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Review

Considerations in deriving quantitative cancer criteria for inorganic arsenic exposure *via* inhalation

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ABSTRACT

The inhalation unit risk (IUR) that currently exists in the United States Environmental Protection Agency's (US EPA's) Integrated Risk Information System was developed in 1984 based on studies examining the relationship between respiratory cancer and arsenic exposure in copper smelters from two US locations: the copper smelter in Anaconda, Montana, and the American Smelting And Refining COmpany (ASARCO) smelter in Tacoma, Washington. Since US EPA last conducted its assessment, additional data have become available from epidemiology and mechanistic studies. In addition, the California Air Resources Board, Texas Commission of Environmental Quality, and Dutch Expert Committee on Occupational Safety have all conducted new risk assessments. All three analyses, which calculated IURs based on respiratory/lung cancer mortality, generated IURs that are lower (*i.e.*, less restrictive) than the current US EPA value of 4.3×10^{-3} $(\mu g/m^3)^{-1}$. The IURs developed by these agencies, which vary more than 20-fold, are based on somewhat different studies and use different methodologies to address uncertainties in the underlying datasets. Despite these differences, all were developed based on a cumulative exposure metric assuming a low-dose linear dose–response relationship. In this paper, we contrast and compare the analyses conducted by these agencies and critically evaluate strengths and limitations inherent in the data and methodologies used to develop quantitative risk estimates. In addition, we consider how these data could be best used to assess risk at much lower levels of arsenic in air, such as those experienced by the general public. Given that the mode of action for arsenic supports a threshold effect, and epidemiological evidence suggests that the arsenic concentration in air is a reliable predictor of lung/respiratory cancer risk, we developed a quantitative cancer risk analysis using a nonlinear threshold model. Applying a nonlinear model to occupational data, we established points of departure based on both cumulative exposure ($\mu g/m^3$-years) to arsenic and arsenic concentration ($\mu g/m^3$) *via* inhalation. Using these values, one can assess the lifetime risk of respiratory cancer mortality associated with ambient air concentrations of arsenic for the general US population.

Contents

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1. Introduction

Regulatory agencies have been engaged in the development of quantitative criteria for use in arsenic cancer risk assessment for several decades (*e.g.*, CARB, 1990; NRC, 2001; US EPA, 2001, 2003, 2005a, 2010). Most of the focus has been on characterizing risk *via* the oral route of exposure, with less attention – particularly at the federal level – on developing arsenic risk criteria for inhalation exposures. The United States Environmental Protection Agency (US EPA) developed the current inhalation unit risk (IUR) for its Integrated Risk Information System (IRIS) in 1984 (US EPA, 2003) based on studies examining the relationship between respiratory cancer and arsenic exposure in copper smelters at two US locations: the smelter in Anaconda, Montana (Brown and Chu, 1983; Higgins et al., 1982; Lee-Feldstein, 1983), and the American Smelting And Refining COmpany (ASARCO) smelter in Tacoma, Washington (Enterline and Marsh, 1980, 1982). Using an absolute-risk linear model, US EPA analyzed each cohort and used the geometric mean of the two calculated IURs to establish the still-current IRIS value of 4.29×10^{-3} $(\mu g/m^3)^{-1}$. In 1998, US EPA revised the IRIS file for ingested inorganic arsenic but did not revise the IUR (US EPA, 2003).

Since US EPA conducted its last assessment, additional data have become available from both epidemiology and mechanistic studies that better inform a quantitative assessment of arsenic toxicity *via* inhalation. Several new cohort studies have been conducted (*e.g.*, Ronnskar Sweden copper smelter, UK tin smelter studies, Chinese mine study), and updated data have been published from the cohorts on which US EPA based its IUR (*i.e.*, Anaconda, TACOMA). In addition, a number of recent supporting studies have been published that provide more analysis of the relationship between inhaled arsenic and cancer (*e.g.*, Binks et al., 2005; Lundstrom et al., 2006).

According to a scoping meeting in January 2012, US EPA intends to update risk assessment criteria for arsenic in IRIS, including a revised IUR (the timing of this update is unclear, however). The National Academy of Sciences, which has been mandated to review and provide input on the arsenic assessment, is not specifically looking at inhalation dose–response issues (NRC, 2013).

We have identified three new assessments conducted since US EPA's 1984 assessment, specifically by the California Air Resources Board (CARB) (1990), Texas Commission of Environmental Quality (TCEQ) (Erraguntla et al., 2012), and Dutch Expert Committee on Occupational Safety (DECOS) (2012). All three analyses calculated IURs based on respiratory/lung cancer mortality that are lower (*i.e.*, less restrictive) than the current US EPA IUR of 4.3×10^{-3} $(\mu g/m^3)^{-1}$.

These analyses, all of which utilize updated datasets, bring into focus the many challenges and uncertainties associated with developing an arsenic IUR and could help inform the development of a new IUR by US EPA. The IURs developed by these agencies vary more than 20-fold, are based on somewhat different studies, and use different methodologies and approaches to address uncertainties in the data (*e.g.*, smoking, effects of respirator use on exposure, exposure metric). Still, these recent analyses share many common features, including the assumption of a linear dose–response relationship at low doses and that cumulative exposure (as opposed to concentration) best characterizes arsenic's carcinogenic potency *via* inhalation.

The goal of this paper is to contrast and compare the analyses conducted by these agencies and critically evaluate strengths and limitations inherent in the data and methodologies used to develop quantitative risk estimates. As part of this assessment, we give detailed consideration on how high-end occupational exposure relates to the evaluation of health risk at the much lower exposures typically experienced by the general public. This assessment is carried out in the context of a plausible carcinogenic threshold for arsenic, which is supported by arsenic epidemiology data (oral and inhalation) and an understanding of arsenic's carcinogenic mechanism of action. In light of evidence of a threshold, we explore arsenic carcinogenicity risk *via* inhalation using a margin-of-exposure (MOE) approach.

2. Available epidemiological studies with dose–response data appropriate for risk assessment

Compared to ingested inorganic arsenic, the carcinogenicity of inhaled arsenic is less studied. Nonetheless, several epidemiological analyses have evaluated the relationship between inhaled arsenic and cancer, mainly in copper smelter worker populations. While many of these studies are useful for evaluating a causal relationship between inorganic arsenic and cancer, far fewer studies provide information in a way that is useful in constructing a dose–response relationship. Three copper smelter cohorts, in particular, have robust datasets that can be used (with caveats) to develop a quantitative understanding of arsenic dose–response *via* inhalations: the Anaconda, Tacoma, and Ronnskar (Sweden) cohorts. All of the IUR analyses we identified since US EPA's 1984 assessment (CARB, 1990; DECOS, 2012; Erraguntla et al., 2012) have drawn on information from these cohorts. Multiple studies are available on each cohort (see Table 2.1), with more recent publications reflecting a more updated dataset and more refined analyses.