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Quantitative assessment of lung and bladder cancer risk and oral exposure to inorganic arsenic: Meta-regression analyses of epidemiological data

Heather N. Lynch[a], Ke Zu[a], Erin M. Kennedy[a], Thuy Lam[a], Xiaobin Liu[a], Daniella M. Pizzurro[a], Christine T. Loftus[b], Lorenz R. Rhomberg[a,*]

[a] Gradient, 20 University Road, Cambridge, MA 02138, USA
[b] Department of Environmental and Occupational Health Sciences, University of Washington, Seattle, 4225 Roosevelt Way NE, Suite 301, Seattle, WA 98105, USA

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ABSTRACT

Inorganic arsenic (iAs) in drinking water varies geographically and is prevalent worldwide. While exposures in the US are generally low, there are some areas with higher levels of naturally occurring iAs (potentially > 100 μg/L) where residents rely on unregulated drinking water wells. Much of the evidence on the association between iAs and cancer comes from epidemiological studies conducted in South American and Asian populations. These populations have generally been exposed to much higher levels of iAs and have differing underlying characteristics, both of which make comparing them to Western populations difficult. A key question is whether and how one should extrapolate from these high exposure studies to estimate cancer risk at lower exposures. We conducted an independent analysis to determine the most appropriate cancer endpoints, studies, and models to support an oral carcinogenicity assessment of iAs, taking into consideration factors that affect the apparent potency of iAs across geographically and culturally distinct populations. We identified bladder and lung cancer as high-priority endpoints and used meta-regression to pool data across studies from different regions of the world to derive oral cancer slope factors (CSFs) and unit risks (excess risk per μg/L) for iAs based on the background risks of bladder and lung cancer in the US. We also calculated concentrations of iAs in water that are not likely to result in cancer risk above what is considered acceptable by the United States Environmental Protection Agency (US EPA). While we derived these factors assuming a linear, no-threshold relationship between iAs and cancer risk, we also evaluated the shape of the dose-response curves and assessed the evidence for overall nonlinearity. Overall, we found that the incremental risks of bladder and lung cancer associated with iAs were relatively low. The sensitivity analyses we conducted suggested that populations with relatively high iAs exposures appeared to drive the pooled cancer risk estimates, but many of our other tested assumptions did not substantially alter these estimates. Finally, we found that the mode of action evidence supports there being a threshold, but making a robust quantitative demonstration of a threshold using epidemiological data is difficult. When considered in the context of typical exposure levels in the US, our potency estimates indicate that iAs-induced cancer risk is much lower than observed bladder and lung cancer incidences. This suggests that the low iAs levels to which much of the general US population is exposed likely do not result in substantial additional cancer risk.

* Corresponding author.
E-mail addresses: hlynch@gradientcorp.com (H.N. Lynch), kzu@gradientcorp.com (K. Zu), ekennedy@gradientcorp.com (E.M. Kennedy), tlam@gradientcorp.com (T. Lam), xliu@gradientcorp.com (X. Liu), dpizzurro@gradientcorp.com (D.M. Pizzurro), cloftus@uw.edu (C.T. Loftus), lrhomberg@gradientcorp.com (L.R. Rhomberg).

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1. Introduction

Arsenic occurs naturally in water, soil, and food. Hundreds of studies have assessed the relationship between arsenic in drinking water and adverse health effects, and it has been established that high levels of inorganic arsenic (iAs)[1,2] can cause skin, bladder, and lung cancer. The association between iAs and lower levels of iAs exposure (*i.e.*, < 100–200 μg/L) remains an area of continuing research, but much of the available evidence suggests that iAs could be a threshold carcinogen (Abernathy et al., 1996; Byrd et al., 1996; Cohen et al., 2013; Doak et al., 2007; Lamm et al., 2007; Lamm et al., 2014; Lamm et al., 2015; Tsuji et al., 2014a). The potential for iAs to cause or promote other types of cancer (*e.g.*, kidney, liver) has not been established (NRC, 2013; Cohen et al., 2013).

The body of evidence for the carcinogenic potential of iAs is predominated by studies in humans, and to date, governmental agencies have not generally employed the limited animal evidence for quantitative risk assessment. Prior to about 2000, rodent carcinogenicity assays did not show any evidence of iAs-induced cancer (NRC, 1999; Rossman et al., 2004), possibly due to the observation that rodents rapidly and efficiently metabolize iAs into less toxic metabolites (Vahter and Norin, 1980 Vahter, 1994). Newer models have shown that rodents are susceptible to carcinogenicity from various arsenic compounds, and when models are appropriately designed, animal data can be used in carcinogenic hazard assessment of iAs exposure in humans (Cohen et al., 2013). However, the few available animal carcinogenicity bioassays available for iAs compounds are generally not of high enough quality to use in dose-response modeling (US EPA, 2010). One major issue with the available animal evidence is the fact that iAs metabolism, and thus the potential for adverse effects, varies greatly across different species. Humans appear to be unique relative to commonly tested animal carcinogenesis models in that they produce more toxic arsenical metabolites than most other mammals (Vahter, 1994). Thus, it appears that humans are more susceptible to iAs-induced carcinogenesis, making human epidemiological studies most appropriate to evaluate iAs dose-response relationships. While human data are often used in regulatory risk assessment, meta-regression of human epidemiological data for the quantification of risk is relatively uncommon. Quantitative analyses of human data have many benefits, but also a unique set of challenges.

The United States Environmental Protection Agency (US EPA) published its first assessment of the health effects of iAs in 1988 and has been working on an updated Integrated Risk Information System (IRIS) assessment since 2003 (US EPA, 2016). The most recent draft of the IRIS assessment was released in 2010 (US EPA, 2010); an updated draft is expected in 2017. In 2013, the National Academy of Sciences National Research Council (NRC) released a review of the state of the science for iAs, providing many recommendations for US EPA's assessment going forward, particularly with respect to dose-response assessment. In particular, NRC recognized that because the majority of iAs data come from epidemiological studies, dose-response analyses must consider those studies' potential biases (*e.g.*, exposure misclassification). The most robust iAs datasets come from populations with very high exposures (predominantly in South Asia and South America), while the results from populations with lower exposure levels (mostly in Western countries) are more limited and uncertain. Differences in factors that affect the true iAs dose among populations, including cooking methods and dietary patterns, water intake, nutritional deficiencies, and metabolic factors, all complicate the application of many key studies when determining the most appropriate exposure metric for use in risk assessment (*e.g.*, urinary iAs levels, average water iAs concentration, various cumulative measures) and extrapolating risk estimates from one population to another (NRC, 2013; Chu and Crawford-Brown, 2006). Ultimately, these issues affect the ability to draw conclusions regarding potential cancer risks from iAs exposure in American populations.

We conducted an independent analysis to determine the most appropriate cancer endpoints, studies, and models to support an oral carcinogenicity assessment of iAs, taking into consideration factors that affect the apparent potency of iAs across geographically and culturally distinct populations. The goal of our assessment was to derive an oral cancer slope factor (CSF) and a unit risk for iAs based on the background risks of bladder and lung cancer in the US. We also used our results to assess the specific cancer risk from iAs exposure relative to background risks in the State of Texas. The CSF is a measure of the potency of iAs; *i.e.*, it represents the relationship between the “dose” of iAs and cancer risk, represented as the incremental risk of cancer per specific unit of iAs intake (typically per mg/kg-day). The unit risk is an estimate of the increased theoretical risk of cancer development from a given increment of exposure to iAs, expressed as a concentration in drinking water (per μg/L). We also calculated estimates of the concentration of iAs in water (in μg/L) that would be unlikely to result in cancer risk above the upper end of what is considered acceptable by US EPA (*i.e.*, an incidence of 1 case of cancer in 10,000 individuals).

Overall, as discussed in detail below, we used meta-regression to conduct an aggregated dose-response analysis that averaged iAs intake across studies of different concentrations of iAs in water and water ingestion rates. We also qualitatively considered potential heterogeneity among studies with regard to important factors such as nutrition, genetics, and other differences that affect an individual's ability to metabolize iAs. The CSFs we derived represent more objective measures of incremental cancer risk from iAs exposure compared to those previously derived using a single dataset (*e.g.*, the Southwest Taiwanese cohort, as utilized in US EPA, 2010).

Our analysis was performed as follows: We first completed a comprehensive literature search of the epidemiology of the association between iAs and all cancer sites, cross-checked our results to ensure completeness of our epidemiological database, then completed an independent qualitative assessment of the literature. After we evaluated what we considered the most robust and relevant cancer sites, we assessed all relevant studies for overall study quality and selected studies with sufficient information for dose-response analysis. In conjunction with the epidemiological analysis, we also conducted a broad, qualitative assessment of the posited modes of action (MoAs) whereby iAs may cause the selected cancer types. We then conducted a dose-response analysis using meta-regression methods to pool results across studies and completed a number of sensitivity analyses to test the effect of various assumptions. Our pooled analysis weighed study-specific risk estimates by their precision and accounted for within-study correlations. The resulting risk estimates, while indicating a relatively low risk

[1] Abbreviations: iAs, Inorganic Arsenic; US EPA, United States Environmental Protection Agency; IRIS, Integrated Risk Information System; NRC, National Research Council; CSF, Cancer Slope Factor; MoA, Mode of Action; NTP, National Toxicology Program; OHAT, Office of Health Assessment and Translation; LOD, Limit of Detection; CV, Coefficient of Variation; SES, Socioeconomic Status; BMI, Body Mass Index; ICD, International Classification of Disease; HEALS, Health Effects of Arsenic Longitudinal Study; BFD, Blackfoot Disease; MMA^{V}, Monomethylarsonic Acid; RR, Relative Risk; CI, Confidence Interval; SMR, Standard Mortality Ratio; OR, Odds Ratio; SRRE, Summary Relative Risk Estimate; iAs^{V}, Arsenate; iAs^{III}, Arsenite; MMA^{III}, Monomethylarsonous Acid; DMA^{III}, Dimethylarsinous Acid; DMA^{V}, Dimethylarsinic Acid; PNP, Purine Nucleoside Phosphorylase; As3MT, Arsenic Methyl Transferase; SAM, S-Adenosylmethionine; GI, Gastrointestinal; ppm, Parts Per Million; PBPK, Physiologically Based Pharmacokinetic; i.v., Intravenous; NOAEL, No-Observed-Adverse-Effect Level; ppb, Parts Per Billion; PMI, Primary Methylation Index; SMI, Secondary Methylation Index; *N6AMT*, N-6 Adenine-Specific DNA Methyltransferase 1; *GSTO1*, Glutathione S-Transferase Omega 1; *GSTO2*, Glutathione S-Transferase Omega 2; *XRCC3*, X-Ray Repair Cross Complementing 3; *GSTP1*, Glutathione-S-Transferase Pi 1; *GSTM1*, Glutathione S-Transferase Mu 1; *CYP1A*, Cytochrome P450 1A1; *EPHX1*, Epoxide Hydrolase 1; *SULT1A1*, Sulfotransferase 1A1; MIE, Molecular Initiating Event; BMDL, Benchmark Dose Level; NOEL, No Effect Level; IC50, Half Maximal Inhibitory Concentration; miRNA, Micro-RNA; ROS, Reactive Oxygen Species; GSH, Glutathione; 8-OHdG, 8-Hydroxy-2′-Deoxyguanosine; HIF-1α, Hypoxia-Inducible Factor 1-Alpha; Ln(RR), Log-Transformed Relative Risk.

[2] Note that almost all arsenic in water is the inorganic form (Cohen et al., 2013).