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An updated inhalation unit risk factor for arsenic and inorganic arsenic compounds based on a combined analysis of epidemiology studies

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ABSTRACT

The United States Environmental Protection Agency (USEPA) developed an inhalation unit risk factor (URF) of 4.3E-03 per μg/m^3 for arsenic in 1984 for excess lung cancer mortality based on epidemiological studies of workers at two smelters: the Asarco smelter in Tacoma, Washington and the Anaconda smelter in Montana. Since the USEPA assessment, new studies have been published and exposure estimates were updated at the Asarco and Anaconda smelters and additional years of follow-up evaluated. The Texas Commission on Environmental Quality (TCEQ) has developed an inhalation URF for lung cancer mortality from exposures to arsenic and inorganic arsenic compounds based on a newer epidemiology study of Swedish workers and the updates of the Asarco and Anaconda epidemiology studies. Using a combined analysis approach, the TCEQ weighted the individual URFs from these three epidemiology cohort studies, to calculate a final inhalation URF of 1.5E-04 per μg/m^3. In addition, the TCEQ also conducted a sensitivity analysis, in which they calculated a URF based on a type of meta-analysis, and these results compared well with the results of the combined analysis. The no significant concentration level (i.e., air concentration at 1 in 100,000 excess lung cancer mortality) is 0.067 μg/m^3. This value will be used to evaluate ambient air monitoring data so the general public in Texas is protected against adverse health effects from chronic exposure to arsenic.

1. Introduction

The United States Environmental Protection Agency (USEPA) developed an inhalation unit risk factor (URF) for arsenic of 4.3E-03 per μg/m^3 in 1984 (USEPA, 1984). The last revision of URF for arsenic by USEPA's Integrated Risk Information System (IRIS) was in 1998 (USEPA, 1998) and at that time, changes to the URF value or a reassessment was not suggested. USEPA's URF was for excess lung cancer mortality based on two epidemiological studies of workers exposed to arsenic. The USEPA's final URF was the estimated geometric mean of the maximum likelihood URFs based on the workers at the Asarco smelter in Tacoma, Washington (Enterline and Marsh, 1982) and the Anaconda smelter in Montana (Brown and Chu, 1983a,b,c; Lee-Feldstein, 1983; Higgins et al., 1982).

Several epidemiological studies have been reported in arsenic-exposed smelter workers that indicate that inhalation exposure to inorganic arsenic increases the risk of lung cancer. The TCEQ conducted a comprehensive literature search of all the available epidemiology studies that reported health effects from exposure to arsenic and inorganic arsenic compounds. All these studies were evaluated for exposure information and other confounding information. From these studies, the TCEQ considered the following four epidemiology studies to contain adequate dose–response data for an updated assessment of the carcinogenic potential of arsenic and the development of a URF:

- Enterline et al. (1987a, 1995) updates of the Asarco smelter in Tacoma, Washington;
- Lubin et al. (2000, 2008) updates of the Anaconda smelter in Montana studies;
- Ronnskar Copper Smelter cohort study in Sweden (Järup et al., 1989; Viren and Silvers, 1994),
- Jones et al. (2007) updates of the UK smelter (Binks et al., 2005; Jones et al., 2007).

While, the TCEQ's arsenic peer review panel agreed that these studies were the most appropriate for deriving a URF, they additionally recommended excluding the Jones et al. (2007) study (UK study) because it used a weighted cumulative exposure to arsenic as the dose metric as opposed to the standard cumulative exposure. Other epidemiology studies without adequate dose–response data added to the weight-of-evidence that arsenic exposure is associated with lung cancer.

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1.1. Tacoma smelter

The Enterline and Marsh (1982) study used exposure estimates inferred from the Pinto et al. (1976) study. The Pinto et al. (1976) study reported an association between airborne arsenic concentrations and urinary arsenic concentrations. Thereafter, Enterline et al. (1987a) reported that Pinto et al. (1976) did not take into account prior arsenic exposures through diet. This resulted in high baseline levels of urinary arsenic that did not depict the true relationship between urinary arsenic measurements and workplace airborne arsenic levels. While the USEPA's URF from the Tacoma smelter based on the Enterline and Marsh (1982) study did not use the updated exposure estimates with additional years of follow-up included in Enterline et al. (1987a, 1995), the TCEQ used the updated exposure estimates to calculate an updated URF from the study because they represent more realistic estimates for cumulative exposure for workers.

1.2. Montana smelter

Similarly, for the Montana smelter, Lubin et al. (2000, 2008) updated exposure estimates that included additional years of follow-up. The exposure estimates calculated by Lubin et al. (2000) were adjusted to take into account the reduction in exposure due to the use of air filtration masks in heavy-exposure areas. This resulted in more representative arsenic cumulative exposure estimates that were lower than the exposure estimates in the Brown and Chu (1983a,b,c), Lee-Feldstein (1983) and Higgins et al. (1982) studies used in USEPA's derivation of URFs. The TCEQ used the updated exposure estimates from the Lubin (2000, 2008) studies to calculate a URF because they represent more realistic estimates for cumulative exposure for workers, especially in heavy exposure areas where respirators were used.

1.3. Sweden smelter

In addition to the Tacoma and Montana smelter studies, more recent studies based on Swedish smelter workers (Järup et al., 1989; Viren and Silvers, 1994) were included by TCEQ in the derivation of the URF. The Swedish smelter studies were not available to the USEPA when they finalized the inhalation URF in 1984 (USEPA, 1984). Järup et al. (1989) concluded that lung cancer mortality was related to the estimated average intensity of exposure to arsenic but not to duration. The TCEQ used these exposure estimates to calculate a URF because these studies accounted for the circumstances where in the workers were exposed to higher concentrations of arsenic over shorter durations as opposed to lower concentrations over longer durations and are realistic estimates of cumulative exposure for workers, especially for shorter-term workers.

1.4. UK smelter

Another study considered by the TCEQ for dose–response analyses was the Jones et al. (2007) study. Jones et al. (2007) investigated the relationships between excess lung cancer mortality at a tin smelter in Humberside, UK and inhalation exposure to lead, antimony, arsenic, cadmium and radioactivity, with the aim of identifying the cause or causes of the excess lung cancer and quantitative measures of exposures. The cohort was composed of male former employees at the tin smelter initially investigated by Binks et al. (2005). Jones et al. (2007) results indicated there were no significant associations found between lung cancer mortality and simple cumulative exposure to any of the substances studied. However, when cumulative exposures were weighted according to time since exposure and attained age, significant associations were found between lung cancer mortality and exposures to arsenic, lead and antimony. Although the TCEQ included information from the Jones et al. (2007) study in the TCEQ's arsenic Development Support Document (DSD) (TCEQ, 2012) because it had adequate dose–response information, the results were not used in the final URF calculation because of potential confounding by co-exposures and because a different dose metric than the cumulative exposure used for the other three cohorts could not be combined (i.e., the "weighted cumulative exposure") and was not was not generally accepted by the TCEQ's arsenic peer-reviewers.

1.5. Updated TCEQ arsenic inhalation URF

The main purpose of this paper is to present the procedures used in the development of an inhalation URF based on an updated inhalation carcinogenic assessment. The USEPA's inhalation URF for arsenic derived in 1984 was based on outdated epidemiological data. The TCEQ derived an inhalation URF using updated epidemiological data and updated exposure estimates of the two studies included in the USEPA (1984) assessment in addition to a recent epidemiological study based on a Swedish cohort. The TCEQ used combined analysis techniques to obtain a final URF that summarized the data from three different studies.

It is important to conduct an up-to-date toxicity assessment of arsenic based on the most recent scientific data. There is an air pollutant watch list in Texas for arsenic as well as other metals. The updated URF will be used to evaluate TCEQ's ambient air monitoring data and modeled ground-level air concentrations for the TCEQ's air permitting program.

This paper is a summary of the carcinogenic section of the TCEQ's arsenic DSD (TCEQ, 2012) that underwent an external scientific peer review organized by Toxicology Excellence for Risk Assessment and two public comment periods. The final arsenic DSD and response to comments are posted on the TCEQ website (TCEQ, 2012). Please refer to ATSDR (2007) and TCEQ (2012) for additional information on these studies as well as for a detailed discussion on the weight of evidence (WOE) from the epidemiological studies that show arsenic exposure to be associated with lung cancer.

2. Materials and methods

Several epidemiological studies of arsenic-exposed smelter workers have reported that inhalation exposure to inorganic arsenic increases the risk of lung cancer. ATSDR (2007) concluded that chronic inhalation exposure to inorganic arsenic increases the risk of lung cancer. The TCEQ considered three epidemiological studies of workers exposed to arsenic to use in a combined analysis to develop an updated URF. The three studies had adequate dose–response data and similar dose metrics so that a combined analysis approach could be used to derive a final URF. Detailed information on the studies and discussions on the inclusion of the studies are available in the arsenic DSD (TCEQ 2012). Summary information for these studies is provided in Table 1 and historical information on the three studies is discussed in the later sections.

The TCEQ guidelines for carcinogenic assessments (TCEQ 2006) employ the four-step risk assessment process formalized by the National Research Council (1983, 1994, 2001), and uses procedures recommended in the most recent USEPA cancer guidelines (2005a,b) and the scientific literature. For chronic adverse effects determined to be associated with linear dose–response relationships in the low-dose region, which is the default assumption for arsenic based on a MOA analysis, the TCEQ adopts or derives URFs. For adverse effects associated with a linear dose–response, it is assumed that an effects threshold does not exist. Therefore, a linear