 times higher than those who are not exposed at that dose level. As shown in Figure 3, the only studies that show a predicted log OR of 1 or greater are Chiou et al[3] and Chiou et al.[4] Bates et al[14] suggest that arsenic is beneficial in reducing bladder cancer up to 80 μg/L. The other 7 studies find a positive but weak relationship at exposure levels lower than 50 μg/L. More recent studies are more likely to demonstrate little or no dose–response relationship between bladder cancer and chronic exposure to low doses of ingested arsenic.

Dose–Response Relationship for 5 Selected Studies on Lung Cancer and Arsenic Axposure

The 5 lung cancer studies have exposure levels ranging from <5 μg/L to <300 μg/L. Note that the lung cancer studies have approximately the same range of exposure as the bladder cancer studies. As before, we construct dose–response graphs for arsenic exposure and lung cancer (Figure 4).

Unlike bladder cancer, no study finds therapeutic results from exposure to arsenic. There are 2 studies that show a predicted log OR of 1 or greater. These are Chiou et al[3] and Smith et al.[19] However, Smith et al[19] only finds a log OR > 1 when the exposure level is nearly 200 μg/L. Similar to bladder cancer, more recent studies are more likely to find little or no dose–response relationship between lung cancer and low doses of ingested arsenic.

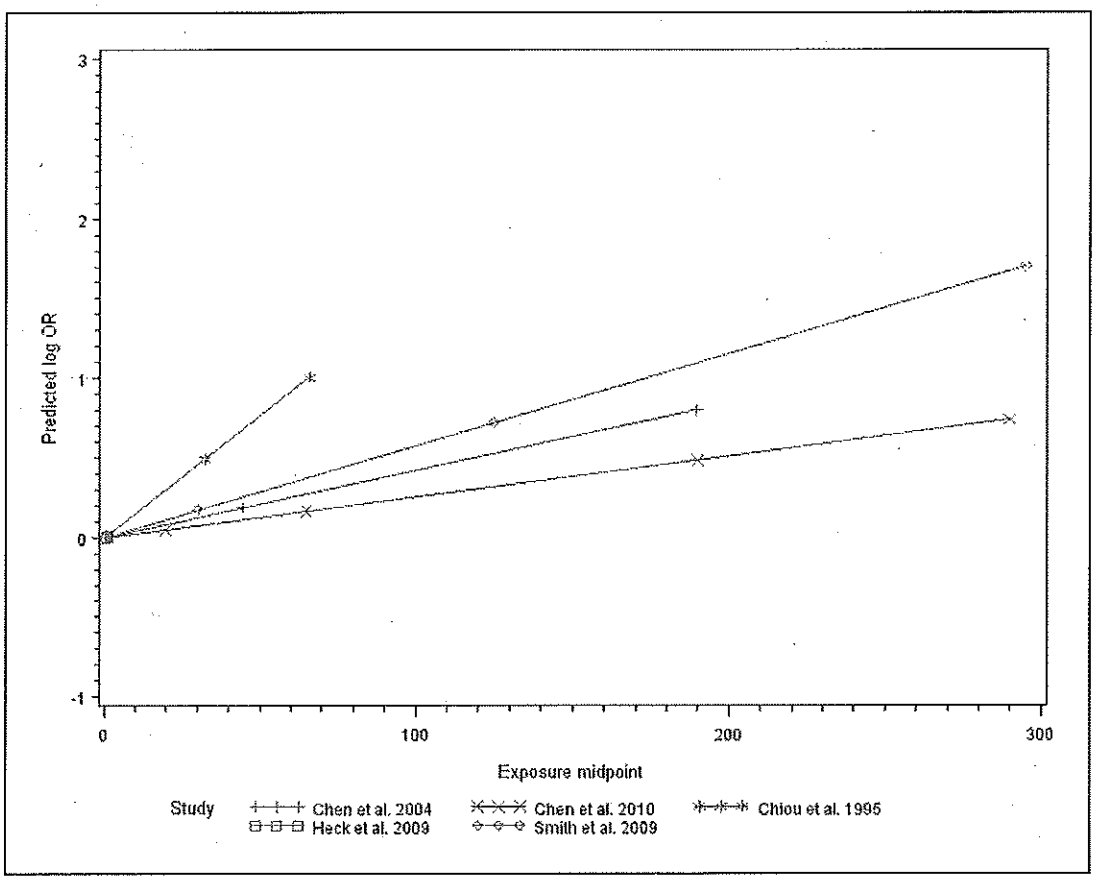

Figure 4. Lung cancer predicted log odds ratio (OR) versus exposure plot from five studies

Results

The dose–response relationships for both bladder cancer and lung cancer are not always consistent. In our dose–response model, the reference category is the lowest arsenic concentration. The dose concentration is the difference between the exposure midpoint of a category (X) and the midpoint of the reference category (X_0). The slope coefficients, the standard errors, and the corresponding 95% confidence intervals are presented in Table 3 for bladder cancer studies and in Table 4 for lung cancer studies. The bladder cancer studies are found to be homogeneous in terms of the slope coefficients by the test of homogeneity ($P = .2508$ and F-statistic = 1.51). The lung cancer studies are found to be heterogeneous in terms of slope coefficients by the test of homogeneity ($P < .0001$, F-statistic = 37.68). Although the results of this test of homogeneity dictate whether a fixed-effects model (for homogeneous studies) or a random-effects model (for heterogeneous studies) is to be used to combine the slope coefficients ($\hat{\beta}$), the test itself is not a powerful one. Nonetheless, we used a fixed-effects model to combine the slope coefficients of bladder cancer studies and a random-effects model to combine the slope coefficients of lung cancer studies.

The combined $\hat{\beta}_{bladder}$ is 0.002387 with a 95% confidence interval of (−0.00007, 0.00485) for the 10 bladder cancer studies. The combined $\hat{\beta}_{lung}$ is 0.01082 with a 95% confidence interval of (−0.00417, 0.02581) for the 5 lung cancer studies. We also estimated the overall slope coefficient from the lung cancer studies since 2000. The combined $\hat{\beta}_{lung2000}$ from these studies is 0.00458 with a 95% confidence interval of (−0.00967, 0.01883).

The forest plot from the meta-analysis for bladder cancer is shown in Figure 5. Figure 6 shows the forest plot from the meta-analysis for lung cancer. The overall $\hat{\beta}$ is shown at the top of each

Table 3. Estimated Slope Coefficients, Standard Errors, and 95% Wald Confidence Interval for Bladder Cancer Studies

Study	Estimated Slope Coefficient	Standard Error	95% Confidence Interval
Karagas et al (2004)[10]	0.00644	0.01607	(−0.02506, 0.03794)
Michaud et al (2004)[11]	0.06509	0.01394	(0.03777, 0.09241)
Steinmaus et al (2003)[12]	0.00608	0.00335	(−0.00049, 0.01265)
Chiou et al (2001)[4]	0.02888	0.00064804	(0.02761, 0.03015)
Kurttio et al (1999)[13]	0.6135	0.83355	(−1.02026, 2.24726)
Bates et al (2004)[14]	−0.00842	0.00851	(−0.02510, 0.00826)
Bates et al (1995)[15]	0.00762	0.00777	(−0.00761, 0.02285)
Moore et al (2003)[16]	0.00214	0.00119	(−0.00019, 0.00447)
Chiou et al (1995)[3]	0.01809	1.5817×10^{-6}	(0.01809, 0.01809)
Meliker et al (2010)[17]	0.00072298	0.01973	(−0.03795, 0.03939)
Overall	0.002387	0.001255	(−0.00007, 0.00485)

Table 4. Estimated Slope Coefficients, Standard Errors, and 95% Wald Confidence Interval for Lung Cancer Studies

Study	Estimated Slope Coefficient	Standard Error	95% Confidence Interval
Heck et al (2009)[18]	0.00505	0.14667	(0.29252, −0.28242)
Smith et al (2009)[19]	0.00578	0.0013	(0.00833, 0.00323)
Chen et al (2010)[20]	0.00255	0.00028555	(0.00311 0.00199)
Chen et al (2004)[21]	0.00422	0.0037968	(0.01166, −0.00322)
Chiou et al (1995)[3]	0.01525	0.00239	(0.01993, 0.01057)
Overall since 2000	0.004581	0.007272	(0.01883, −0.00967)
Overall	0.01082	0.00765	(0.02581, −0.00417)

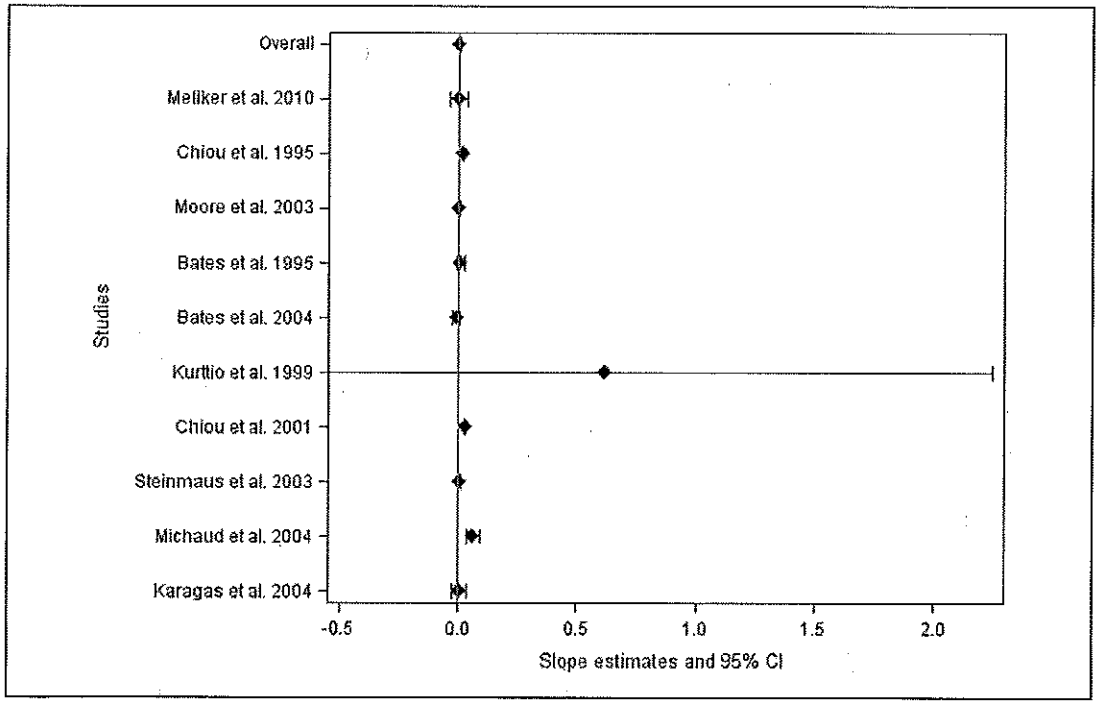

Figure 5. Combined slope estimate from 10 bladder cancer studies

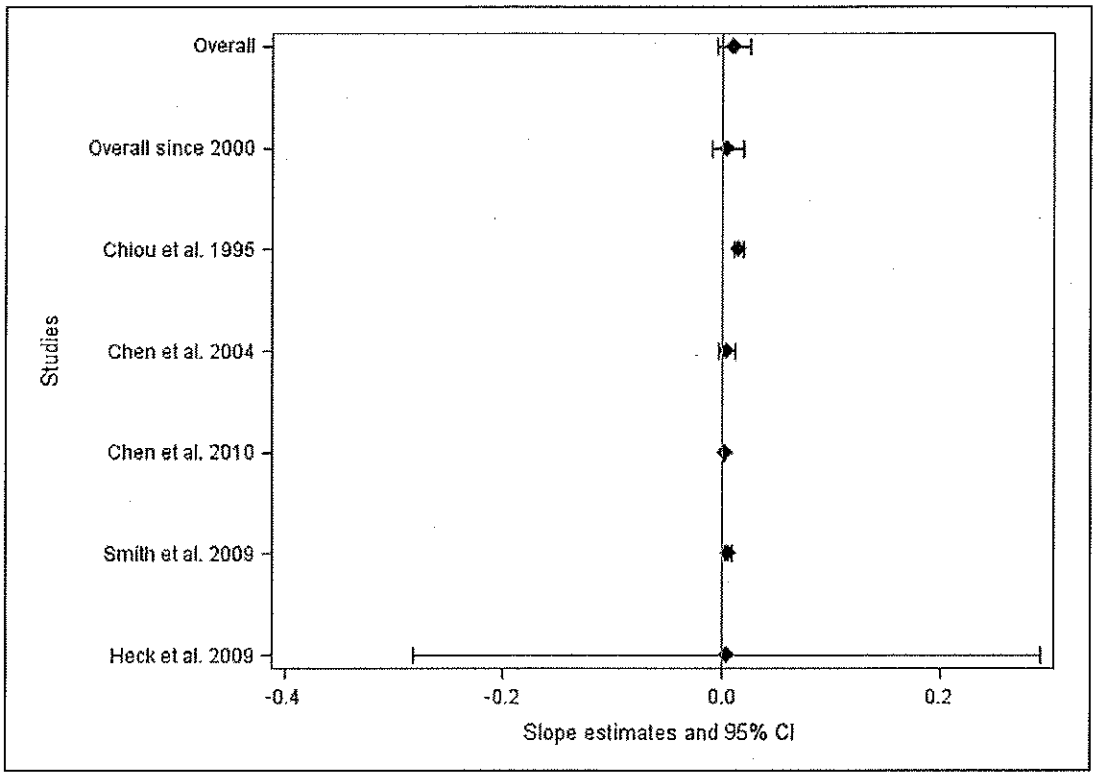

Figure 6. Combined slope estimate from 5 lung cancer studies

figure. In Figure 6, we also include the overall $\hat{\beta}$ for the lung cancer studies that were published since 2000.

Forest Plots

The length of the confidence interval of the true slope coefficient β for Kurttio et al[13] is wider than that of the other studies (Figure 5). This is because of the large variability in the estimated slope coefficient from this study. Of the included studies, Kurttio et al[13] have the highest slope estimate. The other studies have estimated slope coefficient estimates near zero with very tight confidence intervals. The other 9 studies imply that the risk of bladder cancer from low-dose exposure to ingested arsenic is very low.

The length of the confidence interval of the true slope coefficient β for Heck et al[18] is wider than that of the other studies (Figure 6). This is because of the large variability in the estimated slope coefficient from this study. All the studies have estimated slope coefficient estimates near zero. All studies except for Heck et al[18] have narrow confidence intervals. The 5 studies imply that the risk of lung cancer from low-dose exposure to ingested arsenic is very low.

Estimated Absolute Risk of Bladder and Lung Cancer From Ingested Arsenic

Although the dose–response plots in Figures 3 and 4 show that in general there is a positive relationship between exposure and predicted OR, the meta-analysis results given in Figures 5 and 6 show that there is little risk of bladder cancer or lung cancer at low exposure levels. The predicted OR can be calculated from the predicted log OR using the combined slope estimates $\hat{\beta}$ of the dose–response models as follows:

Table 5. Prevalence Rates for Bladder and Lung Cancers

	All States			Kentucky 2000+			Utah 2000+		
	All	Females	Males	All	Females	Males	All	Females	Males
Bladder	0.0012	0.00052	0.00213	0.000934	0.000439	0.00145	0.00047	0.000217	0.00072
Lung	0.00096	0.00093	0.00102	0.00147	0.0014	0.00154	0.00025	0.00025	0.00025

$$\text{Ln OR}_i = \beta_i X_i,\ i = \text{bladder or lung} \tag{2}$$

$$\text{OR}_i = \exp(\beta_i X_i), \tag{3}$$

where X is the ingested arsenic concentration in units of μg/L. The combined slope coefficient estimate for the bladder cancer studies is $\hat{\beta}_{\text{bladder}} = 0.002387$ and the combined slope coefficient estimate for the lung cancer studies is $\hat{\beta}_{\text{lung}} = 0.1082$. Equations 4 and 5 are obtained by substituting these values into Equations 2 and 3.

$$\ln \text{OR}_{\text{bladder}} = 0.002387X \text{ or } \text{OR}_{\text{bladder}} = \exp(0.002387X), \tag{4}$$

$$\ln \text{OR}_{\text{lung}} = 0.01082X \text{ or } \text{OR}_{\text{lung}} = \exp(0.01082X). \tag{5}$$

Finally, the absolute risks (ARs) of bladder and lung cancers are calculated by multiplying the excess odds ratio (EOR) by the prevalence rates (PR) of bladder and lung cancers collected from the National Cancer Institute.[23] The formula for AR can be written as follows:

$$\text{AR}_i = \text{PR}_i \times \text{EOR}_i = \text{PR}_i \times (\text{OR}_i - 1) = \text{PR}_i \times \exp(\hat{\beta}X - 1),\quad i = \text{bladder or lung}. \tag{6}$$

The "All State" prevalence rates for both lung and bladder cancers in Table 5 are from the National Cancer Institute (1975-2008).[23] Utah and Kentucky were included to determine how sensitive bladder and lung cancer rates are to smoking prevalence in a state. Utah has the lowest smoking rate in the United States and Kentucky has the highest. Because the prevalence data for Kentucky are only available since 2000, to make results comparable, we also included data for Utah since 2000.

Using Equation 6 and the prevalence rates given in Table 3, we calculated the absolute risk of bladder and lung cancer for all of the population, the male population, and the female population. The absolute risks of bladder cancer at MCLs of 0, 1, 3, 5, 10, 20, 30, 40, 50, 80, 100, 150, 200, 250, and 300 μg/L are shown in Figure 7. The absolute risks of lung cancer are shown in Figure 8. Figure 9 shows the absolute risks of lung cancer since 2000. Figure 7 shows that males have a higher risk of bladder cancer than females at all levels of MCL. Also on average, states with higher smoking levels are more prone to bladder cancer than states with fewer smokers. This shows that smoking has a positive impact on bladder cancer risk from ingested arsenic. The absolute risk from lung cancer (Figures 8 and 9) is higher than the risk for bladder cancer (Figure 7) for all groups. People living in Kentucky have the highest absolute risk and people living in Utah have the lowest absolute risk. The absolute risk of lung cancer from ingested arsenic correlates highly with smoking rates.

As mentioned above, studies that have been published since 2000 find a lower risk of lung cancer from ingested arsenic. Figure 9 shows the absolute risk of lung cancer from ingested arsenic. The absolute risk of lung cancer from ingested arsenic in Figure 9 is lower than in Figure 8.

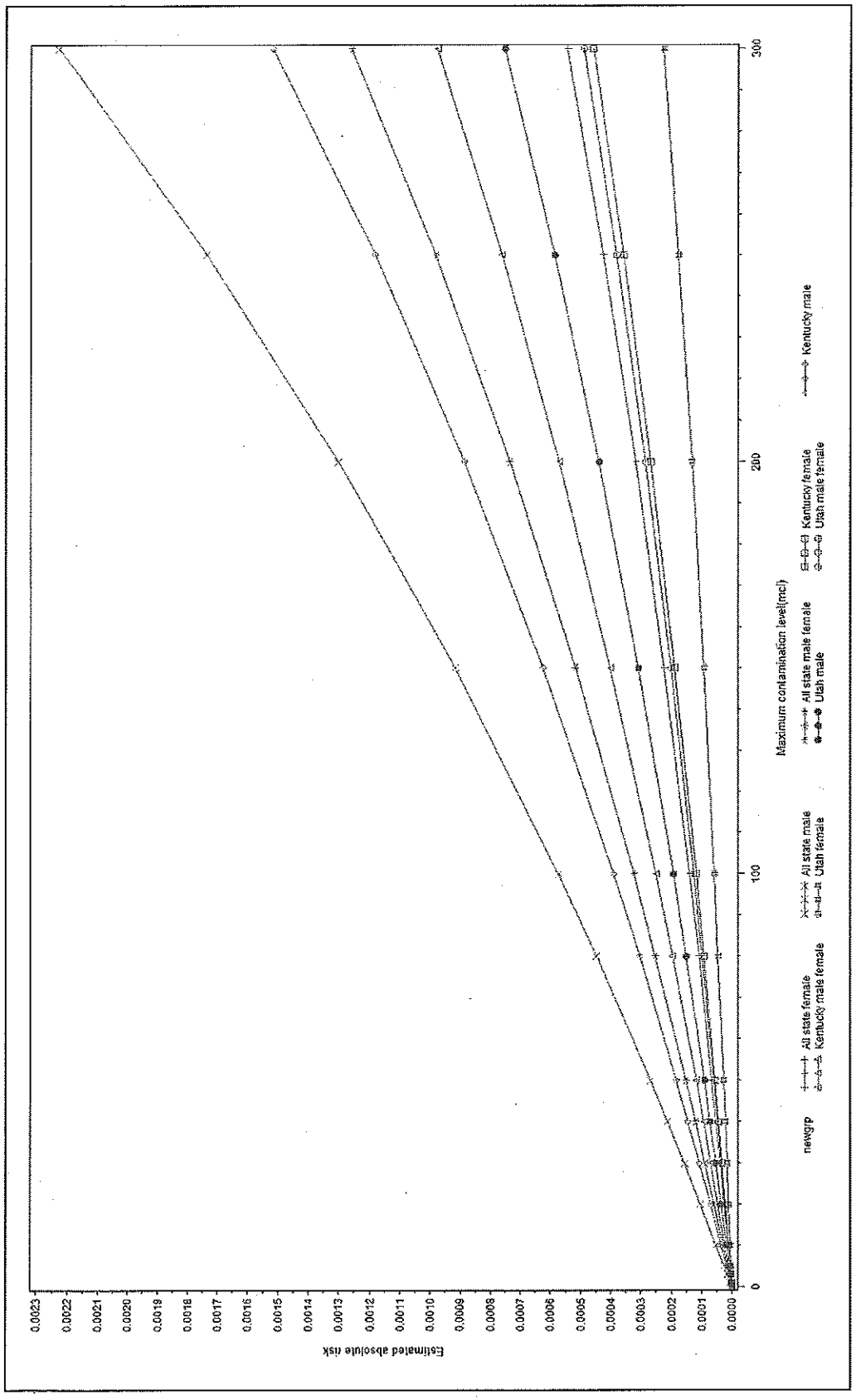

Figure 7. Absolute risk of bladder cancer from ingested arsenic

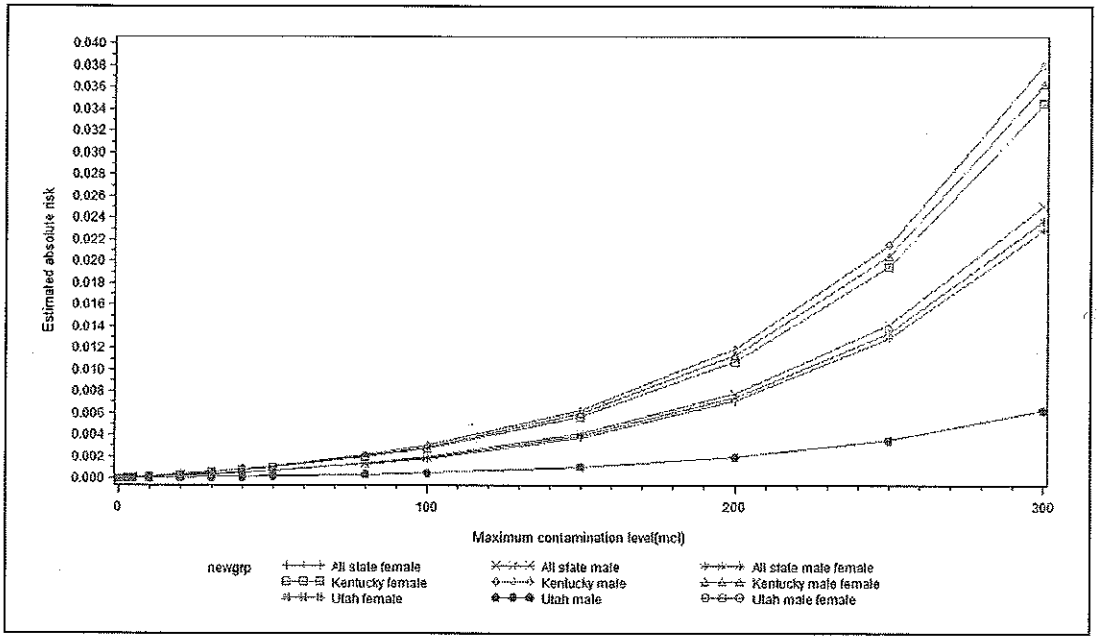

Figure 8. Absolute risk of lung cancer from ingested arsenic

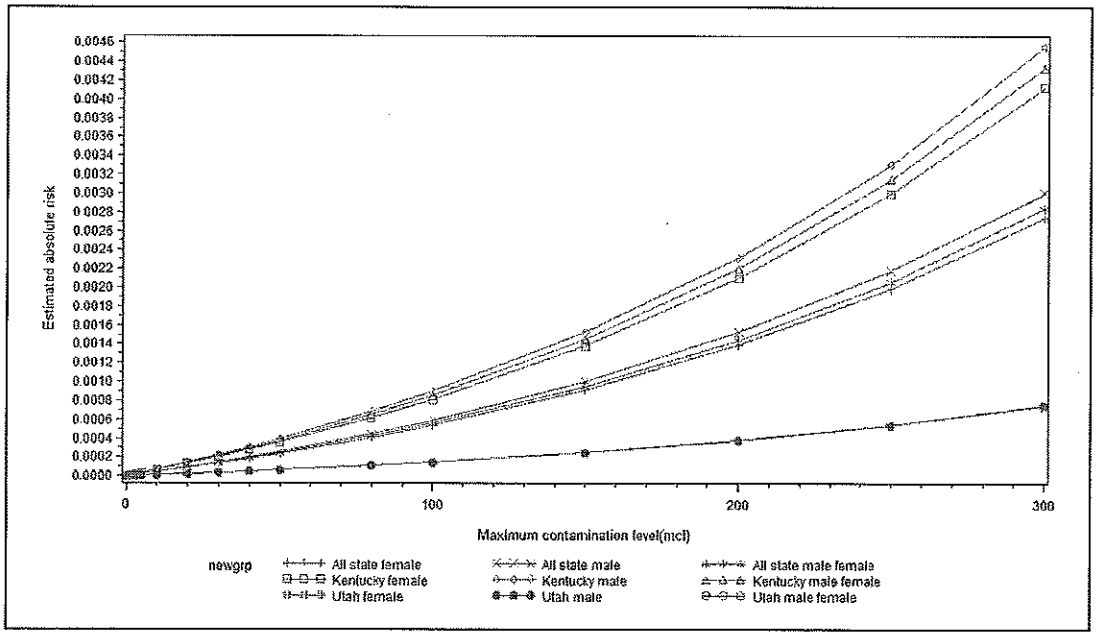

Figure 9. Absolute risk of lung cancer from ingested arsenic since 2000

However, the risk of lung cancer at MCL of 20 μg/L is 7 times higher than in Utah. Smoking seems to have a significant effect on the absolute risk from ingested arsenic for lung cancer.

Discussion

Figures 7 to 9 show the AR of bladder cancer and lung cancer. To compare the AR with other studies, we multiply the AR values by 100 000. Table 6 shows the estimated AR per

Table 6. Estimated Absolute Risk (AR) for Bladder and Lung Cancers per 100 000 Population

Maximum Contamination Level (μg/L)	All States			Kentucky			Utah		
	All	Females	Males	All	Females	Males	All	Females	Males
Bladder									
3	0.86	0.37	1.53	0.67	0.32	1.04	0.34	0.16	0.52
5	1.44	0.63	2.56	1.12	0.53	1.73	0.56	0.26	0.86
10	2.91	1.26	5.14	2.26	1.06	3.50	1.13	0.52	1.74
50	15.25	6.60	26.98	11.84	5.56	18.37	5.95	2.75	9.11
100	32.43	14.05	57.37	25.18	11.84	39.06	12.64	5.85	19.38
Lung									
3	3.17	3.06	3.36	4.85	4.61	5.09	0.84	0.83	0.84
5	5.35	5.15	5.65	8.17	7.77	8.58	1.41	1.40	1.41
10	10.99	10.59	11.62	16.79	15.98	17.63	2.89	2.88	2.91
50	69.05	66.53	72.99	105.47	100.38	110.75	18.16	18.07	18.26
100	187.65	180.82	198.37	286.63	272.18	300.99	49.37	49.11	49.62
Lung 2000									
3	1.33	1.31	1.41	2.03	1.93	2.14	0.35	0.35	0.35
5	2.23	2.19	2.36	3.40	3.24	3.58	0.59	0.58	0.59
10	4.51	4.43	4.77	6.89	6.56	7.23	1.19	1.18	1.19
50	24.76	24.38	26.18	37.82	36.00	39.72	6.51	6.48	6.55
100	55.90	55.18	59.09	85.38	81.27	89.66	14.71	14.63	14.78

100 000 for bladder cancer, lung cancer, and lung cancer since 2000. The estimated ARs per 100 000 are shown for MCLs of 3, 5, 10, 50, and 100 μg/L. The estimated ARs per 100 000 are also shown for males, females, and both males and females (all) in all states, Kentucky, and Utah.

For an MCL of 10 μg/L, the *AR* for bladder cancer in all states for both males and females is 2.91. This implies that there are estimated to be about 2.91 additional bladder cancer cases per 100 000 people. Higher MCLs correspond to higher estimated absolute risk per 100 000 people. For bladder cancer, all states have higher estimated AR per 100 000 than in Kentucky or Utah. Also, men are at much greater risk from bladder cancer than women.

Looking at lung cancer since 2000, the estimated AR per 100 000 for an MCL of 10 μg/L for all states and both males and females is 4.51, compared with 2.91 for bladder cancer. For the studies since 2000, in every case other than men in Utah, the AR per 100 000 for lung cancer is higher than the AR per 100 000 for bladder cancer. Also, Kentucky has a much higher estimated AR per 100,000 than Utah. Assuming that the major difference between Utah and Kentucky is smoking, it implies that smoking increases people's risk of lung cancer from ingestion of arsenic. Though men usually have higher AR for bladder and lung cancer, men have much greater risks for bladder cancer than for lung cancer.

Conclusions

Our absolute risk estimates show that there is evidence that exposure to ingested arsenic increases both bladder and lung cancer risks. Our results are comparable to two previous meta-analysis studies on bladder cancer conducted by Chuand and Crawford-Brown[8] and Mink et al.[9] Studies since 2000 show a lower risk from exposure to ingested arsenic. However, the value

given by Wildavsky[2] who argued that clear evidence of carcinogenicity exists only at 250 to 300 μg/L seems high especially for smokers. Smoking seems to greatly increase the risk of bladder and lung cancer from ingested arsenic.

Note that our study has several limitations. With the data from the selected studies there is no scope for (*a*) conducting exposure assessments, (*b*) validating the precision of the exposure and outcome measures, or (*c*) addressing the interacting impact of other risk factors or the mediating impact of extraneous factors. However, we conducted a homogeneity test and found that the studies on bladder cancer that we included in our study were similar. However, the homogeneity test found that the studies on lung cancer were dissimilar.

This article suggests that a quantitative systematic analysis could be applied to assess the carcinogenicity risk from other environmental agents. However, results should be interpreted with caution because of the mentioned limitations.

A general limitation to any systematic review or meta-analysis is the possible publication bias. Publication bias may occur when the research results that are published in the literature are systematically underrepresentative of all the completed studies in a particular area. An in-depth analysis on publication bias with respect to meta-analysis on arsenic ingestion and the risk of internal cancer is beyond the scope of this article and will be addressed in future research.

Declaration of Conflicting Interests

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