OAPTF

Organic Arsenical Products Task Force

Luxembourg-Pamol, Inc. • Drexel Chemical Company

November 15, 2010

Via E-Mail

Angela Nugent, Ph.D.
Designated Federal Officer
Science Advisory Board (1400R)
U.S. Environmental Protection Agency
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Re: Comments for November 22, 2010, Public Teleconference of the Chartered SAB to Conduct a Quality Review of an SAB Workgroup Review of an EPA Draft Report, "Toxicological Review of Inorganic Arsenic: . . . Summary Information on the Integrated Risk Information System (IRIS)" (External Review Draft , February 2010)

Dear Dr. Nugent:

These comments are submitted by the Organic Arsenical Products Task Force (OAPTF)[1] in connection with the forthcoming November 22, 2010, public teleconference recently announced by the U.S. Environmental Protection Agency (EPA) Science Advisory Board (SAB) to conduct a quality review of a revised draft report from an SAB Workgroup that addresses the February 2010 external review draft "Toxicological Review of Inorganic Arsenic: . . . Summary Information on the Integrated Risk Information System (IRIS)" (draft IRIS Assessment).[2] As is evident from the summary in the *Federal Register* notice announcing the teleconference, and from the activities underway throughout 2010, SAB and Workgroup review of the draft IRIS Assessment is ongoing, with an eye to revising, updating, and refining the draft to reflect the best available science.

It has come to our attention that EPA employees who are in lead roles in developing the draft IRIS Assessment -- and who, as such, would be expected to act as even-handed scientists, open to fresh information and an evolving database -- have in effect pre-judged key factors in the Assessment and have gone public with those judgments by publishing

[1] The OAPTF consists of Drexel Chemical Co. and Luxembourg-Pamol, Inc.

[2] 75 Fed. Reg. 65481 (Oct. 25, 2010).

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an article in a widely-read, open-access journal. By their action, these employees have crossed a boundary into a realm of questionable judgment, raising concerns about the intellectual integrity of this critically important toxicological review and assessment process.

The particulars are as follows. In October 2010, many months into the current SAB review of EPA's draft IRIS Assessment, several EPA scientists and contractors published in the National Institute of Environmental Health Sciences' journal *Environmental Health Perspectives* (*EHP*) an article entitled "Utility of Recent Studies to Assess the National Research Council 2001 Estimates of Cancer Risk From Ingested Arsenic" (*EHP* article or Utility of Recent Studies article).[3] The stated objective was "to evaluate the impact of recent epidemiological literature on the National Research Council's (NRC 2001) assessment of lung and bladder cancer risks from ingesting low concentrations (< 100 μ/L) of arsenic-contaminated water."[4]

EPA's current draft IRIS Assessment, in addressing cancer risks associated with inorganic arsenic in drinking water, relies largely on the methodology and data from the NRC 2001 study that is the focus of the *EHP* article. The NRC 2001 methodology and data are among the key aspects of the draft IRIS Assessment that have been criticized severely in the public comments on the draft and, as such, presumably are subject to enhanced scrutiny by SAB reviewers. In the view of these public commenters, EPA's risk estimates, based on the cancer slope factor proposed in the draft IRIS Assessment -- which rely primarily on data from Taiwan -- are inconsistent with post-NRC 2001 data from the U.S. and abroad that show an absence of adverse health effects from low-level exposures to arsenic in drinking water. These commenters also have observed that EPA has not afforded due consideration to the data from the newer studies published during the last decade.

The *EHP* article states that the authors reviewed 14 post-NRC 2001 epidemiological studies of lung and/or bladder cancer risk deemed useful for analysis and have concluded that these studies "lack either the statistical power or the information necessary to evaluate the NRC bladder and lung cancer risk estimates."[5] The authors further conclude that

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[3] Herman Gibb, *et al.*, *Utility of Recent Studies to Assess the National Research Council 2001 Estimates of Cancer Risk From Ingested Arsenic*, Environmental Health Perspectives, ephonline.org (Oct. 28, 2010), available at http://dx.doi.org. A copy of the article is appended.

[4] *Id*. at 3.

[5] *Id*. at 21.

although "the ecologic nature of the Taiwanese studies on which the NRC [2001] estimates are based present certain limitations," the study data have "particular strengths in that they describe lung and bladder cancer risks resulting from lifetime exposure in a large population and remain the best data on which to do quantitative risk assessment."[6] These conclusions essentially reiterate EPA's position on the cancer slope factor-based risk estimates taken in the draft IRIS Assessment and throughout the SAB review process to date. Coincidentally or not, they also appear to reinforce one of the weakest and most controversial aspects of the draft Assessment.[7]

On closer inspection, the similarities between the conclusions in the October 2010 *EHP* article and the February 2010 draft IRIS Assessment are not surprising; there is significant overlap among the authors -- indeed, the lead authors of the draft IRIS Assessment are among the authors of the *EHP* article. Specifically, the authors of the *EHP* article include two EPA scientists -- Reeder Sams and Santhini Ramasamy -- employed, respectively, by EPA's National Center for Environmental Assessment and EPA's Office of Water.[8] Dr. Ramasamy is listed as the lead author, and Dr. Sams as the co-lead author, of the draft IRIS Assessment.[9] Thus, EPA's two leaders of the IRIS Assessment effort have donned authorial hats in connection with the "Utility of Recent Studies" article -- a literature review that addresses, and opines categorically, on issues at the core of the IRIS Assessment.

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6 *Id*. at 3.

7 For example, while the Taiwanese study population was large, measurement methods when the data were developed some 60 years ago were very different, such that those data are now questionable in several key aspects. Because of the weak evidence from the Taiwanese data, EPA is inappropriately relying on a set of chosen assumptions for the calculation of the slope factor. The OAPTF and others have addressed this issue in previously-submitted comments.

8 Gibb, *et al.*, *supra* note 3, at 1.

9 U.S. Environmental Protection Agency, *Toxicological Review of Inorganic Arsenic: Summary Information on the Integrated Risk Information System (IRIS)* (Mar. 2009) at ix. At the time the draft IRIS Assessment was prepared, Dr. Ramasamy was with EPA's Office of Science and Technology in the Office of Water, and Dr. Sams was with EPA's National Center for Environmental Assessment.

Two more EPA employees, Dr. Chao Chen and Mr. Paul White, both of the National Center for Environmental Assessment, also are among the authors of the *EHP* article while also listed as contributors to the draft IRIS Assessment.[10] Additionally, EPA employees Dr. Danelle Lobdell and Dr. Timothy Wade, both among the authors of the *EHP* article, served as internal EPA reviewers for the draft IRIS Assessment.[11] Indeed, there is only one EPA employee among the authors of the *EHP* article who (along with the private sector-contractor authors) is *not* listed as a lead author, co-author, contributor, or internal reviewer of the draft IRIS Assessment. Preparation of the *EHP* article was funded by EPA's National Center for Environmental Assessment, which, along with EPA's Office of Water, reviewed the piece and approved it for publication.[12] A disclaimer states, nonetheless, that the views expressed in the article do not necessarily reflect the views or policies of EPA.[13]

While the coinciding viewpoints between the *EHP* article and the draft IRIS Assessment is hardly surprising -- based on the overlap in authorship -- what *is* both surprising and troubling is that key EPA employees actively engaged with a still-evolving draft document currently undergoing SAB review and subject to public participation, would step, midstream, into what is, in effect, a simultaneous advocacy role in another forum.[14] While the author-employees might assert that they simply are presenting the results of a literature review to interested readers in the environmental health field, this does not alter the conclusion that they are -- most inappropriately -- wearing two hats. This is one hat too many. Not only does the timing of the "Utility of Recent Studies" article raise questions about its purpose, but the repetition of positions taken in the draft IRIS Assessment process seems to underscore that the EPA employees most instrumental in developing and refining the Assessment are implacably

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10 Gibb, *et al.*, *supra* note 3, at 1; Draft IRIS Assessment, *supra* note 9, at x.

11 Gibb, *et al.*, *supra* note 3, at 1; Draft IRIS Assessment, *supra* note 9, at xi, xii.

12 Gibb, *et al.*, *supra* note 3, at 2.

13 *Id.*

14 EPA employees have advocated in defense of these data in yet another outside forum. A poster with similar information appeared at the annual meeting of the Society of Toxicology (SOT) in March 2010, ahead of the April 2010 SAB Workgroup meeting. Given the SOT audience, the poster might be considered an effort to influence the forthcoming SAB review.

wedded to their original positions and unwilling to give serious credence to the more recent studies discussed in detail in the public comments.

At a minimum, the publication of the *EHP* article by lead scientists for, and contributors to, the draft IRIS Assessment raises questions about whether these EPA employees are sufficiently open-minded to give genuine consideration and credence to competing viewpoints as the IRIS Assessment process continues. The apparent tunnel-vision evidenced in the article likewise raises questions about their scientific objectivity -- whether they are stuck in a universe of data at least a decade old, data that were open to viable criticism even at the time of the NRC 2001 report.

The disclaimer preceding the *EHP* article that the views expressed there are not necessarily those of EPA fails to address adequately this situation. Although the fact that the literature review summarized in the article was funded by EPA is not necessarily inconsistent with such a disclaimer, the real-world meaning becomes fuzzy when the EPA scientists expressing views in the article are the same ones spearheading the development of the draft IRIS Assessment. This concern is reinforced by the absence of any mention in the article of the overlap between its co-authors and the authors of the draft Assessment, an omission that is puzzling under the circumstances.

These overlapping roles raise Information Quality Act (IQA)[15] concerns as well. Although the draft IRIS Assessment notes that it is not to be considered a "dissemination" of information for IQA purposes,[16] it goes without question that the final version will qualify as a dissemination by EPA of highly "influential scientific risk assessment information" subject to the highest standards of quality.[17] If the final version reflects the same unwillingness to consider fairly the post-2001 data on low-concentration arsenic exposures that is reflected in both the draft

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15 Treasury and General Government Appropriations Act for Fiscal Year 2001, Pub. L. No. 106-554, § 515(a), 44 U.S.C. § 3516 (notes).

16 Draft IRIS Assessment, *supra* note 9, at ii.

17 U.S. Environmental Protection Agency, Guidelines for Ensuring and Maximizing the Quality, Objectivity, Utility, and Integrity of Information Disseminated by the Environmental Protection Agency, EPA/260R-02-008 (Oct. 2002) at 21-22.

Assessment and the *EHP* article, the "objectivity" and the consequent "utility" of the final Assessment will be subject to question.[18]

Additionally, even if the draft IRIS Assessment is not a dissemination of information by EPA, arguably the publication of the article in question in the *EHP* is subject to IQA standards. *EHP* is a peer-reviewed monthly journal published by the National Institute of Environmental Health Sciences (NIEHS) within National Institutes of Health and the Department of Health and Human Services. According to the description on its website, "[w]ith an impact factor of 6.19, *EHP* is the top monthly journal in public, environmental, and occupational health and the second-ranked monthly journal in environmental sciences."[19] Disseminating the "Utility of Recent Studies" article in *EHP* while the IRIS Assessment process is still in review and development raises doubts, for the reasons noted above, as to the "objectivity" of the Assessment, irrespective of whether the article cleared the journal's peer-review process. Arguably, dissemination of the article through the medium of the *EHP* effectively counters EPA's assertion that the draft IRIS Assessment is not subject to information quality standards. Certainly, disseminating the article without disclosing several of the authors' connection to the IRIS Assessment is an omission that should be corrected.

At this point in the SAB's review of the draft IRIS Assessment, it is not too late -- although time is dwindling -- for the SAB reviewers to articulate to EPA the steps the latter must take to objectify and improve the Assessment development process for inorganic arsenic. We suggest the following:

- The SAB should not accept the IRIS Assessment as final and should direct that it must be revised to take account of scientific literature that so far has been omitted. EPA also should be directed, in so doing, to give fair and realistic consideration to research that may support points of view different from those to which EPA has adhered over the years.

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18 *See id*. at 15 (referring to "objectivity" as "whether the disseminated information is being presented in an accurate, clear, complete, and unbiased manner, and as a matter of substance, is accurate, reliable, and unbiased" and "utility" as "the usefulness of the information to the intended users."). Information that does not meet the "objectivity" criterion is unlikely, also, to be useful to the intended users.

19 *See* Environmental Health Perspectives, EHP Journal Information at http://ehp03.niehs.nih.gov/static/information/action.

- The SAB should direct EPA to provide full answers to the recommendations in the 2007 SAB report.

- The SAB should conduct a review of the draft Assessment in full, a step that has not been taken. Publication of the "Utility of Recent Studies" article, among other publications, have suggested that lead EPA participants have a preconceived agenda. Accordingly, the SAB's review should be thorough, going beyond the charge questions and looking at all aspects of the Assessment, including those de-emphasized by EPA.

Beyond this, EPA employees and contractors should forbear from publishing or otherwise presenting their positions on scientific issues connected with the IRIS Assessment process while it is still underway, and they similarly should forbear from engaging in any conduct that could be considered advocacy for those positions, whether in a separate governmental or non-governmental forum of any kind.

The OAPTF appreciates the SAB's consideration of these comments. Please let us know if you have any questions.

Sincerely,

Michal Eldan, Ph.D.

Attachment
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Ms. Rebecca M. Clark (w/attachment) (via e-mail)
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Utility of Recent Studies to Assess the National Research Council 2001 Estimates of Cancer Risk from Ingested Arsenic

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NIEHS
National Institute of Environmental Health Sciences

National Institutes of Health
U.S. Department of Health and Human Services

Utility of Recent Studies to Assess the National Research Council 2001 Estimates of Cancer Risk from Ingested Arsenic

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Short running head: Recent Studies on Arsenic and Lung/Bladder Cancer

Key words: arsenic, bladder, cancer, dose response, drinking water, lung, risk assessment

Abbreviations used in the manuscript:

As	arsenic
BMI	Body Mass Index
CI	confidence interval
L	liter
MCL	Maximum Contaminant Level
NRC	National Research Council
OR	odds ratio
RR	relative risk
SE	standard error
SEER	Surveillance Epidemiology End Results
SMR	Standardized Mortality Ratio
U.S. EPA	United States Environmental Protection Agency
µg	microgram

Abstract

Objective: The purpose of this review is to evaluate the impact of recent epidemiologic literature on the National Research Council's (NRC 2001) assessment of the lung and bladder cancer risks from ingesting low concentrations (< 100 μg/L) of arsenic-contaminated water.

Data Sources, Extraction and Synthesis: PubMed was searched for epidemiologic studies pertinent to the lung and bladder cancer risk estimates from low-dose arsenic exposure. Articles published from 2001, the date of the National Research Council's assessment, through September 2010 were included. Fourteen epidemiologic studies on the lung and/or bladder cancer risk were identified as potentially useful for the analysis.

Conclusions: Recent epidemiologic studies investigating the risk of lung and bladder cancer from low arsenic exposure are limited in their ability to detect the NRC estimates of risk because of size and less than lifetime exposure. Although the ecologic nature of the Taiwanese studies on which the NRC estimates are based present certain limitations, the data from these studies have particular strengths in that they describe lung and bladder cancer risks resulting from lifetime exposure in a large population and remain the best data on which to do quantitative risk assessment. Continued followup of a population in northeastern Taiwan, however, offers the best opportunity to improve the cancer risk assessment for arsenic in drinking water. Future studies of arsenic < 100 μg/L in drinking water and lung and bladder cancer risk should consider adequacy of the sample size, the synergistic relationship of arsenic and smoking, duration of arsenic exposure, age when exposure began and ended, and histologic subtype.

INTRODUCTION

In 1996, U.S. EPA's Office of Water requested the National Research Council (NRC) to independently review the available scientific database for the health effects of arsenic in drinking water and evaluate the validity of the 1988 assessment. The result was NRC's report, *Arsenic in Drinking Water* (NRC 1999). The report analyzed bladder cancer risks from arsenic ingestion using mortality data from a southwest Taiwanese population (Wu et al. 1989; Chen et al. 1992).

In January 2001, EPA issued a Maximum Contaminant Level (MCL) of 10 µg/L for arsenic (U.S. EPA 2001a) using the newly available data. The January 23, 2006 compliance date for the arsenic standard, gave EPA time to reassess the scientific and cost issues and to seek further public input on the arsenic regulation (U.S. EPA 2001b). As part of this re-evaluation, the NRC was requested to update its 1999 report. The resulting report, *Arsenic in Drinking Water – 2001 Update* (NRC 2001), concluded that: (1) there was a sound database on the carcinogenic effects of arsenic in humans that was adequate for the purpose of risk assessment and (2) lung and bladder cancer should continue to be the focus of arsenic risk assessment for regulatory decision-making. The NRC report also concluded that the human data from southwestern Taiwan (Chen et al. 1992; Chen et al. 1988a; Wu et al. 1989), used by U.S. EPA (2001a) in its risk assessment, remained the most appropriate data to determine lifetime cancer risk estimates. Table 1 contains the NRC estimates of excess lifetime lung and bladder cancer risks.

The purpose of this review is to evaluate whether the recent literature on arsenic and lung and bladder cancer is consistent with, or contradicts, the NRC (2001) with respect to cancer risk at low (≤ 100 µg As/L) concentrations of arsenic in drinking water. PubMed was searched for all epidemiology studies on arsenic in drinking water and lung/bladder cancer published since 2001

through September 2010. Search terms used included arsenic, water, cancer, lung or bladder, and epidemiology. As of September 2010, 195 studies and articles were identified in a PubMed search. Studies considered in this review specifically assessed lung and bladder cancer outcomes and exposure to low levels (≤ 100 μg/L) of arsenic in drinking water. Studies not assessing lung and bladder cancer from low arsenic exposure and studies not specific to exposure from drinking water were excluded. Fourteen epidemiologic studies which examined the risk of lung and bladder cancer from low arsenic concentrations (≤ 100 μg/L) in drinking water were identified (Baastrup et al. 2008; Bates et al. 2004; Chen et al. 2010a; Chen et al. 2010b; Chen et al. 2004; Han et al. 2009; Heck et al. 2009; Karagas et al. 2004; Lamm et al. 2004; Meliker et al. 2010; Meliker et al. 2007; Michaud et al. 2004; Mostafa et al. 2008; Steinmaus et al. 2003).

Ability of an Epidemiology Study to Detect the Excess Risks Estimated by NRC (2001)

The lung and bladder cancer risks estimated by NRC (2001) were based on an ecological study of a population in an arsenic-endemic area of southwest Taiwan. The study was unique in many aspects. Exposure began early in the 20th Century, and the population was extremely stable (Wu et al. 1989). Chen et al. (1992) commented that the affected population lived in a confined area and shared similar socioeconomic status, living environments, lifestyles, dietary patterns, and even medical facilities; the only major difference in environmental exposures in the population appeared to be the differences in arsenic concentrations in drinking water. Assuming that the effect of arsenic is additive to the background risk, risks of arsenic-induced lung and, in particular, bladder cancer would be easier to detect in Taiwan than in the United States because of lower background risks in Taiwan. The age-adjusted bladder cancer incidence is 4 times lower in southeastern Asia than in North America; the age-adjusted lung cancer incidence is

about 40% lower in males and about three times lower in females in southeastern Asia than in North America (IARC 2008).

While many strengths existed for quantitative risk assessment, the study had some limitation given its ecologic design. Drinking water arsenic concentrations for those in the study were based on the median value for the wells in the village. NRC recognized that use of the median value presented some uncertainty, but a sensitivity analysis suggested that use of the median value would present little effect on the risk estimate (NRC 2001). NRC further commented that the use of an external comparison population minimized the effect of exposure misclassification on the risk assessment.

The arsenic exposure in the southwest Taiwan population was reported to have begun about 1900 to 1910 (Tseng et al. 1968). The arsenic exposure therefore could be considered to be life-long in the population that was the basis of the NRC cancer risk estimates. This is a particularly important consideration if the latency period from exposure to development of disease is long or if arsenic has different effects at different life stages. While data on arsenic concentrations do not exist for each year that the population was exposed, Chen et al. (1988b) indicate that arsenic concentrations in the wells in the endemic area were stable over an approximately 13-year period, and it is reasonable to assume that the concentrations were stable over a longer period of time.

For several reasons, it would be difficult for epidemiologic studies to detect the NRC estimated cancer risks in the United States. First, the excess lung and bladder cancer lifetime risks for low arsenic exposures are small compared to the background lifetime risks for these diseases. At 10 μg As/L, U.S. EPA's current MCL for arsenic in drinking water (U.S. EPA 2001c), the excess

risk for lung cancer would be 30-50-fold lower than the lifetime risk of lung cancer in the U.S. The excess risk for bladder cancer would be approximately 8-14-fold lower than the lifetime risk of bladder cancer in the U.S. The gender-specific lung and bladder cancer excess and relative risks (RR) from lifetime exposure to 10 µg As/L, are compared in Table 2. The excess risk is the risk derived by the NRC for 10 µg As/L; the RR is the excess risk plus the background risk in the U.S. (SEER 2006a,b) divided by the background risk. The highest RR estimated from arsenic in drinking water is for bladder cancer in females, largely a result of the fact that the background risk for bladder cancer in females in the United States (0.0094, See Table 2) is the lowest among those considered (lung cancer males, females; bladder cancer males, females). Age-standardized male and female lung and bladder cancer incidence follows a similar pattern worldwide (female bladder cancer incidence < incidence of male bladder cancer, female lung cancer, male lung cancer) (IARC 2007). Evidence that the RRs from arsenic exposure in the drinking water are highest for bladder cancer in females is supported by studies in Chile (Marshall et al. 2007) and Taiwan (Chen et al. 1985).

Secondly, the study population on which the NRC estimates are based is determined to have lifetime or near to lifetime exposure. Finding other populations with lifetime exposure would be difficult. In addition to the shorter exposure duration experienced by those with less than lifetime exposure, exposures at some life stages (e.g. infant vs. adult) could present more risk than at other life stages (Halmes et al. 2000; Waalkes et al. 2007; Smith et al. 2006). Both of these exposure issues would diminish the ability of a study to detect the risks estimated by NRC.

Finally, dietary arsenic would play a much greater role in misclassification of exposure at low doses than it would at high doses (Uchino et al. 2006; Kile et al. 2007; Cantor and Lubin 2007).

As the NRC noted, the detection of the theoretical risks which they estimated would require a large population consuming drinking water containing arsenic over an extended period of time.

Table 3 demonstrates the sample sizes needed to detect the bladder cancer risk from lifetime arsenic exposure in females based on the NRC estimates and a background lifetime bladder cancer risk among females in the U.S. from SEER (2006a,b), assuming 80% statistical power and a Type I error (false positive rate) of $p = 0.05$. Sample sizes were estimated using STATA 10. The sample size needed to detect an excess bladder cancer risk in females is smaller than the sample size needed to detect a lung cancer risk in females or a lung or bladder cancer risk in males since the RR for bladder cancer in females is greater (Table 2). Less than lifetime exposure and exposure misclassification will increase the sample sizes described in Table 3. Furthermore, if lung and bladder cancer risks exist at low doses, they could be overestimated by the NRC's linear model of high dose exposure. Thus, for several reasons, the sample sizes described in Table 3 are conservative, and the sample sizes required to detect arsenic-induced cancer risks could actually be much greater. The approach used for the sample size calculations presented in Table 3 is also applicable to unmatched case-control studies. It should be clear that sample size calculations are essentially approximate, and it is not practical to present here more precise calculations under all conceivable conditions (e.g., matched vs. unmatched, discrete vs. continuous variables etc). Even under the same condition such as discrete (or categorized) variable, the sample size can depend on the number of categories involved. For instance, it has been demonstrated by Metha and Hilton (1993) and others that sample sizes calculated under conditional and non-conditional distributions could differ significantly depending on the number of categories for the target variable involved.

EPIDEMIOLOGY STUDIES CONDUCTED SINCE THE NRC REPORT

The epidemiologic studies examining the risk of lung and/or bladder cancer risk published since NRC (2001) include four cohort (Baastrup et al. 2008; Chen et al. 2004, Chen et al. 2010a; Chen et al. 2010b), seven case-control (Bates et al. 2004; Heck et al. 2009; Karagas et al. 2004; Michaud et al. 2004; Mostafa et al. 2008; Steinmaus et al. 2003; Meliker et al. 2010), and three ecologic studies (Han et al. 2009; Lamm et al. 2004; Meliker et al. 2007). Seven studies examined bladder cancer risk (Chen et al. 2010b, Meliker et al. 2010, Bates et al. 2004, Karagas et al. 2004, Michaud et al. 2004, Lamm et al. 2004, Steinmaus et al. 2003), four examined lung cancer risk (Chen et al. 2010a, Heck et al. 2010, Mostafa et al. 2010, Chen et al. 2004) and three examined both lung and bladder cancer risk (Han et al. 2009, Baastrup et al. 2008, Meliker et al. 2007). Of these 14 studies, 11 used arsenic concentration in drinking water as the measure of arsenic exposure (Baastrup et al. 2008; Bates et al. 2004; Chen et al. 2004; Chen et al. 2010a; Chen et al. 2010b; Han et al. 2009; Heck et al. 2009; Lamm et al. 2004; Meliker et al. 2007; Meliker 2010; Mostafa et al. 2008; Steinmaus et al. 2003). Three studies (Heck et al. 2009; Karagas et al. 2004; Michaud et al. 2004) examined toenail arsenic as a surrogate measure of exposure. Toenail arsenic is believed to primarily represent ingested arsenic. Table 4 briefly describes the 14 epidemiologic studies and indicates whether there is any evidence of significantly ($p < 0.05$) increased lung or bladder cancer risks associated with drinking water concentrations < 100 µg As/L. Brief summaries of each study are provided below.

Cohort Studies

Chen et al. 2010a and 2010b studied 8,086 northeastern Taiwanese residents. Drinking water concentration was reported at time of enrollment. A total of 3,901 well water samples were

collected from 4,584 (85.1 percent) households during the home interview. No information on the arsenic concentration of the well water at prior residences was obtained. Detailed residential history and corresponding well-water arsenic concentration were used to calculate cumulative exposure as well as starting and ending age of exposure and duration of exposure. Chen et al. 2010a studied various exposure metrics such as the effect of age when started or stopped drinking water containing arsenic, years of drinking well water, and cumulative exposure in estimating lung cancer risk. Relative risks were adjusted for age, gender, education, cigarette smoking status, and alcohol consumption at enrollment. The relative risks (RR) and 95% confidence intervals (CI) for 100 to 300 and > 300 µg As/L when compared to < 10 µg As/L were 1.54 (0.97, 2.46) and 2.25 (1.43, 3.55), respectively. There was no apparent increased risk at concentrations between 10 and 100 µg As/L, but when duration of exposure was accounted for, all levels of exposure including low concentrations were in the direction of an increased risk of lung cancer. These associations tended to increase with longer durations of exposure. A synergistic effect of arsenic exposure and cigarette smoking was found for squamous and small cell carcinomas, but not for adenocarcinoma.

Chen et al. 2010b identified 45 incident cases of urinary cancer. Data showed a significant ($p < 0.001$) monotonic increasing risk of urinary cancer with arsenic concentration. Compared to those consuming < 10 µg As/L, the age and sex-adjusted RRs (95% CI) for 10 to 49.9, 50 to 99.9, 100 to 299.9, and ≥ 300 µg As/L were 1.7 (0.56, 5.19), 2.49 (0.73, 8.59), 4.18 (1.3, 12.8), and 7.73 (2.69, 22.3), respectively. The trend was highly significant ($p < 0.001$). Urinary cancer RRs (95% CI) for cumulative arsenic exposures 400 to 1,000, 1,000 to 5,000, 5,000 to 10,000, and ≥ 10,000 µg/L-y were 1.16 (0.29, 4.64), 2.44 (0.91, 6.5), 3.88 (1.18, 12.7), and 7.55 (2.79, 20.4), respectively, compared to < 400 µg/L-y. There was a monotonic increase in risk with

cumulative exposure. The association with arsenic was found to be strongest for urothelial cancer (transitional cell carcinoma).

Baastrup et al. 2008 reported on 56,378 Danish men and women aged 50 to 64 at enrollment between 1993 and 1997, who were followed until date of first cancer diagnosis, emigration, death or August 1, 2003. Time-weighted average exposure and cumulative exposure to arsenic were based on residential history between 1970 and 2003. Arsenic concentrations for utilities were based on data for 1987 though 2004, with most measurements taken between 2002 and 2004. The average at each water utility was assumed to represent the arsenic concentrations throughout the study period of 1970 to 2003. Questionnaires administered to study participants assessed potential lifestyle, occupational and environmental risks. Two hundred and fourteen bladder cancer cases and 402 lung cancer cases occurred during the follow-up period. The time-weighted arsenic exposure of the cohort members ranged from 0.05 to 25.3 µg/L with a median and mean concentration of 0.7 µg/L and 1.2 µg/L, respectively. Incidence rate ratios, adjusted for a variety of different variables, found no association between the time-weighted average or cumulative exposures and lung or bladder cancer. Risks were not reported by gender.

Chen et al. 2004 described 2,503 residents of southwest Taiwan and 8,088 residents of northeast Taiwan followed for an average period of 8 years. All those in the cohort had consumed arsenic-contaminated water for more than 50 years. Those in the cohort from southwest Taiwan included a group of blackfoot-diseased patients that were age, sex, and residentially matched with healthy community controls. Each study participant was administered a structured questionnaire to obtain socio-demographic, residential and occupational history, well water intake history, and cigarette and alcohol consumption information. Average arsenic

concentration in drinking water was used as the exposure metric. RRs and 95% CI were estimated by Cox proportional hazards models. Adjustment variables in the final model included age, sex, years of schooling, study cohort (blackfoot disease and matched controls; residents of the arsenic-endemic areas in southwest and northeast Taiwan), smoking status, and habitual alcohol consumption. One hundred thirty-nine new, pathologically confirmed, lung cancer cases were identified. When compared to the referent group of < 10 µg/L, the adjusted RRs (95% CIs) for lung cancers were 1.09 (0.63, 1.91); 2.28 (1.22, 4.27); 3.03 (1.62, 5.69); and 3.29 (1.60, 6.78) for average arsenic concentrations of 10 to 99, 100 to 299, 300 to 699, and > 700 µg/L, respectively. The trend was statistically significant. A strong synergism was found between arsenic in water and cigarette consumption. For those smoking ≥ 25 pack-years, RRs (95% CIs) for lung cancers were 3.8 (1.29, 11.2), 5.93 (2.19, 16.1), and 11.10 (3.32, 37.2) for average arsenic concentrations of < 10, 10 to 699, and ≥ 700 µg/L, respectively.

Case-Control Studies

Meliker et al. 2010 studied 411 bladder cancer cases and 566 controls in 11 counties of southeastern Michigan, USA. Cases diagnosed between 2000 and 2004 were ascertained from the Michigan Cancer Surveillance program. Controls were frequency matched to cases on age, gender, and race. Study participants were required to have lived in the defined area for at least five years. Water consumption, dietary habits, smoking, medical history, and residential and occupational history were determined by questionnaire. Lifetime arsenic exposure was determined based on residential history. No association between bladder cancer and arsenic concentration in drinking water was observed. Risks were not reported by gender.

Heck et al. 2009 studied 223 incident lung cancer cases from state cancer registries and 238 controls from a commercial database, frequency matched by five-year-age group and sex, in 10 counties in New Hampshire and Vermont. Participants were interviewed in-person and gave biological samples (blood, toe nail, oral buccal brushing, and mouthwash for oral cells). Arsenic exposure was based on toenail clippings. Small-cell and squamous-cell carcinoma of the lung [OR = 2.75; 95% CI = 1.00, 7.57] was associated with toenail arsenic concentration ≥ 0.114 μg/g, versus < 0.05 μg/g. The authors also observed an elevated risk of lung cancer among participants with a history of lung disease and toenail arsenic ≥ 0.05 μg/g (OR = 4.78; 95% CI = 1.87, 12.2) as compared to individuals with low toenail arsenic and no history of lung disease.

Mostafa et al. 2008 published a study of 2,811 male lung cancer cases and 1,183 male controls in Bangladesh. The study compared primary lung cancer cases to cases with benign lung lesions. Arsenic exposure was determined through a sampling of tube wells by the British Geological Survey and responses to questionnaires on residence and tube well use. Among smokers, the RRs (95% CI), in comparison to the reference group (< 10 μg As/L), were 1.25 (0.96, 1.62), 1.37 (0.92, 2.03), and 1.65 (1.25, 2.18) for concentrations 11 to 50, 51 to 100, and 101 to 400 μg As/L, respectively. Among non-smokers, there was neither an increasing trend in OR nor a statistically significant OR at any exposure level.

Bates et al. 2004 described 114 incident bladder cancer cases in Argentina from previously determined “high” and “medium” exposure counties matched on age, sex, and county with 114 controls. Cases were between the ages of 20 and 80, lived in the high and medium exposure counties between 1996 and 2000, and alive at the time of the study. Controls were identified from voter registration records. Residential history, smoking, consumption of fluids, and

occupational and medical history data was collected. Water samples were collected at the current residence and all previous residences and analyzed for arsenic. Where the well at a former residence was closed, a sample was collected from a nearby (proxy) well. Exposure was defined by average arsenic concentration, time weighted water arsenic consumption adjusted for total fluid consumption, and consumption of well water during 10-year intervals prior to the interview. No evidence of an association between measures of exposure, based on arsenic concentration, and bladder cancer was found. Well water consumption for 51 to 70 years prior to the interview was found to be associated with an increased bladder cancer risk among ever smokers (OR = 2.5; 95% CI = 1.1, 5.5) but not among never smokers. Mean, median, and range time-weighted arsenic exposure levels, respectively, were 20, 1.3, and 0 to 212 µg/L for cases and 45, 1.2, and 0 to 997 µg/L for controls, when proxy wells were excluded. Risks were not reported by gender.

Karagas et al. 2004 reported 383 cases of transitional cell carcinoma of the bladder identified from the New Hampshire, USA cancer registry and 641 general population controls. Toenail arsenic was used as the measure of exposure. There was an increased risk of transitional cell bladder cancer among ever smokers at the highest toenail arsenic concentration. No increased risk was noted among all subjects or never smokers at any concentration. The geometric mean values of toenail arsenic (standard error of the geometric mean) were 0.087 µg/g (SE = 0.003 µg/g) and 0.090 µg/g (SE = 0.002 µg/g) for cases and controls, respectively.

Michaud et al. 2004 studied 280 bladder cancer cases and 293 controls (all male) in Southwest Finland. Cases and controls were smokers at the time of enrollment into the Alpha-Tocopherol, Beta-Carotene Prevention Study. ORs were estimated from unconditional logistic regression

models adjusted for age, date at toenail collection, trial intervention group (Alpha-Tocopherol or Beta-Carotene), number of cigarettes/day, and number of years of smoking. No relationships between toenail arsenic concentrations and bladder cancer risk were found. Median toenail arsenic concentrations were 0.110 µg/g (range = 0.014 to 2.62 µg/g) and 0.105 µg/g (range = 0.017 to 17.5 µg/g) for cases and controls, respectively.

Steinmaus et al. 2003 studied 181 primary bladder cancer cases and 328 controls in California and Nevada. Cases diagnosed between 1994 and 2000 were identified from the Nevada Cancer Registry and the Cancer Registry of Central California. Population controls were age and gender matched. Arsenic measurements for all community-supplied drinking water wells were obtained from the health departments of the respective states. Questionnaires were administered to all participants. Arsenic exposures were classified by the highest one year average, highest five year average, highest 20 year average, and cumulative exposure. The percentages of cases and controls consuming different concentrations of arsenic (0 to 19, 20 to 79, 80 to 120, and > 120 µg/L) were similar, the vast majority consuming 0 to 19 µg/L. The only significant associations were found after a 40-year lag in ever smokers exposed to > 80 µg As/day (OR=3.67; 95% CI = 1.43, 9.42). Risks were not reported by gender.

Ecologic Studies

Han et al. 2009 compared cancer incidence by the arithmetic mean arsenic concentrations ofground water in 44 counties in Idaho, USA. Arsenic concentrations for the counties were based on approximately 1,990 ground water sources sampled between 1991 and 2005. Newly diagnosed cases of cancer of the bladder, kidney and renal pelvis, liver and bile duct, lung and bronchus, and non-Hodgkin's lymphoma from 1991 to 2005 were identified from the Cancer

Registry of Idaho. Counties were grouped into arsenic water concentrations of < 2 µg/L (n = 23), 2 to < 10 µg/L (n = 16), and ≥ 10 µg/L (n = 5). A regression analysis, controlling for smoking, race, gender, BMI, and population density, found no evidence of an association between arsenic and cancer incidence in the 44 counties.

Lamm et al. 2004 studied 133 U.S. counties that depend exclusively on groundwater. Bladder cancer standardized mortality ratios (SMR) for white males, from 1950 to 1979, were plotted against median county arsenic concentrations in groundwater. SMRs for white males were not related to the median or mean county arsenic concentrations. Median county arsenic concentrations ranged from 3 to 60 µg/L. 82% of the population studied was assumed to have consumed 3 to 5 µg As/L.

Meliker et al. 2007 investigated six counties in southeastern Michigan. Deaths for the 6 counties and for the state of Michigan from 1979 to1997 were used to estimate the sex-specific SMRs. Data from Michigan Department of Environmental Quality from 1983 through 2002 were used to estimate county-level mean and median arsenic concentrations for the six counties and for the rest of Michigan. The SMRs for lung, bronchus and trachea cancer and for bladder cancer were not significantly increased among the six counties as a whole. The SMRs for lung, trachea, and bronchus cancer were significantly increased in both males and females in Genesee County, the most populous, urban, and racially diverse of the six counties. The six-county study area had a population-weighted mean arsenic concentration of 11.00 µg/L and a population-weighted median of 7.58 µg/L. The population-weighted mean in the remainder of Michigan was 2.98 µg/L with a median of 1.27 µg/L.

DISCUSSION

As indicated by Table 4, few studies reported significantly increased risks of lung or bladder cancer from exposure to < 100 µg As/L. That does not suggest, however, that the lung and bladder cancer risks estimated by NRC are incorrect. The sample sizes, with Type I error = 0.05 and Power = 0.80, needed to detect the NRC-estimated risks of bladder cancer in females are relatively large (Table 3). The sample sizes needed to detect lung cancer in females or lung or bladder cancer in males would be even larger. None of the studies conducted since the NRC report had sample sizes large enough to detect the risks estimated by the NRC. Nevertheless, there is evidence of increased lung and bladder cancer risk from exposures < 100 µg As/L in the recent studies, particularly in the studies by Chen et al. (2010a,b). The monotonic dose response seen across all exposures in Chen et al. (2010b) and the significant trend ($p<0.001$) for dose response provides strong evidence for the bladder cancer risks seen at the lower exposures.

The three case-control studies which examined the risks of bladder cancer from low arsenic drinking water concentration drew cases and controls from arsenic endemic areas (Bates et al. 2004; Steinmaus et al. 2003; Meliker et al. 2010). The reason for drawing cases and controls from the same area is of course to minimize potential differences other than the factor under study (i.e., arsenic). Drawing cases and controls from the same area, however, may also reduce the difference in arsenic exposure requiring a larger sample size to determine whether an excess risk exists for a given exposure. Exposure misclassification probably further reduced the difference between groups. Since the estimated exposure difference between cases and controls was minimal in each of these studies, the statistical power to detect the excess risks predicted by the NRC would also have been minimal.

Two of the case-control studies which examined bladder cancer risk (Karagas et al. 2004; Michaud et al. 2004) used toenail arsenic as the measure of exposure. According to Karagas et al. (2000), 1 µg As/L water corresponds to 0.1 µg As/g toenail, while a doubling of toenail arsenic concentration is associated with a 10-fold increase in water arsenic in samples with ≥ 1 µg As/L. Based on this relationship, cases and controls in all three studies would have been exposed to approximately ≤ 1 µg As/L. Even if this level of exposure were assumed to be lifetime, the power of the Karagas et al. (383 cases, 641 controls) and Michaud et al. (280 cases, 293 controls) studies to detect the bladder cancer risk estimated by the NRC (2001) would have been minimal. Toenail arsenic is considered a reliable indicator of arsenic exposure with the strongest relationship being to drinking water arsenic exposure (Adair et al. 2006). When the concentration of arsenic in water is low, however, the contribution of arsenic to toenail arsenic concentrations becomes less clear as other sources (e.g. food, air, dermal absorption) become more important (Slotnick and Nriagu 2006).

Han et al. (2009), Lamm et al. (2004), and Meliker et al. (2007) were ecologic studies. The exposure metric in all three studies was an average exposure measurement by county, a much larger geopolitical unit than the villages in the Taiwan study. Lamm et al. (2004) relied on USGS data for mean and median arsenic concentrations by county (Focazio et al. 1999). The USGS data were based on as few as five wells per county and were not restricted to wells used for drinking water. All three ecologic studies were conducted in the United States where the population is very transient – much more transient than, for example, the southwest Taiwanese population that is the basis of the NRC risk estimates. The U.S. Bureau of the Census (1998) reported that the median duration in a residence for those in the U.S. is only 5.2 years. Also, the U.S. population consumes different sources of fluids in addition to potentially contaminated well

water (e.g., tap water from other jurisdictions, bottled beverages, etc.) while those in southwest Taiwan likely consumed well water as their principal, if not the only, source of fluids. Furthermore, both the Lamm et al. (2004) and Meliker et al. (2007) studies examined bladder cancer mortality rather than incidence. The NRC estimates are for cancer incidence. Since the five-year survival rate for bladder cancer is approximately 80% (SEER 2009), studies based on bladder cancer mortality would underestimate the risks described by NRC. Lastly, the arsenic exposures in all three studies were very low (< 10 µg/L). Han et al. (2009) compared incidence of cancer for different sites by low (< 2 µg/L), medium (2 to 9 µg/L), and high (≥ 10 µg/L) arsenic counties. The median arsenic concentrations in the counties studied by Lamm et al. (2004) were 3 to 60 µg/L, with 65% of the counties and 82% of the population in the range of 3 to 5 µg/L. The six Michigan counties studied by Meliker et al. (2007) had population-weighted mean and median arsenic concentrations of 11.00 µg/L and 7.58 µg/L, respectively, compared to 2.98 µg/L and 1.27 µg/L for the remainder of the state. The differences are relatively small.

Some of the recent studies suggest that the ability of an epidemiologic study of arsenic exposure to detect a lung or bladder cancer risk could be impacted by the number of smokers in the study population. Steinmaus et al. (2003), Bates et al. (2004) and Karagas et al. (2004) all report an increased risk of bladder cancer in smokers, but not nonsmokers, exposed to relatively low concentrations of arsenic in drinking water. The ecologic study by Meliker et al. (2007) found a significant increase in lung cancer mortality for the most urbanized of the six arsenic-endemic counties (Genesee County). Since the prevalence of smoking in the most urbanized county was expected to be higher than in the other five counties, the authors suggested the significant elevation in lung cancer mortality is due to the synergy between arsenic and smoking. An earlier study by Kurttio et al. (1999) also presents evidence of an interaction between smoking and

arsenic with respect to bladder cancer while Mostafa et al. (2008), Chen et al. (2004), and Ferreccio et al. (2000) suggest an interaction between smoking and arsenic with respect to lung cancer. Chen et al. (2010a) found a synergistic effect of arsenic exposure and cigarette smoking for squamous and small cell carcinomas of the lung, but not for adenocarcinoma. The authors also reported that a relationship between smoking, arsenic, and lung cancer was evident by the significantly elevated RRs among exposed smokers compared to exposed non-smokers.

The study by Chen et al. (2010b) found that drinking arsenic-contaminated water since birth had a higher urinary cancer risk than beginning to drink arsenic-contaminated later in life. Smith et al. (2006) in a study of lung cancer risk in an arsenic-endemic area where drinking water concentrations were relatively high found that early lifetime exposure may convey a greater risk for lung cancer. Marshall et al. (2007), Bates et al. (1995, 2004), and Steinmaus et al. (2003) found that the latency for arsenic-induced cancer was particularly long, indicating that a 40 to 50 year follow-up may be required to detect an excess risk.

The recent studies by Chen et al. (2010a, b) are noteworthy for their potential to improve the quantitative risk assessment for arsenic. The population is relatively large (8,086) and includes a large number exposed since birth. Arsenic drinking water concentrations range from < 10 µg/L to > 300 µg/L. Individual drinking water measurements are available for most in the cohort as opposed to the village measurements on which the NRC risk estimates are based. Data are also available on age of the individuals, gender, education, cigarette smoking, habitual alcohol consumption, age when the individuals started drinking arsenic-contaminated well water, and age when the individual stopped drinking arsenic-contaminated well water. Additional follow-up of this cohort will provide a valuable database for future risk assessments. Individual data

from the study will be needed to do a quantitative risk assessment. The Health Effects of Arsenic Longitudinal Study (HEALS) of an arsenic-exposed cohort of almost 20,000 in Bangladesh (Ahsan et al. 2005; Chen et al. 2009) may also be of utility in the future in assessing cancer risk at low arsenic exposures. The study has collected individual data on smoking, education, socioeconomic status, skin lesions, arsenic exposure (including biomarkers of exposure), and other variables.

CONCLUSION

The NRC estimated excess *lifetime* lung and bladder cancer risks based on a *lifetime* of exposure to arsenic in drinking water. Since 2001, several studies have evaluated lung and bladder cancer risk in persons consuming low concentrations of arsenic in drinking water (≤100 μg/L). These studies lack either the statistical power or the information necessary to evaluate the NRC bladder and lung cancer risk estimates. Validating the NRC estimated risks is problematic given the sample sizes needed, the long latency involved, and the greater need to control for confounders at low arsenic drinking water concentrations. Some of the recent studies, however, suggest that lung and bladder cancer risks are increased at concentrations ≤ 100 μg As/L. Future studies on arsenic ingestion and lung and bladder cancer risk would benefit by considering the adequacy of the sample size, the synergistic relationship of arsenic and smoking, duration of arsenic exposure, age when exposure began and ended, and examination by histological type. While the data from southwest Taiwan continue to provide the best basis for the quantitative risk assessment of lung and bladder cancer from ingested arsenic, individual data from the continued follow-up of the population studied by Chen et al. (2010a,b) should provide an excellent database on which to improve the assessment.

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Table 1. NRC (2001)[a] estimates of lifetime cancer risks per 10,000 people in relation to arsenic concentration.

Concentration (µg As/L)	Lung Cancer Risk		Bladder Cancer Risk	
	Females	Males	Females	Males
3	5	4	4	7
5	9	7	6	11
10	18	14	12	23
20	36	27	24	45

[a] Reprinted with permission from Arsenic in Drinking Water 2001 Update © 2001 by the National Academy of Sciences, Courtesy of the National Academies Press, Washington, D.C.

Table 2. Excess Lifetime Risks, Background U.S. Lifetime Risks and Relative Lifetime Risks for Bladder and Lung Cancer by Gender from a Lifetime Consumption of 10 µg As/L

Type of Cancer By Gender	NRC Excess Lifetime Risk[a]	Background Lifetime Risk[b]	NRC Relative Lifetime Risk[c]
Bladder (males)	0.0023	0.0315	1.07
Bladder (females)	0.0012	0.0094	1.13
Lung (males)	0.0014	0.0689	1.02
Lung (females)	0.0018	0.0554	1.03

[a] From NRC (2001), page 12
[b] From SEER (2006a,b). Lifetime risk is through age 85.
[c] Relative Lifetime Risk = (Excess Lifetime Risk + Background Lifetime Risk) / Background Lifetime Risk

Table 3. Sample sizes required for 80% statistical power and Type I error = 0.05 to detect bladder cancer in a cohort study of females for a range of arsenic concentrations

Arsenic (µg/L)	Excess Risk[a]	RR[b]	Sample Size (80% power)
100	0.012	2.28	672
50	0.006	1.64	2,381
20	0.0024	1.26	13,613
10[c]	0.0012	1.13	52,640
3	0.0004	1.04	462,527

[a]Estimates from NRC (2001)
[b] The RR is the background [(Excess Lifetime Risk + Background Lifetime Risk) / Background Lifetime Risk]. The lifetime risk for women up to age 85 for bladder cancer, years 2004-2006 is .0094 (.94%) (SEER 2006a,b)
[c] 10 µg/L is the current EPA MCL for arsenic (U.S. EPA 2001c)
Sample sizes were calculated using STATA 10.

Table 4. Studies published since 2001 which examined the risk of lung and/or bladder cancer for arsenic concentrations in drinking water < 100 μg/L

Authors	Study Size	Location	Cancer Type	Measures of Association (95% CI)
Cohort Studies				
Chen et al. 2010a	8,086	Northeastern Taiwan	Lung	<10 μg/L: RR=1.0 10-49.9 μg/L: RR=1.10 (0.74-1.63) 50-99.9 μg/L: RR=0.99 (0.59-1.68) 100-299 μg/L: RR=1.54 (0.95-2.46) ≥300 μg/L: RR=2.25 (1.43-3.55) p_{trend}= 0.001
Chen et al. 2010b	8,086	Northeastern Taiwan	Urinary	<10 μg/L: RR=1.0 10-49.9 μg/L: RR=1.66 (0.53-5.21) 50-99.9 μg/L: RR=2.42 (0.69-8.54) 100-299 μg/L: RR=4.13 (1.32-12.9) ≥300 μg/L: RR=7.80 (2.64-23.1) p_{trend}< 0.001
Baastrup et al. 2008	56,378	Denmark	Bladder Lung	0.7 μg/L: IRR=1.01 (0.93-1.11) 0.7 μg/L: IRR=0.99 (0.92-1.07)
Chen et al. 2004	2,503 8,088	Southwest Taiwan Northeast Taiwan	Lung	<10 μg/L: RR=1.0 10-99 μg/L: RR=1.09 (0.63-1.91) 100-299 μg/L: RR=2.28 (1.22-4.27) 300-699 μg/L: RR=3.03 (1.62-5.69) ≥700 μg/L: RR=3.29 (1.60-6.78) P_{trend}<0.001
Case-Control Studies				
Heck et al. 2009	223 Cases 238 Controls	New Hampshire and Vermont, USA	Lung	N/A - exposure measurement was toenail arsenic.
Bates et al. 2004	114 Cases 114 Controls	Argentina	Bladder	For arsenic exposure 1-10 years prior to interview including proxy well measurements: 0-10 μg/L: OR=1.00 > 10 μg/L: OR=0.75 (0.4-1.7)
Karagas et al. 2004	338 Cases 641 Controls	New Hampshire, USA	Bladder	N/A - exposure measured by toenail arsenic.
Meliker et al. 2010	411 Cases 566 Controls	Southeastern Michigan, USA	Bladder	<1 μg/L: OR=1.00 1-10 μg/L: OR=0.84 (0.63-1.12) >10 μg/L: OR=1.10 (0.65-1.86)
Michaud et al. 2004	280 Cases 293 Controls	Southwest Finland	Bladder	N/A - Exposure measured by toenail arsenic
Mostafa et al. 2008	2,811 Cases 1,183 Controls	Bangladesh	Lung	<u>Smokers</u> ≤ 10 μg/L: OR=1.0 11≤50 μg/L: OR=1.25 (0.96-1.62) 51≤100 μg/L: OR=1.37 (0.92-2.03) 101-400 μg/L: OR=1.65 (1.25-2.18) <u>Nonsmokers</u> ≤ 10 μg/L: OR=1.0 11≤50 μg/L: OR=0.90 (0.62-1.33) 51≤100μg/L: OR=1.10 (0.62-1.96)

Authors	Study Size	Location	Cancer Type	Measures of Association (95% CI)
				101-400 µg/L: OR=0.94 (0.62-1.41)
Steinmaus et al. 2003	181 Cases 328 Controls	California and Nevada, USA	Bladder	For arsenic exposures with a 40-year lag and highest 20- year average: ≤10µg As/day: OR=1.0 10-80 µg As/day: OR=1.28 (0.53,3.11) >80 µg As/day: OR=1.70 (0.73,3.96)
Ecologic Studies				
Han et al. 2009	44 Counties	Idaho, USA	Bladder	Pearson correlation coefficient of arsenic in ground water and bladder cancer incidence = 0.02 (p=0.9)
			Lung	Pearson correlation coefficient of arsenic in ground water and lung cancer incidence = 0.25 (p=0.1)
Lamm et al. 2004	133 Counties	USA	Bladder	3-60 µg/L (82% 3-5 µg/L): Regression analysis found no association of bladder cancer mortality with arsenic in drinking water.
Meliker et al. 2007	6 Counties	Southeastern Michigan, USA	Bladder	7.58 µg/L (population-weighted median): SMR = 0.94 (0.82-1.08)
			Lung	7.58 µg/L (population-weighted median): SMR = 1.02 (0.98-1.06)