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Epidemiologic Studies of Low-Level Arsenic Exposure in Drinking Water and Bladder Cancer: A Review and Meta-analysis

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Acronyms and Abbreviations

95% CI	95% confidence interval
ED_{01}	1% effective dose
EPA	U.S. Environmental Protection Agency
MCL	maximum contaminant level
mRR	meta-relative risk
NRC	National Research Council
ppb	parts per billion
SMR	standardized mortality ratio

Executive Summary

The current drinking water standard for arsenic of 50 μg/L, or 50 parts per billion (ppb), is in effect until 2006. The pending standard maximum contaminant level (MCL) is 10 μg/L. Risk analyses and dose-response modeling conducted by the National Research Council (NRC) and the U.S. Environmental Protection Agency (EPA) have relied primarily on data from studies conducted in southwestern Taiwan and have been used to support the revised MCL in drinking water. Arsenic levels in artesian wells in southwestern Taiwan have exceeded 1,000 μg/L, whereas drinking water arsenic levels in the United States and other areas with low exposure are typically below 100–200 μg/L. It is not known whether models derived from studies in southwestern Taiwan accurately predict the risk of cancer in populations that differ according to arsenic concentrations in water, as well as other potentially important characteristics (e.g., nutritional status).

We conducted a review and meta-analysis to address the following questions:

1. Is there a significant association between exposure to low levels of arsenic in drinking water and bladder cancer?
2. Are the relative risks from epidemiologic studies of low-level arsenic in drinking water and bladder cancer within the range of 1.2–2.5 as would be predicted by the dose-response curves based on data from the Taiwan studies (NRC 2001)?

A quantitative meta-analysis will improve the precision of the estimate of the association between exposure to low levels of arsenic in drinking water and bladder cancer. The summary estimate (meta-relative risk [mRR]) calculated from the series of meta-analyses was evaluated to determine whether it is consistent with estimates based on extrapolation from the NRC (2001) models.

Eight studies met our eligibility criteria and were included in the meta-analysis. We generated an mRR estimate, 95% confidence interval, and *p*-value for heterogeneity for each meta-

analysis. Separate models were run for ever smokers and never smokers combined, never smokers only, and ever smokers only. For each of these groups, two models were run. "All exposure category" models were created by extracting the adjusted relative risk estimate from each exposure category in the individual study and "collapsed exposure category" models were created by combining all upper arsenic exposure categories and a crude relative risk was computed for each study using the lowest exposure group was the reference category. A series of subgroup analyses was run, restricting analyses to studies according to characteristics that may have produced variability (heterogeneity) in the meta-analysis results. In addition, we conducted influence analyses and power calculations.

The mRR estimates were slightly elevated, but non-significant, for the analyses that evaluated collapsed (mRR = 1.08, 95% confidence interval [95% CI]: 0.82–1.43) and all exposure (mRR = 1.11, 95% CI: 0.95–1.30) categories of smokers and nonsmokers combined. An inverse association was observed for never smokers (all exposure categories: mRR = 0.81, 95% CI: 0.60–1.08), whereas an increased association was observed for ever smokers (all exposure categories: mRR = 1.24, 95% CI: 0.99–1.56). It is noteworthy that the *p*-values for heterogeneity were elevated (indicating homogeneity across the studies) for the analyses among never smokers (collapsed exposures: 0.724, all exposures: 0.937) as compared to the *p*-values for the analyses among ever smokers (collapsed exposures: 0.162, all exposures: 0.032). Thus, heterogeneity exists among the findings for ever smokers, and results for this subgroup should be considered in light of this variability and interpreted cautiously.

The strengths of this meta-analysis include the ability to summarize, describe, and quantify the relative risks associated with low-level exposure to arsenic and bladder cancer in a number of populations. By combining the studies in a meta-analysis, we were able to improve the precision of the relative risk estimates, as indicated by the narrowing of the 95% CI as compared to the individual studies. In addition, we were able to calculate mRRs in never smokers and ever smokers separately. The findings for never smokers were homogeneous, consistent, and robust, despite differences across studies in how exposure was measured or modeled in the analyses.

The main limitation of this meta-analysis is that the studies analyzed did not all use a consistent measure of exposure or consistent exposure level cutoff points to perform their analyses. Data that were used in each of our tables, and thus, in each of our meta-analyses were extracted directly from the articles. In some cases, categorical data were collapsed and *de novo* relative risk estimates were computed. The extent of our analysis was limited by the data that were available to us in each of the published studies. Such variation in the presentation of data is not uncommon in meta-analyses and does not preclude the ability to analyze the presence or absence of an effect within the exposure range of the study.

Results from this meta-analysis indicate that there is no increased risk of bladder cancer associated with exposure to low levels of arsenic in drinking water. Although there was some evidence of increased mRRs for the analyses restricted to ever smokers, most of the mRRs were not statistically significant and there was evidence of considerable heterogeneity across the studies. Thus, we do not consider the data sufficient to implicate smoking as an effect modifier.

The main results of this meta-analysis are not consistent with the range of relative risks predicted by NRC of 1.2–2.5 (NRC 2001). In fact, the majority of the mRRs observed in this study were less than 1.2, with the exception of the analyses of ever smokers, which ranged from 1.2 to 1.5. These results suggest that the dose-response models and slope factors derived by NRC and EPA based on data from southwestern Taiwan are likely not appropriate for accurately predicting risks of human bladder cancer in the U.S. and similar populations. Data from studies in these populations with typically low concentrations of arsenic in drinking water should be used to inform and validate quantitative risk assessment for exposure to arsenic in drinking water.

Introduction

Data from epidemiologic studies conducted in areas with high levels of arsenic in drinking water have found excess bladder cancer incidence and mortality (Kogevinas and Trichopoulos 2002). A number of studies have been conducted in southwestern Taiwan, where arsenic concentrations in artesian well water exceeded 1,000 μg/L (Chiou et al. 1995; Chen et al. 1985, 1992). Arsenic levels in surface water and groundwater are typically in the general range of 1–10 μg/L (Kogevinas and Trichopoulos 2002). Epidemiologic studies conducted in the United States and other areas with typically low levels (< 100 μg/L) of arsenic in drinking water have not found significantly increased risks of bladder cancer overall (e.g., Bates et al. 1995, 2004; Karagas et al. 2004; Lamm et al. 2004; Lewis et al. 1999; Steinmaus et al. 2003; Tollestrup et al. 2003), although some studies have suggested that there may be an increased risk limited to smokers (Bates et al. 1995; Kurttio et al. 1999). A study conducted among Finnish smokers, however, found no association between inorganic arsenic levels in toenails and incident bladder cancer (Michaud et al. 2004).

The current drinking water standard for arsenic is 50 μg/L, or 50 parts per billion (ppb). This standard was set by the U.S. Public Health Service in 1942, and adopted by the U.S. Environmental Protection Agency (EPA) in 1975. It remains in effect until 2006. The pending standard maximum contaminant level (MCL) is 10 μg/L.

U.S. EPA (2001) conducted a risk analysis, including a dose-response assessment and risk estimation. The National Research Council (NRC) has also done dose-response modeling and has calculated excess lifetime risk estimates (NRC 2001). These EPA and NRC risk assessment models have been used to support the revised MCL in drinking water. These models have relied primarily on data from the Taiwan studies (e.g., Chen et al. 1985, 1992; Morales et al. 2000), and have made assumptions about the nature of the dose-response curves to estimate effects at low doses where data were not available or were considered unreliable by EPA. Whether these models predict accurately the risk of cancer in populations exposed to low levels of arsenic in drinking water has not been evaluated formally. This question could be addressed by comparing

the results of the epidemiologic studies of populations with low exposure to the range of exposures predicted by the EPA dose-response curves.

Of particular relevance to the interpretation of the results of the epidemiologic studies in this respect is the discussion of the 1% effective dose (ED_{01}) calculations based on data from two studies (Chiou et al. 2001; Chen et al. 1985, 1992) and various modeling assumptions for the regression model (e.g., additive, multiplicative, linear dose, log dose) in the NRC report (NRC 2001). The ED_{01} is defined as the concentration of arsenic in drinking water in the study that is associated with a 1% increase in the excess risk of cancer, which in this case is bladder cancer. Based on these models, the risk ratio (relative risk) for bladder cancer associated with arsenic levels of 50 μg/L was estimated to range from approximately 1.2 to 2.5 (NRC 2001, Table 5-3). In its Toxicological Review (U.S. EPA 2005b) and Issue Paper (U.S. EPA 2005a), EPA relies heavily on this modeling (NRC 2001) for estimating cancer risks and calculating a revised cancer slope factor for arsenic.

Thus, the purpose of this review and meta-analysis is designed to address the following questions:

1. Is there a significant association between exposure to low levels of arsenic in drinking water and bladder cancer?

2. Are the relative risks from epidemiologic studies of low-level arsenic in drinking water and bladder cancer within the range of 1.2–2.5 as would be predicted by the dose-response curves based on data from the Taiwan studies (NRC 2001)?

In addition to presenting a qualitative review of the relevant literature, we conducted a meta-analysis to provide a quantitative summary of the results of the epidemiologic studies. Our decision regarding whether to conduct a meta-analysis was guided, in part, by consideration of guidelines proposed by Blair et al. (1995) for when a meta-analysis is appropriate in environmental epidemiology. These considerations included:

1. Lack of consensus on exposure/disease relationship
2. Sufficient comparability of exposure and disease definitions
3. Ability to examine sources of heterogeneity
4. A need to increase statistical power
5. Need for information beyond narrative review.

Several of the individual epidemiologic studies have been criticized in reviews by U.S. EPA (2005a,b) and NRC (2001) for having limited statistical power to identify relative risk estimates between 1.2 and 2.0. Although a meta-analysis will increase statistical power, it is important to remember that increased power cannot overcome the presence of systematic bias (e.g., confounding, measurement error). Furthermore, it has been argued that it is more important to evaluate the precision of a given analysis (i.e., how wide or narrow is the resulting confidence interval?), particularly when the relative risk is expected to be 1.0 (Checkoway et al. 2004).

For the purposes of this review, a quantitative meta-analysis will provide a more precise estimate of the association between low-level arsenic exposure and bladder cancer, and this summary estimate will be evaluated to determine whether it is consistent with estimates based on extrapolation from the NRC models. In addition to improving the precision of a relative risk estimate for a specified exposure level, a meta-analysis can be used to examine sources of heterogeneity across studies, to assess relative risk variations for a range of exposure levels, and to clarify associations across a body of scientific studies. A meta-analysis also allows the opportunity to stratify on variables of particular interest (e.g., smoking status: ever versus never) to evaluate whether the summary relative risk estimates appear to differ between the strata.

Materials and Methods

Meta-analysis is a statistical technique for combining the results from a collection of individual studies, and thus, the individual studies are the primary units of analysis. We evaluated the epidemiologic literature pertaining to low-level arsenic exposure from drinking water and risk of bladder cancer to quantify risk at low exposure levels (e.g., typically <100–200 μg/L water concentrations). Specifically, we reviewed studies that examined associations (i.e., relative risk estimates) between low-level arsenic exposure in drinking water and risk of bladder cancer.

Study Selection

For the initial evaluation of epidemiologic studies, we identified studies that provided relative risk estimates for bladder cancer incidence or mortality endpoints. Further evaluation included the selection of studies that evaluated low-level arsenic in drinking water as the primary exposure of interest, and thus, we excluded studies that evaluated high levels of arsenic concentrations in drinking water, including the series of studies conducted in the Black Foot Disease endemic area of Southwest Taiwan (e.g., Chen et al. 1985, 1992). This exclusion criterion simultaneously resulted in the exclusion of populations that were considered nutritionally deficient. In general, studies provided relative risk estimates based on a range of arsenic exposure levels, and we included studies that provided results for these levels as compared to a reference population, generally the lowest exposure group or a population that was considered not to be exposed to arsenic. Our inclusion/exclusion criteria for the meta-analyses are as follows:

1. Included studies must evaluate bladder cancer incidence or mortality
2. Included studies must be analytical epidemiologic studies with cohort or case-control designs; we excluded ecologic or cross-sectional studies from the meta-analysis (although they were included in our qualitative review)

3. Included studies must evaluate low-level arsenic exposure from drinking water; we excluded studies that examined *only* high-level exposures
4. Included studies must have arsenic as the exposure of primary interest
5. Included studies must provide results or present data that allowed us to calculate relative risk estimates and corresponding confidence intervals
6. Included studies must present risk estimates that are relative to a non-exposed or low-exposed reference population or category, or data that will allow for the calculation of risk estimates relative to a reference category.

After applying these inclusion/exclusion criteria, there were eight studies eligible for the meta-analysis and an additional two studies eligible for the qualitative review.

Description of Bladder Cancer Studies Included in the Meta-analysis

Table 1 shows the main features of the eight studies included in the meta-analysis, including study location and design, exposure index, range of arsenic exposure, and whether and how information on smoking was used in the analysis.

Studies Conducted in the United States

Bates et al. (1995), using data from Utah respondents to the 1978 National Bladder Cancer Study, conducted a case-control study that evaluated low-level arsenic exposure in drinking water and bladder cancer. Newly diagnosed, histologically confirmed cases (n = 117) were frequency matched to controls (n = 266) by age, sex, and geographic area of enrollment. Data on arsenic levels in public drinking water were measured in 1978–1979 using proton-induced x-ray emission spectroscopy from 88 community supplies in Utah. The authors assumed that arsenic levels had remained constant over the years of exposure. Two arsenic exposure indices were used. The first represented cumulative exposure (mg) and the other represented intake

concentration (mg/liter-years). Ranges for quartiles of arsenic exposure were < 19, 19 to < 33, 33 to < 53, and ≥ 53 mg using the cumulative exposure index, and between < 33, 33 to < 53, 53 to < 74, and ≥ 74 mg/liter-years using the intake concentration index. Analyses were stratified by "ever" and "never" smoking status. Compared to the referent category of < 19 mg (cumulative dose), odds ratios greater than 1.0 in each category were reported for ever smokers, whereas odds ratios below 1.0 were reported among never smokers for the 33 to < 53 mg and ≥ 53 mg categories of cumulative exposure. No exposure response trend was observed for never smokers or ever smokers, based on either exposure index analyses.

Karagas et al. (2004) conducted a case-control study in New Hampshire, using incident cases (n = 383) of transitional cell carcinoma of the bladder and 641 general population controls. The state of New Hampshire includes several areas with naturally occurring elevated levels of arsenic in well water. Study participants submitted toenail clipping specimens prior to interview. Arsenic levels in toenails reflect external exposure (e.g., arsenic in soil) as well as ingestion of arsenic in both water and food. Toenail arsenic concentrations ranged from 0.014 to 2.484 μg/g among cases and 0.009 to 1.077 μg/g among controls. In-person interviews ascertained sociodemographic, occupational, tobacco, medical, and household water supply information. Analyses were stratified by increasing categories of toenail arsenic concentration and "ever" and "never" smoking status. In addition, the authors stratified by smoking duration among the ever smokers. Non-significant odds ratios ranging between 0.49 to 1.18 were reported for never smokers. Odds ratios ranging between 0.50 and 2.17 were reported for ever smokers. There was no evidence of an exposure response relationship based on increasing categories of toenail arsenic concentrations.

Lewis et al. (1999) examined the association between drinking water arsenic and mortality outcomes (including bladder cancer) in a cohort of residents from Millard County, Utah. The study cohort was assembled from historical membership records of the Church of Jesus Christ of Latter-day Saints (Mormons). Community drinking water arsenic concentrations were based on measurements performed by the Utah State Health Laboratory. An arsenic exposure index score, derived from the number of years of residence in the community and the median arsenic concentration of community drinking water, was calculated for each person in the cohort. Three

categories of arsenic exposure were created (Low: < 1,000 ppb-years; Medium: 1,000–4,999 ppb-years; High: ≥ 5,000 ppb-years). Three observed "bladder and other urinary organ" deaths were observed in the cohort. For comparison, mortality-specific expected death rates were generated from the white male and white female general population of Utah. Inverse associations for "bladder and other urinary organs" were reported for men (standardized mortality ratio, or SMR = 0.42, 95% CI: 0.08–1.22) and women (SMR = 0.81, 95% CI: 0.10–2.93).

Steinmaus et al. (2003) used a case-control study design to evaluate arsenic ingestion in drinking water and bladder cancer in six counties in western Nevada and Kings County, California. Incident bladder cancer cases (n = 181) who lived in the study area at the time of diagnosis were selected. Population-based controls (n = 328) were frequency matched to cases by five-year age group and gender. Each residence within the study area was linked to a water arsenic measurement for that residence. The Nevada State Health Division and the California Department of Health Services provided arsenic measurements for all community-supplied drinking water within the study area. Daily arsenic intakes (μg/day) for a given year were estimated, as were cumulative exposure (mg) categories. The authors stratified by "ever" and "never" smoking status and 5- and 40-year lag. No significant findings were reported for analyses based on smoking status and/or lag. After adjustment for smoking status and other demographic and lifestyle factors, non-significant increased risks were reported among persons with 6.4–82.8 mg (OR = 1.63, 95% CI: 0.64–4.13) and > 82.8 mg (OR = 1.40, 95% CI: 0.73–2.70) of cumulative exposure, based on 40-year lag analysis.

Studies Conducted Outside the United States

Bates et al. (2004) conducted a population-based case-control study in two counties in Argentina. There were 114 incident transitional cell bladder cancer cases matched with 114 controls on age, sex, and county. Information pertaining to residential history, water sources at each residence, beverage consumption, smoking, occupational history, and medical history was ascertained during home interviews. Water samples were collected from each study participant's current residence or from nearby "proxy wells." A fluid intake-adjusted arsenic

exposure index was created. This metric was calculated by the average of 5 years of highest exposure during the 6 to 40 years before interview, multiplied by the estimated daily tap-water concentration, divided by the estimated daily fluid consumption. Analysis was stratified by "ever" and "never" smoking status. There were no significant associations observed, based on analyses by average arsenic concentration or fluid-intake-adjusted arsenic exposure.

Kurttio et al. (1999) assessed the levels of arsenic in drilled wells in Finland and examined the association between arsenic exposure and risk of bladder and kidney cancer. Sixty-one bladder cancer cases diagnosed between 1981–1995 were selected from a register of persons who lived at an address outside of the municipal drinking water system during 1967–1980. A reference cohort of 275 participants was randomly selected for this case-cohort study. Information on residential history, drinking water consumption, smoking, analgesic and diuretic use, education, and occupation was ascertained using a questionnaire before water sampling was done in 1996. Thus, for some cases, there may have been a 15-year time lapse between the onset of disease and administration of the questionnaire. Questionnaire respondents included the study participant or the next of kin. Well water samples were collected in random order, with study personnel blinded in regard to case or referent status. Tertiles of arsenic concentrations in well water (μg/L), daily dose of arsenic (μg/day), and cumulative dose (mg) of arsenic were analyzed. Analyses were stratified by "smoker" or "never or ex-smoker" status. Relative risks ranged from approximately 0.9 to 1.0 for nonsmokers, with 95% CIs of approximately 0.25 to 3. In contrast, a significant, 10-fold increased risk was observed among smokers exposed to ≥ 0.5 μg/L of arsenic water concentration. This finding, however, was based on only seven observed cases, and the 95% CI was very wide (1.16–92.6).

Michaud et al. (2004) evaluated the relationship between toenail arsenic levels and bladder cancer risk in a cohort of Finnish male smokers. The authors conducted a nested case-control study and identified 280 bladder cancer cases and 293 controls matched by age, toenail collection date, smoking duration, and trial intervention group. All study participants were selected from the Alpha-Tocopherol, Beta-Carotene (ATBC) Cancer Prevention Study. Incident bladder cancer cases were histologically confirmed. Each study participant provided a toenail sample and information on food use. Arsenic levels in toenail samples were determined using

neutron activation analysis. Quartiles of arsenic categories ranged from < 0.050 to > 0.161 μg/g. The median arsenic level was 0.110 μg/g among the cases and 0.105 μg/g among the controls. There were no associations between toenail arsenic levels and risk of bladder cancer (OR range: 1.09–1.13, *p*-value for trend = 0.65).

Chiou et al. (2001) evaluated the association between ingested arsenic and risk of transitional cell bladder cancer in a cohort of 8,102 residents from 18 villages in northeastern Taiwan. There were 10 cases of bladder cancer. Information pertaining to history of well water consumption, residential history, sociodemographic characteristics, cigarette smoking, alcohol consumption, physical activity, history of sunlight exposure, and personal and family medical history was obtained via personal interview. Well water samples were collected during home interviews, and arsenic levels ranged between < 0.15 and 3,482.6 μg/L. Arsenic levels in well water were categorized into four groups: ≤ 10.0, 10.1–50.0, 50.1–100.0, and > 100.0 μg/L. Cigarette smoking ("yes" or "no") was included in the analytical models. After adjustment for age, sex, smoking, and duration of well water drinking, relative risks of bladder cancer increased for each increasing category of arsenic concentration, with relative risks increasing from 1.9 to 15.1. Interpretation of these findings is limited, however, because the increasing exposure quartile categories had one, one, two, and six cases, respectively, and the resulting confidence intervals were very wide.

Description of Ecological Bladder Cancer Studies Not Included in the Meta-analysis

Lamm et al. (2004), using an ecological study design, examined the relationship between arsenic exposure through drinking water and bladder cancer mortality. The authors used county-specific white male bladder cancer mortality data and groundwater arsenic concentration data from 133 U.S. counties that were exclusively dependent on groundwater for their drinking water supply. Analytical categories were grouped by arsenic concentrations in groundwater, with categorical levels ranging between 3.0 and 59.9 μg/L. Observed bladder cancer deaths (n = 4,537) were compared with the expected number of deaths for each county. The authors reported no arsenic-related increase in bladder cancer mortality in their study. In fact, a

significant inverse association between low-level arsenic exposure (3.0 to 59.9 μg/L) and risk of bladder cancer was reported (SMR = 0.94, 95% CI: 0.90–0.98). The Lamm et al. (2004) results were significantly below the risks predicted by NRC (2001) based on the southwest Taiwan data. This was the largest U.S. study that has evaluated arsenic in drinking water and risk of bladder cancer.

Tollestrup et al. (2003) conducted an ecological cohort study to evaluate the association between childhood exposure to ambient arsenic exposure and mortality. The cohort included 1,827 males and 1,305 females who had lived within 2.5 miles of the American Smelting and Refining Company copper smelter and arsenic refinery in Ruston, Washington. The study cohort was identified from school census records and members were born between 1895 and 1925. Exposure was computed as a function of duration and distance of residence from the smelter stack. Exposure intensity was derived as the total number of days spent at a residence located less than 1.0 mile from the smelter stack. Four intensity categories were created on the basis of number of years spent at the residence. Follow-up status was determined through 1990. Each exposure intensity group was compared with the referent category that consisted of cohort members with less than one year of residential history near the smelter. There were only four observed bladder cancer deaths among males and one among females. Among males, two of the bladder cancer deaths occurred in the lowest exposure intensity category, and the only female bladder cancer death occurred in that category (0 to < 1.0 year).

Meta-analysis Methodology

Etiologic interpretation of findings from a single study is often limited by imprecise (low statistical power) relative risk estimates that result from a small sample size or an inadequate number of cases that were exposed to the agent of interest, whether by overall exposure or specific exposure indices. Statistical power refers to the ability to detect an association given that an association truly exists. In general, the bladder cancer studies that we reviewed herein contain moderate to small numbers of persons in arsenic subcategories of drinking water exposure levels; therefore, we used meta-analysis techniques to gain a more precise estimate of the relative risk.

The underlying assumption when combining studies to conduct a meta-analysis is that the studies are homogeneous. When this assumption is violated, and there is heterogeneity among the studies, results must be interpreted cautiously. Heterogeneity may arise as a consequence of inconsistencies of various factors across studies, including disparities in relative risk estimates, individual and environmental exposure measurements, study design, or other methodological factors. Variability across studies was tested by the *p*-value for heterogeneity. In general, the lower the *p*-value the greater the heterogeneity, or variability, across studies. In addition to testing for heterogeneity, we conducted influence analyses by reporting the relative weight (influence) that each study provides in the meta-analysis. In a given meta-analysis, the weights for all of the individual studies (or units of analysis) must sum to one. The studies with the most overall influence, as indicated by their sample size and precision of relative risk estimates, will have the greatest weight value. If an analysis showed evidence of heterogeneity and/or the presence of influential studies, subsequent analyses were run after removing certain studies from each analysis. Specifically, we generated a meta-relative risk (mRR) estimate and a *p*-value for heterogeneity for all studies that were included in each type of analytical category. To quantify the relative influence that an individual study had on the overall model, each study was removed from the model and a new mRR estimate and *p*-value for heterogeneity were computed. The excluded study was then entered back into the model and the next study was removed and analyses were conducted again. This process was repeated for all studies in each type of model. By doing this, it was possible to determine the magnitude of change on the overall mRR estimates that each study was producing, and hence, its influence on the model.

Statistical Methods

We used a random effects model throughout all of our meta-analyses to produce mRR estimates. A random effects model assumes that the variability between study-specific effect sizes is due to sampling error as well as variability in the population of effects. In general, a random effects model allows for between-study variability. This is in contrast to a fixed effects model, which assumes that all variability between study-specific effect sizes is due to sampling error, or subject-level "noise." Random effects models are thus more conservative than fixed effects models because of the additional variability consideration. These two models will yield

different results when variability is prominent (high degree of heterogeneity). On the other hand, in the absence of heterogeneity, a random effects model will reduce to a fixed effects model and results will be comparable. The theoretical framework for fixed and random effects modeling are presented in Appendix A. Variability across studies was examined using a *p*-value for heterogeneity. A *p*-value of 0.10 or less was considered to reflect heterogeneity in the model. We considered studies to be homogeneous, and therefore, most informative, if a model's *p*-value was above 0.10. All analyses were performed using "Episheet," an Excel spreadsheet-based analytical package for meta-analyses (Andersson and Ahlbom 2003).

We created models that evaluated three population groups. The first set of models included all study participants: current, former, or never smokers. The second set of models included study participants who were classified as "never smokers." The third set of models included "ever smokers." For each of these analytical groups, two types of models were run to generate summary relative risk estimates. We created "all exposure category" models by extracting the adjusted relative risk estimate from each exposure category in the individual studies. We also created "collapsed exposure category" models by combining all upper arsenic exposure categories, and for each individual study, a *de novo* crude relative risk estimate was computed using the lowest exposure group as the referent category. For example, in Table 3 of Steinmaus et al. (2003), odds ratios are presented based on tertiles of cumulative arsenic exposure. The exposure categories in their table were < 6.4, 6.4–82.8, and > 82.8 mg. The exposure category of < 6.4 mg was the referent group in their analysis, therefore, we combined the cases of the two upper exposure categories (6.4–82.8 mg: 9 cases; > 82.8 mg: 19 cases) and we combined the controls (6.4–82.8 mg: 13 controls; > 82.8 mg: 33 controls) of the upper two exposure categories. These two collapsed exposure categories were analyzed using the original referent category in the study; thus, a *de novo* crude odds ratio was computed as follows:

Exposure Category	Cases	Controls
≥ 6.4 mg (collapsed exposure category)	28	46
< 6.4 mg (referent)	153	282
***De novo* odds ratio = 1.12 (95% Confidence interval: 0.67–1.86)**		

Note: Adapted from Steinmaus et al. (2003), Table 3, 40-year lag analysis.

For each of the models described above, summary relative risk estimates were generated based on the analysis of all studies that met our inclusion criteria. To examine potential sources of heterogeneity, we ran additional models, restricting the analysis to studies according to characteristics that may be responsible for producing variability.

Results

Table 2 presents the mRR estimates for each population category stratified by type of analysis. In addition, the 95% confidence interval and *p*-value for heterogeneity are included for each analytical category, including collapsed and all exposure categories meta-analyses for smokers and nonsmokers combined, never smokers alone, and ever smokers alone. These are shown for all included studies and for subgroup analyses. Appendix B includes a description of the studies evaluated in each analysis, the individual study results upon which the meta-analysis is based, and the results of each specific meta-analysis.

Figures 1–3 show the point estimates for each study included in the main analyses (including all eligible studies) for smokers and nonsmokers combined, never smokers, and ever smokers, respectively, and the summary estimate (mRR) and 95% confidence intervals. As shown by the width of the confidence intervals, the precision of the mRR estimate was improved as compared to the relative risk estimates of the individual studies. This was particularly apparent in the separate analyses for never smokers (Figure 2) and ever smokers (Figure 3).

The mRR estimates were slightly elevated, albeit not significantly, for the analyses that evaluated collapsed (mRR = 1.08, 95% CI: 0.82–1.43) (Table 2, Table B-1) and all exposure (mRR = 1.11, 95% CI: 0.95–1.30) (Table 2, Table B-2) categories of smokers and nonsmokers combined, based on seven and eight studies, respectively. Findings from these two analyses should be interpreted with caution as both smokers and nonsmokers were included in the analyses. Smoking is a known risk factor for bladder cancer, and results from some individual studies have suggested the possibility that smoking acts as an effect modifier. Subsequent analyses were stratified by "never" (Table 2, Tables B-3 and B-4) and "ever" smoking status (Table 2, Tables B-5 and B-6). An inverse association was observed for never smokers (all exposure categories: mRR = 0.81, 95% CI: 0.60–1.08), whereas an increased association was observed for ever smokers (all exposure categories: mRR = 1.24, 95% CI: 0.99–1.56). It is noteworthy that the *p*-values for heterogeneity were greatly elevated for the analyses among never smokers (collapsed exposures: 0.724, all exposures: 0.937) as compared to the *p*-values for the analyses among ever smokers (collapsed exposures: 0.162, all exposures: 0.032). The

summary findings (composed of individual findings from each study that were included in the analysis) for never smokers, therefore, are homogeneous and the mRR estimate may be considered a valid estimate of bladder cancer risk among never-smokers exposed to low levels of arsenic in drinking water. In contrast, heterogeneity exists among the findings for ever smokers, and results should be considered in light of this variability and interpreted cautiously.

We explored several areas that may have produced heterogeneity across summary findings by generating meta-analyses for the population subgroups presented in Table 2 (and in greater detail in Appendix B, Tables B-8 through B-28). Specifically, we conducted meta-analyses by: a) including studies that evaluated incident cases only (Tables B-7 through B-12), b) excluding studies that used toenail arsenic concentrations, which reflect external exposure to arsenic and internal arsenic exposures in addition to drinking water, as the primary exposure of interest (Tables B-13 through B-18), c) including only studies that evaluated cumulative exposure (Tables B-19 through B-22), and d) evaluating studies conducted in the United States (Tables B-23 through B-28). As mentioned above, findings for never smokers were homogeneous; however, to validate our findings, we calculated mRRs for each of the aforementioned areas. Among the findings for never smokers (all exposure categories), mRR estimates ranged between 0.73 and 0.85, and the *p*-value for heterogeneity ranged between 0.776 and 0.937. The consistency of results provides further evidence that the findings among never smokers are homogeneous and that the risk of bladder cancer among persons with low levels of drinking water arsenic exposure is not elevated. In fact, the results show an inverse association, although non-significant, between arsenic in drinking water and risk of bladder cancer in populations with low-level exposure.

A weak, increased association was observed in the model that included all studies in which the association between low level arsenic exposure and risk of bladder cancer among ever smokers was evaluated (mRR = 1.24, 95% CI: 0.99–1.56). There was, however, significant heterogeneity (*p*-value for heterogeneity = 0.032) based on this analysis of six studies (Bates et al. 1995; Karagas et al. 2004; Steinmaus et al. 2003; Bates et al. 2004; Kurttio et al. 1999; Michaud et al. 2004). To elucidate the source of variability, we stratified the analyses according to the characteristics described above (a through d). Findings among ever smokers varied, with

mRRs ranging between 1.22 and 2.35 (all exposure categories), depending on the type of analytical model. Heterogeneity was still prominent after analyzing incident cases only (*p*-value = 0.043, five studies) (Bates et al. 1995; Karagas et al. 2004; Steinmaus et al. 2003; Bates et al. 2004; Michaud et al. 2004), and after excluding the studies that evaluated toenail arsenic concentrations (*p*-value = 0.006, four studies) (Bates et al. 1995; Steinmaus et al. 2003; Bates et al. 2004; Kurttio et al. 1999). The *p*-value for heterogeneity and mRR, however, moderately increased in the analysis limited to ever smokers in the three studies conducted only in the United States (mRR = 1.46, 95% CI: 1.12–1.90; *p*-value = 0.183) (Bates et al. 1995; Karagas et al. 2004; Steinmaus et al. 2003), and markedly increased for studies that presented results for cumulative exposure (mRR = 2.35, 95% CI: 1.51–3.66; *p*-value = 0.786) (Bates et al. 1995; Steinmaus et al. 2003; Kurttio et al. 1999).

Influence Analyses

We evaluated the relative influence, or magnitude of "effect change," on each of our primary model's mRR estimates (Appendix C). The effect change of the overall model-specific mRR estimate was less than 0.10 for the exclusion of any of the individual studies. The models, therefore, were robust and were not markedly influenced by the findings of any specific study. In two models, the exclusion of Bates et al. (2004) resulted in a statistically significant increased mRR, based on the remaining studies in the model. These two models correspond to Tables C-1 and C-6 in Appendix C. In the all exposure category analysis among ever smokers, for example, the mRR changed from 1.241 (95% CI: 0.988–1.559) to 1.338 (95% CI: 1.101–1.626) after exclusion of Bates et al. (2004). This was a well-conducted study, however, and warrants inclusion in the relevant meta-analysis models. When Bates et al. (1995) was excluded from the same model, a magnitude of change in the opposite direction was apparent. The mRR estimate changed to 1.147 (95% CI: 0.917–1.434).

Statistical Power of the Meta-analysis

We evaluated the statistical power of the meta-analysis to detect mRRs ranging from 0.70 to 2.00, using the methods described by Hedges and Pigott (2001). Results of these calculations are shown in Table 3. Based on the specific studies eligible for analyses ("all studies") of ever and never smokers combined, never smokers only, and ever smokers only, we had statistical power of 91%, 65%, and 78% to detect an mRR of 1.5 for each of these analyses, respectively. We had statistical power of more than 95% to detect an mRR of 2.0 for each type of analysis based on smoking status that included all eligible studies.

Discussion

This review and analysis was conducted to address two questions. The first question asked whether there was an association between bladder cancer and arsenic in drinking water in populations with low-level exposure. The epidemiologic evidence from the individual studies reviewed and results of the meta-analysis do not support an association of low level arsenic exposure in drinking water with risk of bladder cancer.

The results for all studies together may not be as informative as the findings that were stratified by "never" or "ever" smoking status. Smoking is a known risk factor for bladder cancer; therefore, to account for the potential effect-modifying influence of smoking on the relationship between drinking water arsenic exposure and bladder cancer, we stratified our analysis according to smoking status and possible effect modification was noted. The mRRs were in opposite directions for never smokers and ever smokers, but neither was significantly different from unity in the analyses that included all eligible studies. Variability of mRRs and *p*-values indicating heterogeneity were evident across most analyses of ever smokers. In contrast, results were quite similar for never smokers, regardless of analytical stratification. Greater confidence should be placed in the interpretation of findings among never smokers because of the consistency (robustness) of results, based on both the mRRs and *p*-values for heterogeneity. Results for smokers are considered further below.

The second question asked whether relative risks from epidemiologic studies of low-level arsenic in drinking water and bladder cancer were within the range of 1.2–2.5 as would be predicted by the dose-response curves described in the NRC report and based on studies from Taiwan (NRC 2001). The mRRs from "all studies" shown in Table 2 range from 0.8 to 1.2. Thus, the mRR for ever smokers just touches the lower bound of the predicted risk ratio estimates based on extrapolation from EPA's dose-response models. Not only are the mRRs for never smokers below the predicted range, but the upper 95% confidence limit is also below 1.2. Examining all of the mRRs presented in Table 2 shows that the majority of the mRR estimates are less than 1.2, with mRRs from the analyses of smokers being the only exception. As discussed above, results from analyses of ever smokers should be interpreted with caution due to

heterogeneity across the studies as found in the meta-analysis, and a lack of consistent evidence for exposure-response patterns observed across the individual studies.

One of the implications of the above findings is that the data set used to derive the current dose-response curves may not be appropriate given that they do not appear to accurately predict the risk of bladder cancer in populations with low-level exposure to arsenic in drinking water. These models are based on data from southwestern Taiwan, where not only are arsenic levels considerably higher, but the study population also suffers from nutritional deficiency based on their usual diet. These and other sources of variability and uncertainty have been summarized in the NRC report (2001). It has also been suggested that co-carcinogens (e.g., humic acids) may be present in the artesian wells in southwestern Taiwan (Lamm et al. 2003). Thus, it is not surprising that extrapolation from models derived from this population would prove not to be accurate predictors of cancer risk in populations such as the United States or Finland that do not share the same underlying characteristics and that are exposed to different levels of arsenic. The EPA and NRC models generalize to an exposure level below which they have sufficient data. Inclusion of data from studies such as those described in this meta-analysis would likely prove informative in the development and/or validation of future risk assessment models.

The most robust findings in this series of meta-analyses were for the group of never smokers. The mRRs were consistently below 1.0 and the *p*-value for heterogeneity was above 0.65 for each analysis. Thus, there is no apparent risk of bladder cancer in never smokers exposed to low levels of arsenic in drinking water. The mRRs for the analyses that included both ever smokers and never smokers were also consistent. The mRRs for this group were slightly elevated, but were not significantly different from 1.0. The *p*-values for heterogeneity in these analyses were lower than in the analyses of never smokers, and were generally higher in the analyses that evaluated "all exposure categories" as compared to the "collapsed" categories. With the exception of the analyses that excluded the two studies that evaluated arsenic levels in toenails (Michaud et al. 2004; Karagas et al. 2004), the *p*-values indicated sufficient homogeneity in the analyses of "all exposure categories."

There was considerable variability in the results of the meta-analysis for ever smokers, however. When all eligible studies were included, the mRRs were modestly increased, but not statistically

significant. There was an indication of heterogeneity across the studies, based on the *p*-value. Restricting the analyses to various subgroups markedly changed the *p*-value for heterogeneity in the analysis of studies that evaluated cumulative exposure. The *p*-value was also non-significant for studies conducted in the United States. There was some overlap in these two analyses. Bates et al. (1995) and Steinmaus et al. (2003) were both included in the analyses that were stratified by studies conducted in the United States and studies that evaluated cumulative exposure. The difference between these two models was the inclusion of Karagas et al. (2004) in the U.S. analysis and Kurttio et al. (1999) in the cumulative exposure analysis. Interpretation of these two analyses that indicate increased risk of bladder cancer among ever smokers with low levels of arsenic exposure should be done with reservation, because there was no exposure response pattern evident in the individual studies. If a true etiologic association existed for low-level arsenic exposure, one would expect to observe an increasing risk concurrently with increasing arsenic exposure, which was not the case in the individual studies (see Tables B-22 and B-28). Furthermore, information on smoking was limited to smoking status in three of the studies (Bates et al. 1995; Karagas et al. 2004; Kurttio et al. 1999), whereas Steinmaus et al. (2003) provided information on packs smoked per day (less than one versus one or more). Thus, it is not clear whether amount of smoking may play a role in the observed associations.

Given the lack of consistency in the findings from analyses of smokers, it would be premature to consider smoking to be an effect-modifier. This seems especially true given the consistent findings of no association (and, indeed, suggestion of an inverse association) in never smokers. Bates et al. (1995) notes that the association observed in cigarette smokers in their study was not related to arsenic dose and was not statistically significant. Steinmaus et al. (2003) concluded that, in their study, smokers may be at increased risk of bladder cancer if they ingest water containing arsenic at concentrations of approximately 200 μg/L. This level is at the high end of what might be considered "low" exposure.

The strengths of this meta-analysis include the ability to summarize, describe, and quantify the relative risks associated with low-level exposure to arsenic and bladder cancer in a number of populations. By combining the studies in a meta-analysis, we were able to improve the precision of the relative risk estimates, as indicated by the narrowing of the 95% CI as compared

to the individual studies. This is illustrated in Figures 1–3. In addition, we were able to calculate mRRs in never smokers and ever smokers separately.

The main limitation of the meta-analysis is that the studies analyzed did not all use a consistent measure of exposure or consistent exposure level cutoff points to perform their analyses. Data that were used in each of our tables, and thus, in each of our meta-analyses were extracted directly from the articles. In some cases, categorical data were collapsed and *de novo* relative risk estimates were computed. The extent of our analysis was limited by the data that were available to us in each of the published studies; however, this limitation is commonly encountered when conducting meta-analyses and does not preclude the ability to analyze the presence or absence of an effect within the exposure range of the study. The presentation of study-specific findings varied, both for arsenic exposure categories as well as for type of data analysis. The arsenic exposure index and metric for quantification used across these studies included cumulative dose and fluid intake adjusted indices, toenail arsenic concentrations, and residential levels of drinking water exposure. In addition, the ranges of arsenic concentrations varied across studies, which precluded us from categorizing on precisely comparable levels of exposure.

It is possible that different methods of assessing exposure may have produced heterogeneity in the meta-analysis; however, as noted above, the results for never smokers were very robust. Two of the included studies used arsenic concentrations in toenails rather than measures in drinking water to assess arsenic exposure. Arsenic in toenails reflects both internal and external exposures. NRC (2001) suggests that arsenic measures from toenail clippings represent exposures over a period of time of a few weeks that occurred approximately a year before sample collection. Studies by Karagas et al. (2000) and Garland et al. (1993), however, indicate that toenails are a good biomarker for quantifying low-level arsenic exposure and that arsenic levels in toenails remain relatively constant for periods of approximately 6 years. Karagas et al. (2000) has also conducted analyses showing the correlation between arsenic concentration in water and in toenails. Based on these correlations, we estimated the water concentrations in the studies by Karagas et al. (2004) and Michaud et al. (2004) that correspond to the categories of toenail concentrations measured (Table 4). These estimations suggest that the drinking water

arsenic concentrations in these studies are comparable to the other studies included in the meta-analysis.

Conclusions

Results from this meta-analysis indicate that there is no increased risk of bladder cancer associated with exposure to low levels of arsenic in drinking water. Although there was some evidence of increased mRRs for the analyses restricted to ever smokers, most of the mRRs were not statistically significant and there was evidence of considerable heterogeneity across the studies. For the subgroup of studies of ever smokers that appeared to be homogeneous and where risks were significantly elevated, results from the individual studies did not show a pattern of increasing relative risks with increasing exposure. Thus, we do not conclude that smoking is an effect modifier in this meta-analysis.

The main results of this study are not consistent with the range of relative risks predicted by NRC of 1.2–2.5 (NRC 2001). In fact, the majority of the mRRs observed in this study were less than 1.2, with the exception of the analyses of ever smokers, which ranged from 1.2–1.5. These results suggest that the dose-response models and slope factors derived by NRC and EPA based on data from southwestern Taiwan are likely not appropriate for accurately predicting risks of human bladder cancer in the U.S. and similar populations. Data from studies in these populations with typically low concentrations of arsenic in drinking water should be used to inform and validate quantitative risk assessment for exposure to arsenic in drinking water.

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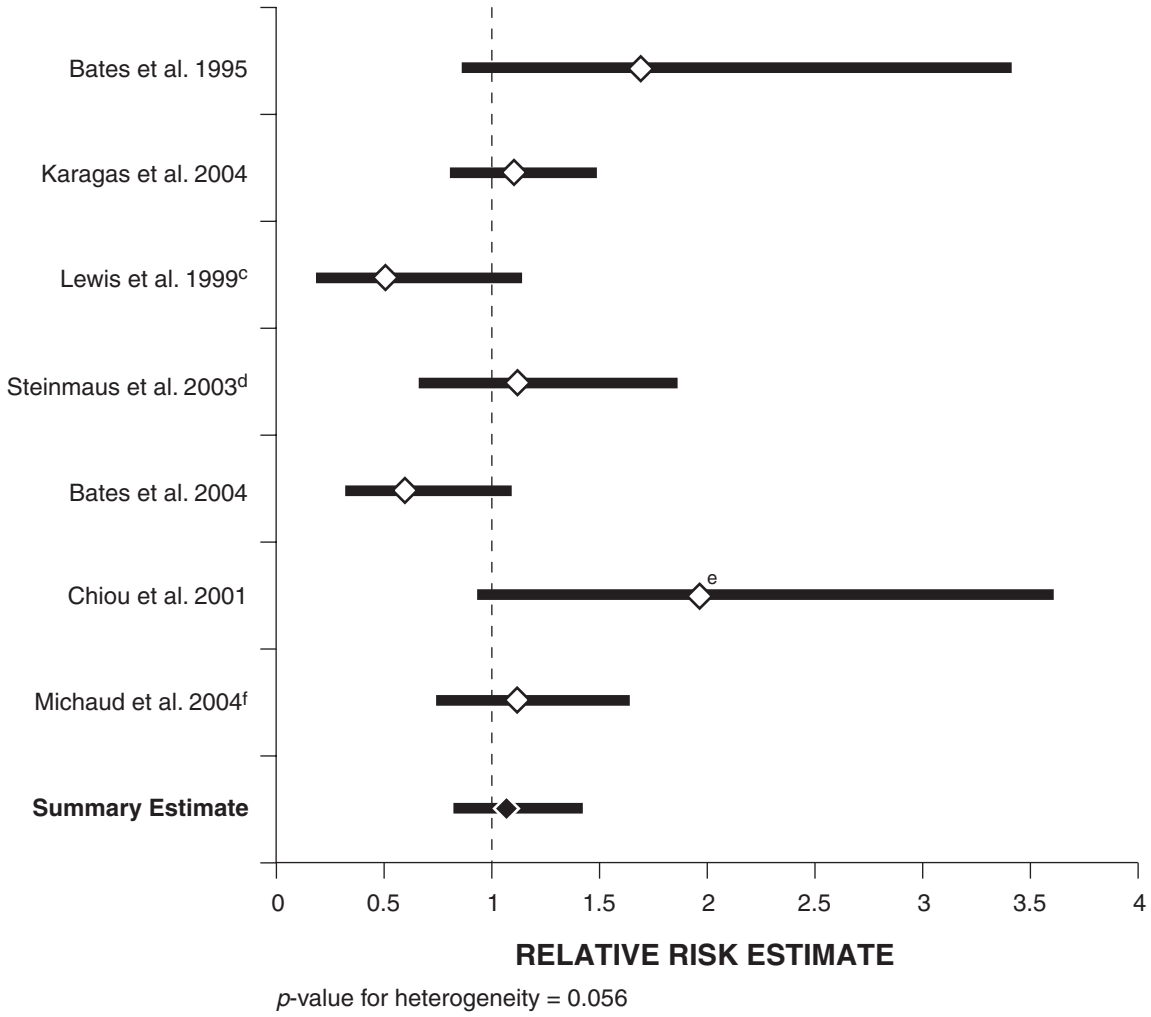
Figures



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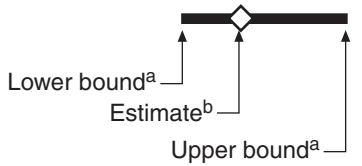

Notes:

[a] Mid-*p* confidence limits.

[b] Individual crude relative risk estimates based on recalculated collapsed exposure category data; calculated using *Episheet*.

[c] Cohort presumed to be nonsmokers, combined men and women and recalculated SMR.

[d] Analysis based on 40-year lag.

[e] Findings provided in text (were not recalculated)

[f] Entire cohort consisted of male smokers.

Figure 1. Arsenic exposure and risk of bladder cancer: Study-specific collapsed exposure categories (findings for smokers and nonsmokers combined)

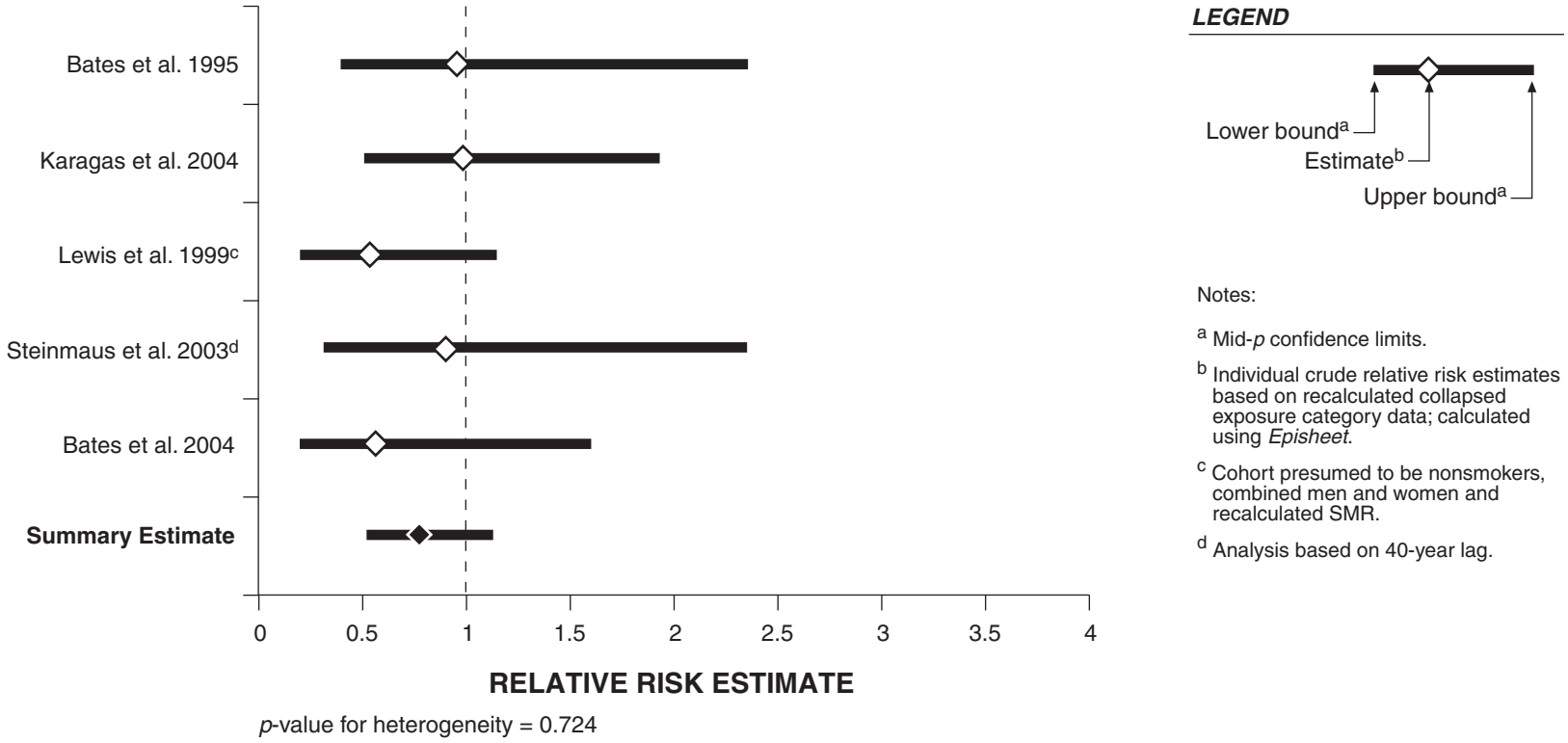

Figure 2. Arsenic exposure and risk of bladder cancer among NEVER SMOKERS: Study-specific collapsed exposure categories

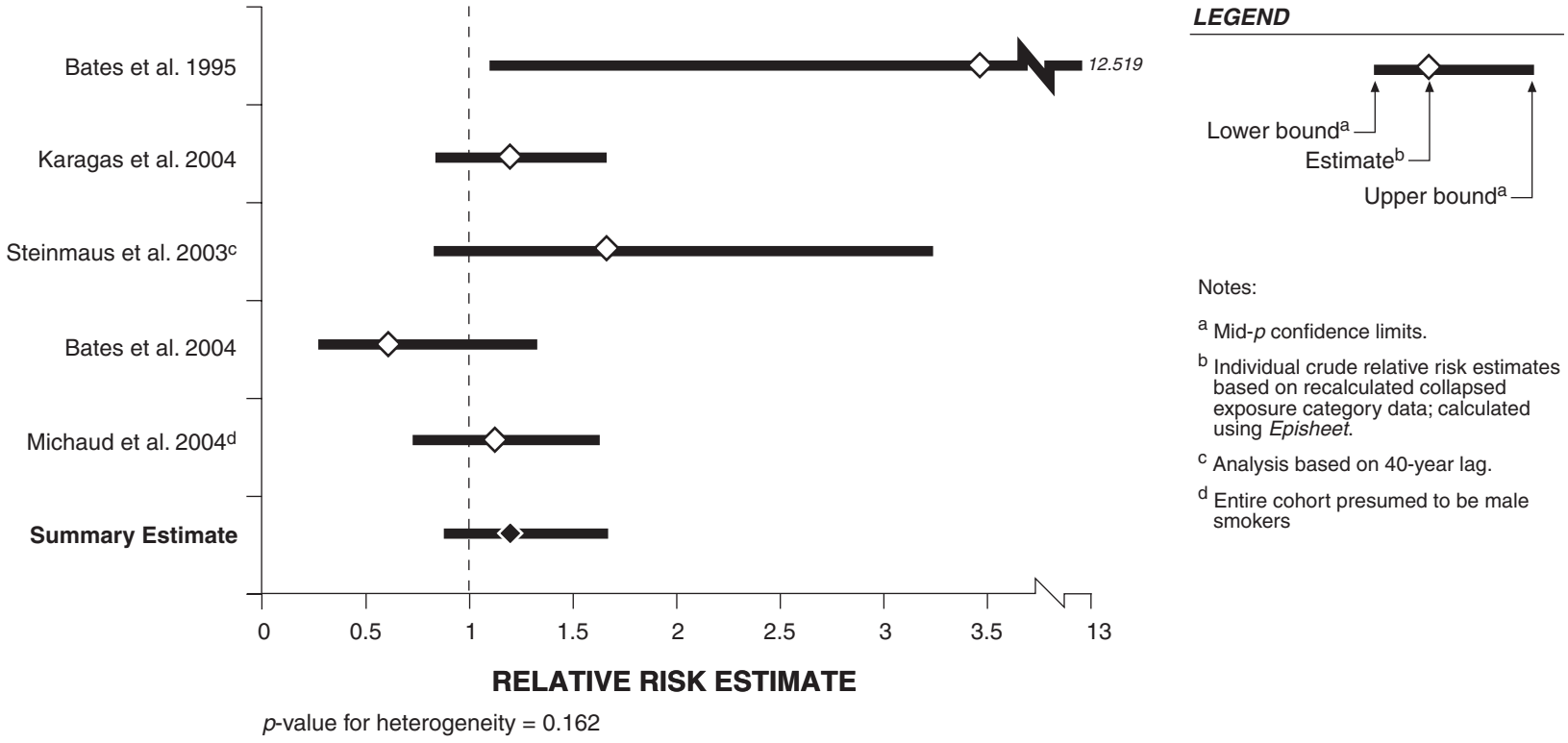

Figure 3. Arsenic exposure and risk of bladder cancer among EVER SMOKERS: Study-specific collapsed exposure categories

Tables

Table 1. Bladder cancer studies evaluated for meta-analysis

Study	Study Location	Arsenic Exposure Index Used in Analysis	Range of Arsenic Exposure	Study Design	Type of Bladder Cancer Data Used in the Analysis	Was Analysis Adjusted or Stratified by Smoking Status?	How Smoking Was Categorized and/or Analyzed
Bates et al. 1995	U.S. (Utah)	Cumulative dose	0.5 to 160 μg/L	Case-control	Incident cases	Yes	Ever and never smoking status.
Karagas et al. 2004	U.S. (New Hampshire)	Toenail arsenic concentrations	< 0.010 to 180 μg/L (as reported in Karagas et al. [2002])	Case-control	Incident cases	Yes	Ever and never smoking status. Also stratified by smoking duration (< 15 years, > 15 years) among ever smokers. Overall analysis also adjusted for smoking status (ever/never).
Lewis et al. 1999	U.S. (Utah)	Number of years of residence in the community and the median concentration of drinking water arsenic in the community	3.5 to 620 ppb Analyzed as < 1,000 ppb-years to ≥ 5,000 ppb-years.	Cohort	Mortality	No	Cohort was presumed to be non-smokers because of Church of Jesus Christ of Latter-day Saints status (Mormons).
Steinmaus et al. 2003	U.S. (Nevada and California)	Cumulative dose	0 to > 1,000 μg/L	Case-control	Incident cases	Yes	Ever and never smoking status. Overall analysis also adjusted for smoking history (< 1 pack/day, >1 pack/day, former smoker, never smoker).
Bates et al. 2004	Argentina	Fluid intake adjusted index	0 to 3,033 μg/L	Case-control	Incident cases	Yes	Ever and never smoking status. Analysis also adjusted for smoking status (ever, never, former) and the highest daily number of cigarettes smoked.
Kurttio et al. 1999	Finland	Concentration of arsenic in water	< 0.05 to 64 μg/L (median 0.14 μg/L)	Case-cohort	Data ascertained by cases or proxy respondents	Yes	Stratified by smoker and never or ex-smoker status. Analysis also adjusted for smoking (never smoked, ex-smoker stopped smoking before 1970, smoker in the 1970s).
Michaud et al. 2004	Finland	Toenail arsenic concentrations	< 0.05 to > 0.161 μg/g	Case-control (nested)	Incident cases	No	Entire cohort was composed of male smokers. Analysis based on number of cigarettes per day and years smoking.
Chiou et al. 2001	Northeastern Taiwan	Concentration of arsenic in water	< 0.15 to 3,482.6 μg/L	Cohort	Incident cases	Yes	All multivariate models adjusted for cigarette smoking.

Note: Source of arsenic exposure for all studies was drinking water.

Table 2. Summary of individual meta-analysis findings

Type of Analysis	Analysis Characteristics	Smokers and Nonsmokers; Collapsed Exposure Categories	Smokers and Nonsmokers; All Exposure Categories	Never Smokers; Collapsed Exposure Categories	Never Smokers; All Exposure Categories	Ever Smokers; Collapsed Exposure Categories	Ever Smokers; All Exposure Categories
All Studies	Meta-relative risk (95% CI)	1.08 (0.82–1.43)	1.11 (0.95–1.30)	0.76 (0.52–1.12)	0.81 (0.60–1.08)	1.21 (0.88–1.66)	1.24 (0.99–1.56)
	p-value for heterogeneity	0.056	0.207	0.724	0.937	0.162	0.032
	Number of studies in analysis	7	8	5	6	4	6
Incident Cases Only	Meta-relative risk (95% CI)	1.17 (0.91–1.51)	1.14 (0.97–1.35)	0.86 (0.55–1.33)	0.85 (0.61–1.19)	1.21 (0.88–1.66)	1.22 (0.97–1.52)
	p-value for heterogeneity	0.119	0.227	0.837	0.871	0.162	0.043
	Number of studies in analysis	6	6	4	4	5	5
Toenail Studies Excluded	Meta-relative risk (95% CI)	1.05 (0.64–1.72)	1.06 (0.76–1.46)	0.69 (0.43–1.09)	0.73 (0.50–1.06)	1.40 (0.56–3.41)	1.38 (0.76–2.51)
	p-value for heterogeneity	0.016	0.048	0.71	0.897	0.042	0.006
	Number of studies in analysis	5	6	4	5	3	4
Cumulative Exposure	Meta-relative risk (95% CI)	1.29 (0.86–1.95)	1.10 (0.81–1.49)		0.79 (0.49–1.30)		2.35 (1.51–3.66)
	p-value for heterogeneity	0.351	0.301		0.776		0.786
	Number of studies in analysis	2	3		3		3
United States Studies	Meta-relative risk (95% CI)	1.10 (0.79–1.53)	1.18 (1.00–1.40)	0.80 (0.53–1.21)	0.83 (0.60–1.16)	1.48 (0.95–2.32)	1.46 (1.12–1.90)
	p-value for heterogeneity	0.161	0.633	0.653	0.789	0.221	0.183
	Number of studies in analysis	4	4	4	4	3	3

Table 3. Power of the meta-analysis to detect specific relative risk (mRR)

	mRR									
	0.70	1.20	1.30	1.40	1.50	1.60	1.70	1.80	1.90	2.00
Ever + Never Smokers (n = 7 studies)	0.83	0.38	0.61	0.79	0.91	0.96	0.99	1.00	1.00	1.00
Never Smokers (n = 5 studies)	0.55	0.23	0.37	0.51	0.65	0.76	0.84	0.90	0.94	0.97
Ever Smokers (n = 5 studies)	0.69	0.29	0.47	0.64	0.78	0.88	0.94	0.97	0.99	0.99

Note: Power calculations based on methods described by Hedges, L.V., and T.D. Pigott. 2001. The power of statistical tests in meta-analysis. Psychol. Methods 6(3):203–217.

mRR - meta-relative risk

Table 4. Estimation of drinking water arsenic concentrations based on correlations with toenail arsenic concentrations

Study	Toenail Arsenic Concentrations (μg/g)	Crude Extrapolations: Drinking Water Arsenic Concentrations (μg/L)
Michaud et al. 2004	< 0.050 (referent)	< 0.01
	0.050 to 0.105	0.01 to 2
	0.106 to 0.161	2 to 10
	> 0.161	> 10
Karagas et al. 2004	0.009 to 0.059 (referent)	<0.01
	0.060 to 0.086	0.01 to 0.1
	0.087 to 0.126	0.1 to 3
	0.127 to 0.193	3 to 11
	0.194 to 0.277	11 to 36
	0.278 to 0.330	36 to 60
	0.331 to 2.484	> 60

Note: Estimations based on Karagas et al. (2001) and Michaud et al. (2004).

Appendix A

Theoretical Framework for Fixed and Random Effects Meta-analysis Modeling

Theoretical Framework for Fixed and Random Effects Meta-analysis Modeling

In a fixed-effects model, the general formula for the weighted average effect size of *k* studies is

$$\bar{T}_{\cdot} = \frac{\sum_{i=1}^{k} w_i T_i}{\sum_{k} w_i} \qquad (1)$$

where T_i is the effect size estimate of the *i*th study, and w_i is the weight associated with it. The weights that minimize the variance of *T.* are given by

$$w_i = \frac{1}{v_i} \qquad (2)$$

where v_i is the variance in each study. The average effect size (*T.*) has a conditional variance (*v.*) given by

$$v_{\cdot} = \frac{1}{\sum_{i=1}^{k} (1/v_i)} \qquad (3)$$

Equations for variance change for the random-effects assumption. The total variance of an effect size estimate is given by

$$V_i^* = \sigma^2 + v_i \qquad (4)$$

where σ^2 is the random effects variance, and v_i is the conditional variance given above. The random effects variance σ^2 calculated is based on a weighted sample estimate Q of the unconditional variance of T_i. In this method, the random variance is estimated by

$$\sigma^2 = \frac{\left[Q - (k-1)\right]}{\sum_{i=1}^{k} w_i - \left[\frac{\sum_{i=1}^{k} w_i^2}{\sum_{i=1}^{k} w_i}\right]} \qquad (5)$$

In the random-effects model, the average effect size ($T.$**)** and its variance ($v.$) are calculated using equations 1 through 3 above; however, V^*_i is substituted for v_i.

Appendix B

Meta-analysis of Studies of Bladder Cancer and Low-Level Exposure to Arsenic in Drinking Water: Detailed Results

List of Tables

Table B-1. Arsenic exposure and risk of bladder cancer: Study-specific upper exposure categories collapsed and recalculated (findings for smokers and nonsmokers combined)

	Study Country	Study Design	Study-Specific Arsenic Exposure Range	Observed Cases or Deaths Among "Exposed"	Type of Relative Risk Estimate	Estimate[a]	Lower Bound[b]	Upper Bound[b]	Relative Weight of Study
Bates et al. 1995	U.S.	Case-control	Cumulative dose: 19 to ≥ 53 mg vs. < 19 mg	57	OR	1.6934	0.8683	3.4145	0.10
Karagas et al. 2004	U.S.	Case-control	Toenail concentrations: 0.06 to 2.284 mcg/g vs. < 0.059 mcg/g	293	OR	1.1010	0.8198	1.4833	0.22
Lewis et al. 1999[c]	U.S.	Cohort	All exposure groups: < 1,000 ppb-years to ≥ 5,000 ppb-years	5	SMR	0.5155	0.1889	1.143	0.09
Steinmaus et al. 2003[d]	U.S.	Case-control	Cumulative dose: 6.4 to > 82.8 mg vs. < 6.4 mg	28	OR	1.1219	0.6677	1.8629	0.15
Bates et al. 2004	Argentina	Case-control	Fluid intake adjusted exposure index: 1.1 to > 80 μg/L vs. ≤ 1.0 μg/L	80	OR	0.5947	0.3209	1.0949	0.12
Chiou et al. 2001	Northeastern Taiwan	Cohort	Entire cohort (range of arsenic concentration: < 0.15 μg/L to 3,482.6 μg/L)	10	SIR	1.96[e]	0.94	3.61	0.12
Michaud et al. 2004[f]	Finland	Case-control (nested)	Toenail concentrations: 0.05 to > 0.161 μg/g vs. < 0.05 μg/g	215	OR	1.1177	0.7617	1.6416	0.19
						Summary Relative Risk = 1.079	**95% CI: 0.816–1.425**		
						p-value for Heterogeneity =	0.056		

Note: OR - odds ratio
SMR - standardized mortality ratio
SIR - standardized incidence ratio

[a] Individual crude estimates based on recalculated collapsed exposure category data; calculated using *Episheet*.

[b] Mid-*p* confidence limits.

[c] Cohort presumed to be nonsmokers, combined men and women and recalculated SMR.

[d] Analysis based on 40-year lag.

[e] Findings provided in text (were not recalculated).

[f] Entire cohort consisted of male smokers.

Table B-2. Arsenic exposure and risk of bladder cancer: Study-specific exposure categories (findings for smokers and nonsmokers combined)

Study (data source)	Study Country	Study Design	Study-Specific Arsenic Exposure Range	Observed Cases or Deaths Among "Exposed"	Type of Relative Risk Estimate	Estimate	Lower Bound	Upper Bound	Relative Weight of Study
Bates et al. 1995 (Table 3)	U.S.	Case-control	Cumulative dose (mg):		OR				
			< 19 (referent)	14					
			19 to < 33	21		1.56	0.8	3.2	0.04
			33 to < 53	17		0.95	0.4	2.0	0.04
			≥ 53	19		1.41	0.7	2.9	0.04
Karagas et al. 2004 (Table 2)	U.S.	Case-control	Toenail concentrations (μg/g):		OR				
			0.009 to 0.059 (referent)	90					
			0.060 to 0.086	119		1.37	0.96	1.96	0.11
			0.087 to 0.126	88		1.08	0.74	1.58	0.10
			0.127 to 0.193	48		1.04	0.66	1.63	0.08
			0.194 to 0.277	21		1.33	0.71	2.49	0.05
			0.278 to 0.330	3		0.41	0.11	1.50	0.01
			0.331 to 2.484	14		1.36	0.63	2.90	0.04
Lewis et al. 1999[a] (Table 4)	U.S.	Cohort	All exposure groups: < 1,000 ppb-years to ≥ 5,000 ppb-years:		SMR				
			Men	3		0.42	0.08	1.22	0.02
			Women	2		0.81	0.10	2.93	0.01
Steinmaus et al. 2003[b] (Table 3)	U.S.	Case-control	Cumulative dose (mg):		OR				
			< 6.4 (referent)	153					
			6.4 to 82.8	9		1.63	0.64	4.13	
			> 82.8	19		1.40	0.73	2.70	0.03
									0.05
Bates et al. 2004 (Table 4)	Argentina	Case-control	Fluid intake adjusted exposure index (μg/L):		OR				
			0 to 1.0 (referent)	34					
			1.1 to 17	21		0.35	0.1	0.9	0.02
			18 to 80	32		0.90	0.3	2.3	0.03
			> 80	27		0.46	0.2	1.3	0.02
Kurttio et al. 1999[c] (Table 6)	Finland	Case-cohort	Concentration of arsenic in water (μg/L):		RR				
			< 0.1 (referent)	26					
			0.1 to 0.5	18		0.81	0.41	1.63	0.04
			≥ 0.5	17		1.51	0.67	3.38	0.03

Table B-2. (cont.)

Study (data source)	Study Country	Study Design	Study-Specific Arsenic Exposure Range	Observed Cases or Deaths Among "Exposed"	Type of Relative Risk Estimate	Estimate	Lower Bound	Upper Bound	Relative Weight of Study
Chiou et al. 2001 (Tables 4 and 5)	Northeastern Taiwan	Cohort	Arsenic concentration in well water (μg/L):		RR[d]				
			0 to 10.0 (referent)	1					
			10.1 to 50.0	1		1.9	0.1	32.2	0.00
			50.1 to 100.0	2		8.1	0.7	98.2	0.00
			> 100.0	6		15.1	1.7	138.5	0.00
Michaud et al. 2004[e] (Table 2)	Finland	Case-control (nested)	Toenail concentrations (μg/g):		OR				
			< 0.050 (referent)	65					
			0.05 to 0.105	71		1.09	0.68	1.74	0.08
			0.106 to 0.161	73		1.13	0.71	1.80	0.08
			> 0.161	71		1.13	0.70	1.81	0.08
				Summary Relative Risk = 1.109		**95% CI: 0.948–1.298**			
					p-value for Heterogeneity =	0.207			

Note: RR - relative risk
OR - odds ratio
SMR - standardized mortality ratio

[a] Cohort presumed to be nonsmokers.

[b] Analysis based on 40-year lag.

[c] Longer latency analysis: exposure in the tenth calendar year and earlier prior to the diagnosis.

[d] Results for transitional cell carcinoma, model adjusted for age, sex, cigarette smoking, concentration and duration of well water drinking.

[e] Entire cohort consisted of male smokers.

Table B-3. Arsenic exposure and risk of bladder cancer among NEVER SMOKERS: Study-specific collapsed exposure categories

Study	Study Country	Study Design	Study-Specific Arsenic Exposure Range	Observed Cases or Deaths Among "Exposed"	Type of Relative Risk Estimate	Estimate[a]	Lower Bound[b]	Upper Bound[b]	Relative Weight of Study
Bates et al. 1995	U.S.	Case-control	Cumulative dose: 19 to ≥ 53 mg vs. < 19 mg	21	OR	0.9375	0.3861	2.3577	0.17
Karagas et al. 2004	U.S.	Case-control	Toenail concentrations: 0.06 to 2.284 mcg/g vs. < 0.059 mcg/g	56	OR	0.9688	0.5020	1.9297	0.31
Lewis et al. 1999[c]	U.S.	Cohort	All exposure groups: < 1,000 ppb-years to ≥ 5,000 ppb-years	5	SMR	0.5155	0.1889	1.143	0.23
Steinmaus et al. 2003[d]	U.S.	Case-control	Cumulative dose: 6.4 to > 82.8 mg vs. < 6.4 mg	6	OR	0.8889	0.3031	2.3520	0.16
Bates et al. 2004	Argentina	Case-control	Fluid intake adjusted exposure index: 1.1 to > 80 μg/L vs. ≤ 1.0 μg/L	20	OR	0.5420	0.1873	1.5992	0.13
						Summary Relative Risk = 0.763	**95% CI: 0.519–1.120**		
						p-value for Heterogeneity =	0.724		

Note: OR - odds ratio
SMR - standardized mortality ratio

[a] Individual crude estimates based on re-calculated collapsed exposure category data; calculated using *Episheet*.

[b] Mid-*p* confidence limits.

[c] Cohort presumed to be nonsmokers, combined men and women and recalculated SMR.

[d] Analysis based on 40-year lag.

Table B-4. Arsenic exposure and risk of bladder cancer among NEVER SMOKERS: Study-specific exposure categories analyzed

Study (Data Source)	Study Country	Study Design	Study-Specific Arsenic Exposure Range	Observed Cases or Deaths Among "Exposed"	Type of Relative Risk Estimate	Estimate	Lower Bound	Upper Bound	Relative Weight of Study
Bates et al. 1995 (Table 3)	U.S.	Case-control	Cumulative dose (mg):		OR				
			< 19 (referent)	10					
			19 to < 33	10		1.09	0.4	3.1	0.08
			33 to < 53	7		0.68	0.2	2.3	0.06
			≥ 53	4		0.53	0.1	1.9	0.05
Karagas et al. 2004 (Table 2)	U.S.	Case-control	Toenail concentrations (mcg/g):		OR				
			0.009 to 0.059 (referent)	15					
			0.060 to 0.086	20		0.85	0.38	1.91	0.13
			0.087 to 0.126	22		1.18	0.53	2.66	0.13
			0.127 to 0.193	11		1.10	0.42	2.90	0.09
			0.194 to 0.277	3		0.49	0.12	2.05	0.04
			0.278 to 0.330	0		--	--	--	
			0.331 to 2.484	0		--	--	--	
Lewis et al. 1999[a] (Table 4)	U.S.	Cohort	All exposure groups: < 1,000 ppb-years to ≥ 5,000 ppb-years:		SMR				
			Men	3		0.42	0.08	1.22	0.08
			Women	2		0.81	0.10	2.93	0.05
Steinmaus et al. 2003[b] (Table 4)	U.S.	Case-control	Cumulative dose (mg):		OR				
			< 6.4 (referent)	23					
			6.4 to 82.8	3		2.65	0.49	14.24	0.03
			> 82.8	3		0.50	0.12	2.05	0.04
Bates et al. 2004 (Table 4)	Argentina	Case-control	Fluid intake adjusted exposure index (μg/L):		OR				
			0 to 1.0 (referent)	9					
			1.1 to 17	4		0.36	0.1	1.7	0.04
			18 to 80	10		0.95	0.2	3.9	0.04
			> 80	6		0.59	0.1	2.9	0.03

Table B-4. (cont.)

Study (Data Source)	Study Country	Study Design	Study-Specific Arsenic Exposure Range	Observed Cases or Deaths Among "Exposed"	Type of Relative Risk Estimate	Estimate	Lower Bound	Upper Bound	Relative Weight of Study
Kurttio et al. 1999[c]	Finland	Case cohort	Concentration of arsenic in water (μg/L):		RR				
(Table 7)			< 0.1 (referent)	8					
			0.1 to 0.5	4		0.95	0.25	3.64	0.05
			≥ 0.5	5		0.87	0.25	3.02	0.06
					Summary Relative Risk = 0.808		**95% CI: 0.603–1.083**		
					p-value for Heterogeneity =	0.937			

Note: OR - odds ratio
RR - relative risk
SMR - standardized mortality ratio

[a] Cohort presumed to be nonsmokers.

[b] Analysis based on 40-year lag.

[c] Never or ex-smokers included in the analysis.

Table B-5. Arsenic exposure and risk of bladder cancer among EVER SMOKERS: Study-specific collapsed exposure categories

Study	Study Country	Study Design	Study-Specific Arsenic Exposure Range	Observed Cases or Deaths Among "Exposed"	Type of Relative Risk Estimate	Estimate[a]	Lower Bound[b]	Upper Bound[b]	Relative Weight of Study
Bates et al. 1995	U.S.	Case-control	Cumulative dose: 19 to ≥ 53 mg vs. < 19 mg	36	OR	3.4737	1.1541	12.519	0.06
Karagas et al. 2004	U.S.	Case-control	Toenail concentrations: 0.06 to 2.284 mcg/g vs. < 0.059 mcg/g	237	OR	1.1949	0.8566	1.6716	0.34
Steinmaus et al. 2003[c]	U.S.	Case-control	Cumulative dose: 6.4 to > 82.8 mg vs. < 6.4 mg	22	OR	1.6834	0.8705	3.2674	0.16
Bates et al. 2004	Argentina	Case-control	Fluid intake adjusted exposure index: 1.1 to > 80 μg/L vs. ≤ 1.0 μg/L	60	OR	0.6240	0.2832	1.3447	0.13
Michaud et al. 2004[d]	Finland	Case-control (nested)	Toenail concentrations: 0.05 to > 0.161 μg/g vs. < 0.05 μg/g	215	OR	1.1177	0.7617	1.6416	0.31
					Summary Relative Risk = 1.206		**95% CI: 0.876–1.662**		
					p-value for Heterogeneity =	0.162			

Note: OR - odds ratio

[a] Individual crude estimates based on recalculated collapsed exposure category data; calculated using *Episheet*.

[b] Mid-*p* confidence limits.

[c] Analysis based on 40-year lag.

[d] Entire cohort composed of male smokers.

Table B-6. Arsenic exposure and risk of bladder cancer among EVER SMOKERS: Study-specific exposure categories analyzed

Study (Data Source)	Study Country	Study Design	Study-Specific Arsenic Exposure Range	Observed Cases or Deaths Among "Exposed"	Type of Relative Risk Estimate[a]	Estimate	Lower Bound	Upper Bound	Relative Weight of Study[a]
Bates et al. 1995 (Table 3)	U.S.	Case-control	Cumulative dose (mg):		OR				
			< 19 (referent)	4					
			19 to < 33	11		3.33	1.0	10.8	0.03
			33 to < 53	10		1.93	0.6	6.2	0.03
			≥ 53	15		3.32	1.1	10.3	0.03
Karagas et al. 2004 (Table 2)	U.S.	Case-control	Toenail concentrations (μg/g):		OR				
			0.009 to 0.059 (referent)	75					
			0.060 to 0.086	99		1.53	1.02	2.29	0.10
			0.087 to 0.126	66		1.02	0.66	1.56	0.10
			0.127 to 0.193	37		1.00	0.60	1.67	0.09
			0.194 to 0.277	18		1.78	0.86	3.67	0.06
			0.278 to 0.330	3		0.50	0.13	1.88	0.02
			0.331 to 2.484	14		2.17	0.92	5.11	0.05
Steinmaus et al. 2003[b] (Table 4)	U.S.	Case-control	Cumulative dose (mg):		OR				
			< 6.4 (referent)	130					
			6.4 to 82.8	6		1.06	0.34	3.33	0.03
			> 82.8	16		2.25	0.97	5.20	0.05
Bates et al. 2004 (Table 4)	Argentina	Case-control	Fluid intake adjusted exposure index (μg/L):		OR				
			0 to 1.0 (referent)	25					
			1.1 to 17	17		0.29	0.1	0.8	0.04
			18 to 80	22		0.88	0.3	2.7	0.03
			> 80	21		0.46	0.2	1.4	0.03
Kurttio et al. 1999 (Table 7)	Finland	Case cohort	Concentration of arsenic in water (μg/L):		RR				
			< 0.1 (referent)	8					
			0.1 to 0.5	3		1.10	0.19	6.24	0.02
			≥ 0.5	7		10.3	1.16	92.6	0.01

Table B-6. (cont.)

Study (Data Source)	Study Country	Study Design	Study-Specific Arsenic Exposure Range	Observed Cases or Deaths Among "Exposed"	Type of Relative Risk Estimate[a]	Estimate	Lower Bound	Upper Bound	Relative Weight of Study[a]
Michaud et al. 2004[c] (Table 2)	Finland	Case-control (nested)	Toenail concentrations (μg/g):		OR				
			< 0.050	65					
			0.05 to 0.105	71		1.09	0.68	1.74	0.09
			0.106 to 0.161	73		1.13	0.71	1.80	0.09
			> 0.161	71		1.13	0.70	1.81	0.09
					Summary Relative Risk = 1.241		**95% CI: 0.988–1.559**		
					p-value for Heterogeneity =	0.032			

Note: OR - odds ratio
RR - relative risk

[a] Relative weight of study will be determined when meta-analysis is performed.

[b] Analysis based on 40-year lag.

[c] Entire cohort consisted of male smokers.

Table B-7. Arsenic exposure and risk of bladder cancer: Study-specific upper exposure categories collapsed and recalculated (findings for smokers and nonsmokers combined from studies that evaluated incident cases only)

	Study Country	Study Design	Study-Specific Arsenic Exposure Range	Observed Cases or Deaths Among "Exposed"	Type of Relative Risk Estimate	Estimate[a]	Lower Bound[b]	Upper Bound[b]	Relative Weight of Study
Bates et al. 1995	U.S.	Case-control	Cumulative dose: 19 to ≥ 53 mg vs. < 19 mg	57	OR	1.6934	0.8683	3.4145	0.10
Karagas et al. 2004	U.S.	Case-control	Toenail concentrations: 0.06 to 2.284 mcg/g vs. < 0.059 mcg/g	293	OR	1.1010	0.8198	1.4833	0.26
Steinmaus et al. 2003[c]	U.S.	Case-control	Cumulative dose: 6.4 to > 82.8 mg vs. < 6.4 mg	28	OR	1.1219	0.6677	1.8629	0.19
Bates et al. 2004	Argentina	Case-control	Fluid intake adjusted exposure index: 1.1 to > 80 μg/L vs. ≤ 1.0 μg/L	80	OR	0.5947	0.3209	1.0949	0.12
Chiou et al. 2001	Northeastern Taiwan	Cohort	Entire cohort (range of arsenic concentration: < 0.15 μg/L to 3482.6 μg/L)	10	SIR	1.96[d]	0.94	3.61	0.12
Michaud et al. 2004[e]	Finland	Case-control (nested)	Toenail concentrations: 0.05 to > 0.161 μg/g vs. < 0.05 μg/g	215	OR	1.1177	0.7617	1.6416	0.21
					Summary Relative Risk = 1.169		**95% CI: 0.908–1.506**		
					p-value for Heterogeneity =	0.119			

Note: OR - odds ratio
SIR - standardized incidence ratio

[a] Individual crude estimates based on recalculated collapsed exposure category data; calculated using *Episheet*.

[b] Mid-*p* confidence limits.

[c] Analysis based on 40-year lag.

[d] Findings provided in text (were not recalculated).

[e] Entire cohort consisted of male smokers.

Table B-8. Arsenic exposure and risk of bladder cancer: Study-specific exposure categories (findings for smokers and nonsmokers combined from studies that evaluated incident cases only)

Study (data source)	Study Country	Study Design	Study-Specific Arsenic Exposure Range	Observed Cases or Deaths Among "Exposed"	Type of Relative Risk Estimate	Estimate	Lower Bound	Upper Bound	Relative Weight of Study
Bates et al. 1995 (Table 3)	U.S.	Case-control	Cumulative dose (mg):		OR				
			< 19 (referent)	14					
			19 to < 33	21		1.56	0.8	3.2	0.04
			33 to < 53	17		0.95	0.4	2.0	0.04
			> 53	19		1.41	0.7	2.9	0.04
Karagas et al. 2004 (Table 2)	U.S.	Case-control	Toenail concentrations (μg/g):		OR				
			0.009 to 0.059 (referent)	90					
			0.060 to 0.086	119		1.37	0.96	1.96	0.12
			0.087 to 0.126	88		1.08	0.74	1.58	0.11
			0.127 to 0.193	48		1.04	0.66	1.63	0.09
			0.194 to 0.277	21		1.33	0.71	2.49	0.06
			0.278 to 0.330	3		0.41	0.11	1.50	0.02
			0.331 to 2.484	14		1.36	0.63	2.90	0.04
Steinmaus et al. 2003[a] (Table 3)	U.S.	Case-control	Cumulative dose (mg):		OR				
			< 6.4 (referent)	153					
			6.4 to 82.8	9					
			> 82.8	19		1.63	0.64	4.13	0.03
						1.40	0.73	2.70	0.05
Bates et al. 2004 (Table 4)	Argentina	Case-control	Fluid intake adjusted exposure index (μg/L):		OR				
			0 to 1.0 (referent)	34					
			1.1 to 17	21		0.35	0.1	0.9	0.03
			18 to 80	32		0.90	0.3	2.3	0.03
			> 80	27		0.46	0.2	1.3	0.02
Chiou et al. 2001 (Tables 4 and 5)	Northeastern Taiwan	Cohort	Arsenic concentration in well water (μg/L):		RR[b]				
			0 to 10.0 (referent)	1					
			10.1 to 50.0	1		1.9	0.1	32.2	0.00
			50.1 to 100.0	2		8.1	0.7	98.2	0.00
			> 100.0	6		15.1	1.7	138.5	0.01

Table B-8. (cont.)

Study (data source)	Study Country	Study Design	Study-Specific Arsenic Exposure Range	Observed Cases or Deaths Among "Exposed"	Type of Relative Risk Estimate	Estimate	Lower Bound	Upper Bound	Relative Weight of Study
Michaud et al. 2004[c] (Table 2)	Finland	Case-control (nested)	Toenail concentrations (μg/g):		OR				
			< 0.050 (referent)	65					
			0.05 to 0.105	71		1.09	0.68	1.74	0.09
			0.106 to 0.161	73		1.13	0.71	1.80	0.09
			> 0.161	71		1.13	0.70	1.81	0.09
					Summary Relative Risk = 1.144		**95% CI: 0.971–1.347**		
					p-value for Heterogeneity =	0.227			

Note: RR - relative risk
OR - odds ratio

[a] Analysis based on 40-year lag.

[b] Results for transitional cell carcinoma, model adjusted for age, sex, cigarette smoking, concentration and duration of well water drinking.

[c] Entire cohort consisted of male smokers.

Table B-9. Arsenic exposure and risk of bladder cancer among NEVER SMOKERS: Study-specific upper exposure categories collapsed and recalculated (findings for studies that evaluated incident cases only)

Study	Study Country	Study Design	Study-Specific Arsenic Exposure Range	Observed Cases or Deaths Among "Exposed"	Type of Relative Risk Estimate	Estimate[a]	Lower Bound[b]	Upper Bound[b]	Relative Weight of Study
Bates et al. 1995	U.S.	Case-control	Cumulative dose: 19 to ≥ 53 mg vs. < 19 mg	21	OR	0.9375	0.3861	2.3577	0.23
Karagas et al. 2004	U.S.	Case-control	Toenail concentrations: 0.06 to 2.284 mcg/g vs. < 0.059 mcg/g	56	OR	0.9688	0.5020	1.9297	0.40
Steinmaus et al. 2003[c]	U.S.	Case-control	Cumulative dose: 6.4 to > 82.8 mg vs. < 6.4 mg	6	OR	0.8889	0.3031	2.3520	0.20
Bates et al. 2004	Argentina	Case-control	Fluid intake adjusted exposure index: 1.1 to > 80 μg/L vs. ≤ 1.0 μg/L	20	OR	0.5420	0.1873	1.5992	0.16
					Summary Relative Risk = 0.859		**95% CI: 0.554–1.332**		
					p-value for Heterogeneity =	0.837			

Note: OR - odds ratio

[a] Individual crude estimates based on re-calculated collapsed exposure category data; calculated using *Episheet*.

[b] Mid-*p* confidence limits.

[c] Analysis based on 40-year lag.

Table B-10. Arsenic exposure and risk of bladder cancer among NEVER SMOKERS: Study-specific exposure categories analyzed (findings for studies that evaluated incident cases only)

Study (Data Source)	Study Country	Study Design	Study-Specific Arsenic Exposure Range	Observed Cases or Deaths Among "Exposed"	Type of Relative Risk Estimate	Estimate	Lower Bound	Upper Bound	Relative Weight of Study
Bates et al. 1995 (Table 3)	U.S.	Case-control	Cumulative dose (mg):		OR				
			< 19 (referent)	10					
			19 to < 33	10		1.09	0.4	3.1	0.10
			33 to < 53	7		0.68	0.2	2.3	0.08
			≥ 53	4		0.53	0.1	1.9	0.07
Karagas et al. 2004 (Table 2)	U.S.	Case-control	Toenail concentrations (mcg/g):		OR				
			0.009 to 0.059 (referent)	15					
			0.060 to 0.086	20		0.85	0.38	1.91	0.17
			0.087 to 0.126	22		1.18	0.53	2.66	0.17
			0.127 to 0.193	11		1.10	0.42	2.90	0.12
			0.194 to 0.277	3		0.49	0.12	2.05	0.05
			0.278 to 0.330	0		--	--	--	
			0.331 to 2.484	0		--	--	--	
Steinmaus et al. 2003[a] (Table 4)	U.S.	Case-control	Cumulative dose (mg):		OR				
			< 6.4 (referent)	23					
			6.4 to 82.8	3		2.65	0.49	14.24	0.04
			> 82.8	3		0.50	0.12	2.05	0.06
Bates et al. 2004 (Table 4)	Argentina	Case-control	Fluid intake adjusted exposure index (μg/L):		OR				
			0 to 1.0 (referent)	9					
			1.1 to 17	4		0.36	0.1	1.7	0.05
			18 to 80	10		0.95	0.2	3.9	0.06
			> 80	6		0.59	0.1	2.9	0.04
					Summary Relative Risk = 0.848		**95% CI: 0.607–1.185**		
					p-value for Heterogeneity =	0.871			

Note: OR - odds ratio

[a] Analysis based on 40-year lag.

Table B-11. Arsenic exposure and risk of bladder cancer among EVER SMOKERS: Study-specific upper exposure categories collapsed and recalculated (findings for studies that evaluated incident cases only)

Study	Study Country	Study Design	Study-Specific Arsenic Exposure Range	Observed Cases or Deaths Among "Exposed"	Type of Relative Risk Estimate	Estimate[a]	Lower Bound[b]	Upper Bound[b]	Relative Weight of Study
Bates et al. 1995	U.S.	Case-control	Cumulative dose: 19 to ≥ 53 mg vs. < 19 mg	36	OR	3.4737	1.1541	12.519	0.06
Karagas et al. 2004	U.S.	Case-control	Toenail concentrations: 0.06 to 2.284 mcg/g vs. < 0.059 mcg/g	237	OR	1.1949	0.8566	1.6716	0.34
Steinmaus et al. 2003[d]	U.S.	Case-control	Cumulative dose: 6.4 to > 82.8 mg vs. < 6.4 mg	22	OR	1.6834	0.8705	3.2674	0.16
Bates et al. 2004	Argentina	Case-control	Fluid intake adjusted exposure index: 1.1 to > 80 μg/L vs. ≤ 1.0 μg/L	60	OR	0.6240	0.2832	1.3447	0.13
Michaud et al. 2004[c]	Finland	Case-control (nested)	Toenail concentrations: 0.05 to > 0.161 μg/g vs. < 0.05 μg/g	215	OR	1.1177	0.7617	1.6416	0.31
					Summary Relative Risk = 1.206		**95% CI: 0.876–1.662**		
					p-value for Heterogeneity =	0.162			

Note: OR = odds ratio

[a] Individual crude estimates based on recalculated collapsed exposure category data; calculated using *Episheet*.

[b] Mid-*p* confidence limits.

[c] Entire cohort composed of male smokers.

[d] Analysis based on 40-year lag.

Table B-12. Arsenic exposure and risk of bladder cancer among EVER SMOKERS: Study-specific exposure categories analyzed (findings for studies that evaluated incident cases only)

Study (Data Source)	Study Country	Study Design	Study-Specific Arsenic Exposure Range	Observed Cases or Deaths Among "Exposed"	Type of Relative Risk Estimate	Estimate	Lower Bound	Upper Bound	Relative Weight of Study
Bates et al. 1995 (Table 3)	U.S.	Case-control	Cumulative dose (mg):		OR				
			< 19 (referent)	4					
			19 to < 33	11		3.33	1.0	10.8	0.03
			33 to < 53	10		1.93	0.6	6.2	0.03
			≥ 53	15		3.32	1.1	10.3	0.03
Karagas et al. 2004 (Table 2)	U.S.	Case-control	Toenail concentrations (μg/g):		OR				
			0.009 to 0.059 (referent)	75					
			0.060 to 0.086	99		1.53	1.02	2.29	0.11
			0.087 to 0.126	66		1.02	0.66	1.56	0.10
			0.127 to 0.193	37		1.00	0.60	1.67	0.09
			0.194 to 0.277	18		1.78	0.86	3.67	0.06
			0.278 to 0.330	3		0.50	0.13	1.88	0.02
			0.331 to 2.484	14		2.17	0.92	5.11	0.05
Steinmaus et al. 2003[a] (Table 4)	U.S.	Case-control	Cumulative dose (mg):		OR				
			< 6.4 (referent)	130					
			6.4 to 82.8	6		1.06	0.34	3.33	0.03
			> 82.8	16		2.25	0.97	5.20	0.05
Bates et al. 2004 (Table 4)	Argentina	Case-control	Fluid intake adjusted exposure index (μg/L):		OR				
			0 to 1.0 (referent)	25					
			1.1 to 17	17		0.29	0.1	0.8	0.04
			18 to 80	22		0.88	0.3	2.7	0.03
			> 80	21		0.46	0.2	1.4	0.03
Michaud et al. 2004[b] (Table 2)	Finland	Case-control (nested)	Toenail concentrations (μg/g):		OR				
			< 0.050	65					
			0.05 to 0.105	71		1.09	0.68	1.74	0.10
			0.106 to 0.161	73		1.13	0.71	1.80	0.10
			> 0.161	71		1.13	0.70	1.81	0.10
					Summary Relative Risk = 1.216	**95% CI: 0.972–1.522**			
					p-value for Heterogeneity =	0.043			

Note: OR - odds ratio

[a] Analysis based on 40-year lag.

[b] Entire cohort consisted of male smokers.

Table B-13. Arsenic exposure and risk of bladder cancer: Study-specific upper exposure categories collapsed and recalculated (findings for smokers and nonsmokers combined, with studies that evaluated toenail concentrations excluded)

	Study Country	Study Design	Study-Specific Arsenic Exposure Range	Observed Cases or Deaths Among "Exposed"	Type of Relative Risk Estimate	Estimate[a]	Lower Bound[b]	Upper Bound[b]	Relative Weight of Study
Bates et al. 1995	U.S.	Case-control	Cumulative dose: 19 to ≥ 53 mg vs. < 19 mg	57	OR	1.6934	0.8683	3.4145	0.19
Lewis et al. 1999[c]	U.S.	Cohort	All exposure groups: < 1,000 ppb-years to ≥ 5,000 ppb-years	5	SMR	0.5155	0.1889	1.143	0.17
Steinmaus et al. 2003[d]	U.S.	Case-control	Cumulative dose: 6.4 to > 82.8 mg vs. < 6.4 mg	28	OR	1.1219	0.6677	1.8629	0.23
Bates et al. 2004	Argentina	Case-control	Fluid intake adjusted exposure index: 1.1 to > 80 μg/L vs. ≤ 1.0 μg/L	80	OR	0.5947	0.3209	1.0949	0.21
Chiou et al. 2001	Northeastern Taiwan	Cohort	Entire cohort (range of arsenic concentration: < 0.15 μg/L to 3,482.6 μg/L)	10	SIR	1.96[e]	0.94	3.61	0.21
					Summary Relative Risk = 1.046		**95% CI: 0.636–1.718**		
					p-value for Heterogeneity =	0.016			

Note: OR - odds ratio
SMR - standardized mortality ratio
SIR - standardized incidence ratio

[a] Individual crude estimates based on recalculated collapsed exposure category data; calculated using *Episheet*.

[b] Mid-*p* confidence limits.

[c] Cohort presumed to be nonsmokers, combined men and women and recalculated SMR.

[d] Analysis based on 40-year lag.

[e] Findings provided in text (were not recalculated).

Table B-14. Arsenic exposure and risk of bladder cancer: Study-specific exposure categories (findings for smokers and nonsmokers combined, with studies that evaluated toenail concentrations excluded)

Study (data source)	Study Country	Study Design	Study-Specific Arsenic Exposure Range	Observed Cases or Deaths Among "Exposed"	Type of Relative Risk Estimate	Estimate	Lower Bound	Upper Bound	Relative Weight of Study
Bates et al. 1995 (Table 3)	U.S.	Case-control	Cumulative dose (mg):		OR				
			< 19 (referent)	14					
			19 to < 33	21		1.56	0.8	3.2	0.09
			33 to < 53	17		0.95	0.4	2.0	0.09
			≥ 53	19		1.41	0.7	2.9	0.09
Lewis et al. 1999[a] (Table 4)	U.S.	Cohort	All exposure groups: < 1,000 ppb-years to ≥ 5,000 ppb-years:		SMR				
			Men	3		0.42	0.08	1.22	0.06
			Women	2		0.81	0.10	2.93	0.05
Steinmaus et al. 2003[b] (Table 3)	U.S.	Case-control	Cumulative dose (mg):		OR				
			< 6.4 (referent)	153					
			6.4 to 82.8	9					
			> 82.8	19		1.63	0.64	4.13	0.07
						1.40	0.73	2.70	0.10
Bates et al. 2004 (Table 4)	Argentina	Case-control	Fluid intake adjusted exposure index (μg/L):		OR				
			0 to 1.0 (referent)	34					
			1.1 to 17	21		0.35	0.1	0.9	0.07
			18 to 80	32		0.90	0.3	2.3	0.07
			> 80	27		0.46	0.2	1.3	0.06
Kurttio et al. 1999[c] (Table 6)	Finland	Case cohort	Concentration of arsenic in water (μg/L):		RR				
			< 0.1 (referent)	26					
			0.1 to 0.5	18		0.81	0.41	1.63	0.10
			≥ 0.5	17		1.51	0.67	3.38	0.08
Chiou et al. 2001 (Tables 4 and 5)	Northeastern Taiwan	Cohort	Arsenic concentration in well water (μg/L):		RR[d]				
			0 to 10.0 (referent)	1					
			10.1 to 50.0	1		1.9	0.1	32.2	0.01
			50.1 to 100.0	2		8.1	0.7	98.2	0.02
			> 100.0	6		15.1	1.7	138.5	0.02
					Summary Relative Risk = 1.055		**95% CI: 0.761–1.461**		
					p-value for Heterogeneity =	0.048			

Footnotes on following page.

Table B-14. (cont.)

Note: OR - odds ratio
SMR - standardized mortality ratio
RR - relative risk

[a] Cohort presumed to be nonsmokers.

[b] Analysis based on 40-year lag.

[c] Longer latency analysis: exposure in the tenth calendar year and earlier prior to the diagnosis.

[d] Results for transitional cell carcinoma, model adjusted for age, sex, cigarette smoking, concentration and duration of well water drinking.

Table B-15. Arsenic exposure and risk of bladder cancer among NEVER SMOKERS: Study-specific upper exposure categories collapsed and recalculated (studies that evaluated toenail concentrations excluded)

Study	Study Country	Study Design	Study-Specific Arsenic Exposure Range	Observed Cases or Deaths Among "Exposed"	Type of Relative Risk Estimate	Estimate[a]	Lower Bound[b]	Upper Bound[b]	Relative Weight of Study
Bates et al. 1995	U.S.	Case-control	Cumulative dose: 19 to ≥ 53 mg vs. < 19 mg	21	OR	0.9375	0.3861	2.3577	0.25
Lewis et al. 1999[c]	U.S.	Cohort	All exposure groups: < 1,000 ppb-years to ≥ 5,000 ppb-years	5	SMR	0.5155	0.1889	1.143	0.34
Steinmaus et al. 2003[d]	U.S.	Case-control	Cumulative dose: 6.4 to > 82.8 mg vs. < 6.4 mg	6	OR	0.8889	0.3031	2.3520	0.23
Bates et al. 2004	Argentina	Case-control	Fluid intake adjusted exposure index: 1.1 to > 80 μg/L vs. ≤ 1.0 μg/L	20	OR	0.5420	0.1873	1.5992	0.18
						Summary Relative Risk = 0.685	**95% CI: 0.431–1.088**		
						p-value for Heterogeneity =	0.707		

Note: OR - odds ratio
SMR - standardized mortality ratio

[a] Individual crude estimates based on recalculated collapsed exposure category data; calculated using *Episheet*.

[b] Mid-*p* confidence limits.

[c] Cohort presumed to be nonsmokers, combined men and women and recalculated SMR.

[d] Analysis based on 40-year lag.

Table B-16. Arsenic exposure and risk of bladder cancer among NEVER SMOKERS: Study-specific exposure categories analyzed (studies that evaluated toenail concentrations excluded)

Study (Data Source)	Study Country	Study Design	Study-Specific Arsenic Exposure Range	Observed Cases or Deaths Among "Exposed"	Type of Relative Risk Estimate	Estimate	Lower Bound	Upper Bound	Relative Weight of Study
Bates et al. 1995 (Table 3)	U.S.	Case-control	Cumulative dose (mg):		OR				
			< 19 (referent)	10					
			19 to < 33	10		1.09	0.4	3.1	0.13
			33 to < 53	7		0.68	0.2	2.3	0.10
			> 53	4		0.53	0.1	1.9	0.09
Lewis et al. 1999[a] (Table 4)	U.S.	Cohort	All exposure groups: < 1,000 ppb-years to > 5,000 ppb-years:		SMR				
			Men	3		0.42	0.08	1.22	0.12
			Women	2		0.81	0.10	2.93	0.09
Steinmaus et al. 2003[b] (Table 4)	U.S.	Case-control	Cumulative dose (mg):		OR				
			< 6.4 (referent)	23					
			6.4 to 82.8	3		2.65	0.49	14.24	0.05
			> 82.8	3		0.50	0.12	2.05	0.07
Bates et al. 2004 (Table 4)	Argentina	Case-control	Fluid intake adjusted exposure index (μg/L):		OR				
			0 to 1.0 (referent)	9					
			1.1 to 17	4		0.36	0.1	1.7	0.06
			18 to 80	10		0.95	0.2	3.9	0.07
			> 80	6		0.59	0.1	2.9	0.06
Kurttio et al. 1999[c] (Table 7)	Finland	Case cohort	Concentration of arsenic in water (μg/L):		RR				
			< 0.1 (referent)	8					
			0.1 to 0.5	4		0.95	0.25	3.64	0.08
			$\geq$ 0.5	5		0.87	0.25	3.02	0.09
				Summary Relative Risk = 0.728			**95% CI: 0.499–1.061**		
					p-value for Heterogeneity =	0.897			

Note: OR - odds ratio
RR - relative risk
SMR - standardized mortality ratio

[a] Cohort presumed to be nonsmokers.

[b] Analysis based on 40-year lag.

[c] Never or ex-smokers included in the analysis.

Table B-17. Arsenic exposure and risk of bladder cancer among EVER SMOKERS: Study-specific upper exposure categories collapsed and recalculated (studies that evaluated toenail concentrations excluded)

Study	Study Country	Study Design	Study-Specific Arsenic Exposure Range	Observed Cases or Deaths Among "Exposed"	Type of Relative Risk Estimate	Estimate[a]	Lower Bound[b]	Upper Bound[b]	Relative Weight of Study
Bates et al. 1995	U.S.	Case-control	Cumulative dose: 19 to ≥ 53 mg vs. < 19 mg	36	OR	3.4737	1.1541	12.519	0.25
Steinmaus et al. 2003[c]	U.S.	Case-control	Cumulative dose: 6.4 to > 82.8 mg vs. < 6.4 mg	22	OR	1.6834	0.8705	3.2674	0.39
Bates et al. 2004	Argentina	Case-control	Fluid intake adjusted exposure index: 1.1 to > 80 μg/L vs. ≤ 1.0 μg/L	60	OR	0.6240	0.2832	1.3447	0.36
						Summary Relative Risk = 1.401	**95% CI: 0.575–3.412**		
						p-value for Heterogeneity =	0.042		

Note: OR = odds ratio

[a] Individual crude estimates based on recalculated collapsed exposure category data; calculated using *Episheet*.

[b] Mid-*p* confidence limits.

[c] Analysis based on 40-year lag.

Table B-18. Arsenic exposure and risk of bladder cancer among EVER SMOKERS: Study-specific exposure categories analyzed (studies that evaluated toenail concentrations excluded)

Study (Data Source)	Study Country	Study Design	Study-Specific Arsenic Exposure Range	Observed Cases or Deaths Among "Exposed"	Type of Relative Risk Estimate	Estimate	Lower Bound	Upper Bound	Relative Weight of Study
Bates et al. 1995 (Table 3)	U.S.	Case-control	Cumulative dose (mg):		OR				
			< 19 (referent)	4					
			19 to < 33	11		3.33	1.0	10.8	0.10
			33 to < 53	10		1.93	0.6	6.2	0.10
			≥ 53	15		3.32	1.1	10.3	0.11
Steinmaus et al. 2003[a] (Table 4)	U.S.	Case-control	Cumulative dose (mg):		OR				
			< 6.4 (referent)	130					
			6.4 to 82.8	6		1.06	0.34	3.33	0.11
			> 82.8	16		2.25	0.97	5.20	0.13
Bates et al. 2004 (Table 4)	Argentina	Case-control	Fluid intake adjusted exposure index (μg/L):		OR				
			0 to 1.0 (referent)	25					
			1.1 to 17	17		0.29	0.1	0.8	0.12
			18 to 80	22		0.88	0.3	2.7	0.11
			> 80	21		0.46	0.2	1.4	0.11
Kurttio et al. 1999 (Table 7)	Finland	Case cohort	Concentration of arsenic in water (μg/L):		RR				
			< 0.1 (referent)	8					
			0.1 to 0.5	3		1.10	0.19	6.24	0.07
			≥ 0.5	7		10.3	1.16	92.6	0.05
					Summary Relative Risk = 1.375	**95% CI: 0.755–2.505**			
					p-value for Heterogeneity =	0.006			

Note: OR - odds ratio
RR - relative risk

[a] Analysis based on 40-year lag.

Table B-19. Arsenic exposure and risk of bladder cancer: Study-specific upper exposure categories collapsed and recalculated (findings for smokers and nonsmokers combined from studies that evaluated cumulative exposure [mg])

	Study Country	Study Design	Study-Specific Arsenic Exposure Range	Observed Cases or Deaths Among "Exposed"	Type of Relative Risk Estimate	Estimate[a]	Lower Bound[b]	Upper Bound[b]	Relative Weight of Study
Bates et al. 1995	U.S.	Case-control	Cumulative dose: 19 to ≥ 53 mg vs. < 19 mg	57	OR	1.6934	0.8683	3.4145	0.34
Steinmaus et al. 2003[c]	U.S.	Case-control	Cumulative dose: 6.4 to > 82.8 mg vs. < 6.4 mg	28	OR	1.1219	0.6677	1.8629	0.66
					Summary Relative Risk = 1.292		**95% CI: 0.857–1.949**		
					p-value for Heterogeneity =	0.351			

Note: OR - odds ratio

[a] Individual crude estimates based on recalculated collapsed exposure category data; calculated using *Episheet*.

[b] Mid-*p* confidence limits.

[c] Analysis based on 40-year lag.

Table B-20. Arsenic exposure and risk of bladder cancer: Study-specific exposure categories (findings for smokers and non-smokers combined from studies that evaluated cumulative exposure [mg])

Study (data source)	Study Country	Study Design	Study-Specific Arsenic Exposure Range	Observed Cases or Deaths Among "Exposed"	Type of Relative Risk Estimate	Estimate	Lower Bound	Upper Bound	Relative Weight of Study
Bates et al. 1995 (Table 3)	U.S.	Case-control	Cumulative dose (mg):		OR				
			< 19 (referent)	14					
			19 to < 33	21		1.56	0.8	3.2	0.15
			33 to < 53	17		0.95	0.4	2.0	0.14
			≥ 53	19		1.41	0.7	2.9	0.15
Steinmaus et al. 2003[a] (Table 3)	U.S.	Case-control	Cumulative dose (mg):		OR				
			< 6.4 (referent)						
			6.4 to 82.8	153					
			> 82.8	9		1.63	0.64	4.13	0.10
				19		1.40	0.73	2.70	0.17
Kurttio et al. 1999[b] (Table 6)	Finland	Case cohort	Cumulative dose (mg):		RR				
			< 0.5 (referent)	27					
			0.5 to 2.0	21		0.81	0.39	1.69	0.14
			≥ 2.0	13		0.53	0.25	1.10	0.15
					Summary Relative Risk = 1.097		**95% CI: 0.808–1.491**		
					p-value for Heterogeneity =	0.301			

Note: OR - odds ratio
RR - relative risk

[a] Analysis based on 40-year lag.

[b] Longer latency analysis: exposure in the tenth calendar year and earlier prior to the diagnosis.

Table B-21. Arsenic exposure and risk of bladder cancer among NEVER SMOKERS: Study-specific exposure categories analyzed (findings from studies that evaluated cumulative exposure [mg])

Study	Study Country	Study Design	Study-Specific Arsenic Exposure Range	Observed Cases or Deaths Among "Exposed"	Type of Relative Risk Estimate	Estimate[a]	Lower Bound[b]	Upper Bound[b]	Relative Weight of Study
Bates et al. 1995 (Table 3)	U.S.	Case-control	Cumulative dose (mg):		OR				
			< 19 (referent)	10					
			19 to < 33	10		1.09	0.4	3.1	0.22
			33 to < 53	7		0.68	0.2	2.3	0.16
			≥ 53	4		0.53	0.1	1.9	0.15
Steinmaus et al. 2003[c] (Table 4)	U.S.	Case-control	Cumulative dose (mg):		OR				
			< 6.4 (referent)	23					
			6.4 to 82.8	3		2.65	0.49	14.24	0.08
			> 82.8	3		0.50	0.12	2.05	0.12
Kurttio et al. 1999[d] (Table 7)	Finland	Case cohort	Cumulative dose (mg):		RR				
			< 0.5 (referent)	7					
			0.5 to 2.0	3		0.66	0.14	3.01	0.10
			≥ 2.0	7		0.74	0.22	2.46	0.17
					Summary Relative Risk = 0.794		**95% CI: 0.487–1.295**		
					p-value for Heterogeneity =	0.776			

Note: OR - odds ratio
RR - relative risk

[a] Individual crude estimates based on recalculated collapsed exposure category data; calculated using *Episheet*.

[b] Mid-*p* confidence limits.

[c] Analysis based on 40-year lag.

[d] Longer latency analysis: exposure in the tenth calendar year and earlier prior to the diagnosis.

Table B-22. Arsenic exposure and risk of bladder cancer among EVER SMOKERS: Study-specific exposure categories analyzed (findings from studies that evaluated cumulative exposure [mg])

Study	Study Country	Study Design	Study-Specific Arsenic Exposure Range	Observed Cases or Deaths Among "Exposed"	Type of Relative Risk Estimate	Estimate[a]	Lower Bound[b]	Upper Bound[b]	Relative Weight of Study
Bates et al. 1995 (Table 3)	U.S.	Case-control	Cumulative dose (mg):		OR				
			< 19 (referent)	4					
			19 to < 33	11		3.33	1.0	10.8	0.14
			33 to < 53	10		1.93	0.6	6.2	0.14
			> 53	15		3.32	1.1	10.3	0.15
Steinmaus et al. 2003[c] (Table 4)	U.S.	Case-control	Cumulative dose (mg):		OR				
			< 6.4 (referent)	130					
			6.4 to 82.8	6		1.06	0.34	3.33	0.15
			> 82.8	16		2.25	0.97	5.20	0.28
Kurttio et al. 1999[d] (Table 7)	Finland	Case cohort	Cumulative dose (mg):		RR				
			< 0.5 (referent)	3					
			0.5 to 2.0	8		4.00	0.71	22.5	0.07
			≥ 2.0	7		3.29	0.56	19.3	0.06
					Summary Relative Risk = 2.347		**95% CI: 1.506–3.657**		
					p-value for Heterogeneity =	0.786			

Note: OR - odds ratio
RR - relative risk

[a] Individual crude estimates based on recalculated collapsed exposure category data; calculated using *Episheet*.

[b] Mid-*p* confidence limits.

[c] Analysis based on 40-year lag.

[d] Longer latency analysis: exposure in the tenth calendar year and earlier prior to the diagnosis.

Table B-23. Arsenic exposure and risk of bladder cancer: Study-specific upper exposure categories collapsed and recalculated (findings for smokers and nonsmokers combined from studies conducted in the United States)

	Study Country	Study Design	Study-Specific Arsenic Exposure Range	Observed Cases or Deaths Among "Exposed"	Type of Relative Risk Estimate	Estimate[a]	Lower Bound[b]	Upper Bound[b]	Relative Weight of Study
Bates et al. 1995	U.S.	Case-control	Cumulative dose: 19 to ≥ 53 mg vs. < 19 mg	57	OR	1.6934	0.8683	3.4145	0.16
Karagas et al. 2004	U.S.	Case-control	Toenail concentrations: 0.06 to 2.284 mcg/g vs. < 0.059 mcg/g	293	OR	1.1010	0.8198	1.4833	0.41
Lewis et al. 1999[c]	U.S.	Cohort	All exposure groups: < 1,000 ppb-years to ≥ 5,000 ppb-years	5	SMR	0.5155	0.1889	1.143	0.13
Steinmaus et al. 2003[d]	U.S.	Case-control	Cumulative dose: 6.4 to > 82.8 mg vs. < 6.4 mg	28	OR	1.1219	0.6677	1.8629	0.30
					Summary Relative Risk = 1.100		**95% CI: 0.794–1.525**		
					p-value for Heterogeneity =	0.161			

Note: OR - odds ratio
SMR - standardized mortality ratio

[a] Individual crude estimates based on re-calculated collapsed exposure category data; calculated using *Episheet*.

[b] Mid-*p* confidence limits.

[c] Cohort presumed to be nonsmokers, combined men and women and recalculated SMR.

[d] Analysis based on 40-year lag.

Table B-24. Arsenic exposure and risk of bladder cancer: Study-specific exposure categories (findings for smokers and nonsmokers combined from studies conducted in the United States)

Study (data source)	Study Country	Study Design	Study-Specific Arsenic Exposure Range	Observed Cases or Deaths Among "Exposed"	Type of Relative Risk Estimate	Estimate	Lower Bound	Upper Bound	Relative Weight of Study
Bates et al. 1995 (Table 3)	U.S.	Case-control	Cumulative dose (mg):		OR				
			< 19 (referent)	14					
			19 to < 33	21		1.56	0.8	3.2	0.06
			33 to < 53	17		0.95	0.4	2.0	0.05
			≥ 53	19		1.41	0.7	2.9	0.05
Karagas et al. 2004 (Table 2)	U.S.	Case-control	Toenail concentrations (μg/g):		OR				
			0.009 to 0.059 (referent)	90					
			0.060 to 0.086	119		1.37	0.96	1.96	0.22
			0.087 to 0.126	88		1.08	0.74	1.58	0.20
			0.127 to 0.193	48		1.04	0.66	1.63	0.14
			0.194 to 0.277	21		1.33	0.71	2.49	0.07
			0.278 to 0.330	3		0.41	0.11	1.50	0.02
			0.331 to 2.484	14		1.36	0.63	2.90	0.05
Lewis et al. 1999[a] (Table 4)	U.S.	Cohort	All exposure groups: < 1,000 ppb-years to ≥ 5,000 ppb-years:		SMR				
			Men	3		0.42	0.08	1.22	0.03
			Women	2		0.81	0.10	2.93	0.02
Steinmaus et al. 2003[b] (Table 3)	U.S.	Case-control	Cumulative dose (mg):		OR				
			< 6.4 (referent)	153					
			6.4 to 82.8	9		1.63	0.64	4.13	0.03
			> 82.8	19		1.40	0.73	2.70	0.07
					Summary Relative Risk = 1.179		**95%CI: 0.996–1.396**		
					p-value for Heterogeneity =	0.633			

Note: OR - odds ratio
SMR - standardized mortality ratio

[a] Cohort presumed to be nonsmokers.

[b] Analysis based on 40-year lag.

Table B-25. Arsenic exposure and risk of bladder cancer among NEVER SMOKERS: Study-specific upper exposure categories collapsed and recalculated (findings from studies conducted in the United States)

Study	Study Country	Study Design	Study-Specific Arsenic Exposure Range	Observed Cases or Deaths Among "Exposed"	Type of Relative Risk Estimate	Estimate[a]	Lower Bound[b]	Upper Bound[b]	Relative Weight of Study
Bates et al. 1995	U.S.	Case-control	Cumulative dose: 19 to ≥ 53 mg vs. < 19 mg	21	OR	0.9375	0.3861	2.3577	0.20
Karagas et al. 2004	U.S.	Case-control	Toenail concentrations: 0.06 to 2.284 mcg/g vs. < 0.059 mcg/g	56	OR	0.9688	0.5020	1.9297	0.36
Lewis et al. 1999[c]	U.S.	Cohort	All exposure groups: < 1,000 ppb-years to ≥ 5,000 ppb-years	5	SMR	0.5155	0.1889	1.143	0.27
Steinmaus et al. 2003[d]	U.S.	Case-control	Cumulative dose: 6.4 to > 82.8 mg vs. < 6.4 mg	6	OR	0.8889	0.3031	2.3520	0.18
						Summary Relative Risk = 0.801	**95% CI: 0.531–1.208**		
						p-value for Heterogeneity =	0.653		

Note: OR - odds ratio
SMR - standardized mortality ratio

[a] Individual crude estimates based on recalculated collapsed exposure category data; calculated using *Episheet*.

[b] Mid-*p* confidence limits.

[c] Cohort presumed to be non-smokers, combined men and women and recalculated SMR.

[d] Analysis based on 40-year lag.

Table B-26. Arsenic exposure and risk of bladder cancer among NEVER SMOKERS: Study-specific exposure categories analyzed (findings from studies conducted in the United States)

Study (Data Source)	Study Country	Study Design	Study-Specific Arsenic Exposure Range	Observed Cases or Deaths Among "Exposed"	Type of Relative Risk Estimate	Estimate	Lower Bound	Upper Bound	Relative Weight of Study
Bates et al. 1995 (Table 3)	U.S.	Case-control	Cumulative dose (mg):		OR				
			< 19 (referent)	10					
			19 to < 33	10		1.09	0.4	3.1	0.10
			33 to < 53	7		0.68	0.2	2.3	0.07
			≥ 53	4		0.53	0.1	1.9	0.07
Karagas et al. 2004 (Table 2)	U.S.	Case-control	Toenail concentrations (mcg/g):		OR				
			0.009 to 0.059 (referent)	15					
			0.060 to 0.086	20		0.85	0.38	1.91	0.17
			0.087 to 0.126	22		1.18	0.53	2.66	0.17
			0.127 to 0.193	11		1.10	0.42	2.90	0.12
			0.194 to 0.277	3		0.49	0.12	2.05	0.05
			0.278 to 0.330	0		--	--	--	
			0.331 to 2.484	0		--	--	--	
Lewis et al. 1999[a] (Table 4)	U.S.	Cohort	All exposure groups: < 1,000 ppb-years to ≥ 5,000 ppb-years:		SMR				
			Men	3		0.42	0.08	1.22	0.10
			Women	2		0.81	0.10	2.93	0.07
Steinmaus et al. 2003[b] (Table 4)	U.S.	Case-control	Cumulative dose (mg):		OR				
			< 6.4 (referent)	23					
			6.4 to 82.8	3		2.65	0.49	14.24	0.04
			> 82.8	3		0.50	0.12	2.05	0.05
					Summary Relative Risk = 0.829		**95% CI: 0.596–1.155**		
					p-value for Heterogeneity =	0.789			

Note: OR - odds ratio
SMR - standardized mortality ratio

[a] Cohort presumed to be nonsmokers.

[b] Analysis based on 40-year lag.

Table B-27. Arsenic exposure and risk of bladder cancer among EVER SMOKERS: Study-specific upper exposure categories collapsed and recalculated (findings from studies conducted in the United States)

Study	Study Country	Study Design	Study-Specific Arsenic Exposure Range	Observed Cases or Deaths Among "Exposed"	Type of Relative Risk Estimate	Estimate[a]	Lower Bound[b]	Upper Bound[b]	Relative Weight of Study
Bates et al. 1995	U.S.	Case-control	Cumulative dose: 19 to ≥ 53 mg vs. < 19 mg	36	OR	3.4737	1.1541	12.519	0.11
Karagas et al. 2004	U.S.	Case-control	Toenail concentrations: 0.06 to 2.284 mcg/g vs. < 0.059 mcg/g	237	OR	1.1949	0.8566	1.6716	0.59
Steinmaus et al. 2003[c]	U.S.	Case-control	Cumulative dose: 6.4 to > 82.8 mg vs. < 6.4 mg	22	OR	1.6834	0.8705	3.2674	0.30
					Summary Relative Risk = 1.484		**95% CI: 0.950–2.318**		
					p-value for Heterogeneity =	0.221			

Note: OR = odds ratio

[a] Individual crude estimates based on recalculated collapsed exposure category data; calculated using *Episheet*.

[b] Mid-*p* confidence limits.

[c] Analysis based on 40-year lag.

Table B-28. Arsenic exposure and risk of bladder cancer among EVER SMOKERS: Study-specific exposure categories analyzed from studies conducted in the United States

Study (Data Source)	Study Country	Study Design	Study-Specific Arsenic Exposure Range	Observed Cases or Deaths Among "Exposed"	Type of Relative Risk Estimate[a]	Estimate	Lower Bound	Upper Bound	Relative Weight of Study[a]
Bates et al. 1995 (Table 3)	U.S.	Case-control	Cumulative dose (mg):		OR				
			< 19 (referent)	4					
			19 to < 33	11		3.33	1.0	10.8	0.04
			33 to < 53	10		1.93	0.6	6.2	0.04
			≥ 53	15		3.32	1.1	10.3	0.05
Karagas et al. 2004 (Table 2)	U.S.	Case-control	Toenail concentrations (μg/g):		OR				
			0.009 to 0.059 (referent)	75					
			0.060 to 0.086	99		1.53	1.02	2.29	0.20
			0.087 to 0.126	66		1.02	0.66	1.56	0.19
			0.127 to 0.193	37		1.00	0.60	1.67	0.15
			0.194 to 0.277	18		1.78	0.86	3.67	0.10
			0.278 to 0.330	3		0.50	0.13	1.88	0.04
			0.331 to 2.484	14		2.17	0.92	5.11	0.07
Steinmaus et al. 2003[b] (Table 4)	U.S.	Case-control	Cumulative dose (mg):		OR				
			< 6.4 (referent)	130					
			6.4 to 82.8	6		1.06	0.34	3.33	0.05
			> 82.8	16		2.25	0.97	5.20	0.08
					Summary Relative Risk = 1.462		**95% CI: 1.124–1.902**		
					p-value for Heterogeneity =	0.183			

Note: OR - odds ratio

[a] Relative weight of study will be determined when meta-analysis is performed.

[b] Analysis based on 40-year lag.

Appendix C

Relative Influence of Each Study on the Overall Model-Specific Meta-relative Risk Estimate (by corresponding table)

Relative Influence of Each Study on the Overall Model-Specific Meta-relative Risk Estimate (by corresponding table)

Table C-1. Combined: Collapsed categories (Table B-1)

Study Excluded	mRR	95% CI	*p*-Value for Heterogeneity	mRR Change
Overall Analysis	**1.079**	**0.816 to 1.425**	**0.056**	
Bates et al. 1995	1.024	0.763 to 1.374	0.058	0.055
Karagas et al. 2004	1.066	0.736 to 1.543	0.031	0.013
Lewis et al. 1999	1.153	0.888 to 1.495	0.123	–0.074
Steinmaus et al. 2003	1.067	0.765 to 1.489	0.031	0.012
Bates et al. 2004	1.17	0.903 to 1.517	0.15	–0.091
Chiou et al. 2001	1.001	0.768 to 1.305	0.135	0.078
Michaud et al. 2004	1.065	0.748 to 1.515	0.031	0.014

Table C-2. Combined: All exposure categories (Table B-2)

Study Excluded	mRR	95% CI	*p*-Value for Heterogeneity	mRR Change
Overall Analysis	**1.109**	**0.948 to 1.298**	**0.207**	
Bates et al. 1995	1.083	0.907 to 1.292	0.141	0.026
Karagas et al. 2004	1.074	0.856 to 1.346	0.122	0.035
Lewis et al. 1999	1.138	0.976 to 1.327	0.263	–0.029
Steinmaus et al. 2003	1.082	0.915 to 1.28	0.167	0.027
Bates et al. 2004	1.174	1.023 to 1.347	0.527	–0.065
Kurttio et al. 1999	1.111	0.94 to 1.314	0.175	–0.002
Chiou et al. 2001	1.102	0.962 to 1.263	0.437	0.007
Michaud et al. 2004	1.097	0.898 to 1.34	0.105	0.012

Table C-3. Never smokers: Collapsed categories (Table B-3)

Study Excluded	mRR	95% CI	*p*-Value for Heterogeneity	mRR Change
Overall Analysis	**0.763**	**0.519 to 1.12**	**0.724**	
Bates et al. 1995	0.73	0.478 to 1.114	0.608	0.033
Karagas et al. 2004	0.684	0.431 to 1.087	0.708	0.079
Lewis et al. 1999	0.859	0.554 to 1.332	0.837	–0.096
Steinmaus et al. 2003	0.741	0.488 to 1.126	0.583	0.022
Bates et al. 2004	0.801	0.531 to 1.208	0.654	–0.038

Table C-4. Never smokers: All exposure categories (Table B-4)

Study Excluded	mRR	95% CI	*p*-Value for Heterogeneity	mRR Change
Overall Analysis	**0.808**	**0.603 to 1.083**	**0.937**	
Bates et al. 1995	0.817	0.59 to 1.131	0.869	–0.009
Karagas et al. 2004	0.728	0.499 to 1.061	0.897	0.08
Lewis et al. 1999	0.855	0.625 to 1.17	0.944	–0.047
Steinmaus et al. 2003	0.795	0.586 to 1.077	0.969	0.013
Bates et al. 2004	0.838	0.614 to 1.194	0.898	–0.03
Kurttio et al. 1999	0.797	0.585 to 1.086	0.871	0.011

Table C-5. Ever smokers: Collapsed categories (Table B-5)

Study Excluded	mRR	95% CI	*p*-Value for Heterogeneity	mRR Change
Overall Analysis	**1.206**	**0.876 to 1.662**	**0.162**	
Bates et al. 1995	1.142	0.875 to 1.491	0.287	0.064
Karagas et al. 2004	1.248	0.748 to 2.082	0.088	–0.042
Steinmaus et al. 2003	1.131	0.786 to 1.628	0.148	0.075
Bates et al. 2004	1.285	0.98 to 1.684	0.307	–0.079
Michaud et al. 2004	1.275	0.78 to 2.084	0.093	–0.069

Table C-6. Ever smokers: All exposure categories (Table B-6)

Study Excluded	mRR	95% CI	*p*-Value for Heterogeneity	mRR Change
Overall Analysis	**1.241**	**0.988 to 1.559**	**0.032**	
Bates et al. 1995	1.147	0.917 to 1.434	0.068	0.094
Karagas et al. 2004	1.239	0.877 to 1.75	0.024	0.002
Steinmaus et al. 2003	1.209	0.95 to 1.538	0.028	0.032
Bates et al. 2004	1.338	1.101 to 1.626	0.215	–0.097
Kurttio et al. 1999	1.216	0.972 to 1.522	0.043	0.025
Michaud et al. 2004	1.299	0.954 to 1.769	0.012	–0.058

Note: CI - confidence interval
mRR - meta-relative risk