Respiratory Cancer and Inhaled Inorganic Arsenic in Copper Smelters Workers: A Linear Relationship with Cumulative Exposure that Increases with Concentration

Jay H. Lubin,1 Lee E. Moore,2 Joseph F. Fraumeni Jr.,3 and Kenneth P. Cantor2

1Biostatistics Branch, Division of Cancer Epidemiology and Genetics, National Cancer Institute, Rockville, Maryland, USA; 2Occupational and Environmental Epidemiology Branch, Division of Cancer Epidemiology and Genetics, Rockville, Maryland, USA; 3Office of the Director, Division of Cancer Epidemiology and Genetics, National Cancer Institute, Rockville, Maryland, USA

BACKGROUND: Inhalation of high levels of airborne inorganic arsenic is a recognized cause of respiratory cancer. Although multiple epidemiologic studies have demonstrated this association, there have been few analyses of the mathematical relationship between cumulative arsenic exposure and risk of respiratory cancer, and no assessment as to whether and how arsenic concentration may modify this association.

OBJECTIVES: The objective is an evaluation of the shape of the relationship between respiratory cancer mortality and cumulative inhaled arsenic exposure among copper smelter workers, and the modification of that relationship by arsenic concentration.

METHODS: We used Poisson regression methods to analyze data from a cohort of arsenic-exposed copper smelter workers under a linear-exponential model for the excess relative risk.

RESULTS: Within categories of arsenic concentration, the association between respiratory cancer and cumulative arsenic exposure was consistent with linearity. The slope of the linear relationship with cumulative exposure increased with increasing arsenic concentration category.

CONCLUSIONS: Our results suggested a direct concentration effect from inhaled inorganic arsenic, whereby the excess relative risk for a fixed cumulative exposure was greater when delivered at a higher concentration and shorter duration than when delivered at a lower concentration and longer duration.

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The International Agency for Research on Cancer (1980, 1987) identifies inhalation of inorganic arsenic as a cause of lung cancer in humans. The evidence has come primarily from epidemiologic studies of miners and smelter workers who inhaled high levels of inorganic arsenic in airborne dust. Although increased risk of lung cancer from inhaled arsenic appears related to direct effects on the respiratory tract, there may be a systemic effect as well, because ingestion of high amounts of inorganic arsenic in drinking water has been associated with lung cancer mortality at levels comparable with occupational risks from inhaled arsenic (Bates et al. 1992; Lubin et al. 2000). Information on the mathematical relationship between cumulative inhaled arsenic exposure and respiratory cancer mortality is limited. Although a comparative evaluation of several occupational cohorts, mostly smelter workers, suggested a concave relationship between respiratory cancer mortality and cumulative arsenic exposure (Hertz-Picciotto and Smith 1993), a subsequent update of one large study revealed that its apparent nonlinearity was an artifact of exposure assessment and that relative risk (RR) trends with cumulative arsenic exposure were consistent with a linear relationship (Lubin et al. 2000). Previous analyses have focused on cumulative arsenic exposure and the shape of the exposure–response relationship, without considering the possible influence of arsenic concentration.

In the present analysis, we applied a novel methodology used previously in a study of smoking-related lung cancer (Lubin and Caporaso 2006) to model cumulative arsenic exposure and arsenic concentration. In particular, we examined the consequences of exposure “delivery,” that is, whether the RR of respiratory cancer at a fixed cumulative exposure delivered at higher arsenic concentration for shorter duration was greater than, equal to, or less than the RR from an equal cumulative exposure delivered at longer duration. We refer to these patterns as direct (increasing), constant (no variation), or inverse (decreasing) “exposure rate” effects.

Standard analyses of joint RRs by duration of arsenic exposure and arsenic concentration for nonexposed individuals as the referent group are problematic for characterizing the effects of arsenic concentration, because cumulative exposure varies. For illustration, consider duration of cigarette smoking, smoking intensity (cigarettes smoked per day), and total pack-years (years of smoking times cigarettes per day divided by 20). In a standard log-linear RR regression model that includes duration of smoking and cigarettes per day, the intensity parameter represents the ln(RR) per cigarette per day at a fixed duration. Interpretation of the duration parameter is similar but at a fixed intensity. A comparison of RRs at two different intensities reflects not only different intensities, but also different total pack-years. For example, at 30 years’ duration, RRs at 20 and 30 cigarettes per day reflect different intensities and different total pack-years—namely, 30 and 45 pack-years, respectively. Thus, RR patterns with duration and intensity cannot be viewed as “independent” because of the intrinsic confounding of pack-years. In contrast, in a model that includes pack-years and cigarettes per day, the parameter for cigarettes per day represents the comparison of risk for exposure delivered at lower intensity for longer duration with risk for an equal total exposure delivered at higher intensity for shorter duration (Lubin and Caporaso 2006). We use this framework to analyze inhalation of airborne inorganic arsenic in a cohort mortality study of smelter workers conducted in Montana (Lee and Fraumeni 1969; Lee-Feldstein 1983; Lubin et al. 1981, 2000).

Our goal of modeling the cumulative airborne arsenic exposure and arsenic concentration is to estimate a descriptive function that defines the modifying effect of concentration on the association between cumulative exposure and respiratory cancer. This effect modification is conceptually similar to the “dose rate effective factor” used in radiation epidemiology that describes for a specific type of radiation the effects on disease risk of total radiation dose delivered at lower (protracted or highly fractionated) dose rates compared with the effects at higher (or acute) dose rates (National Research Council 2006).

Materials and Methods

Data. The cohort study enrolled workers employed at a Montana copper smelter for ≥ 1 year before 1957, with follow-up starting 1 year after initial employment or 1 January 1938, Address correspondence to J.H. Lubin, Biostatistics Branch, Division of Cancer Epidemiology and Genetics, National Cancer Institute, 6120 Executive Blvd., Room 8042, Rockville, MD 20852 USA. Telephone: (301) 496-3357. Fax: (301) 402-0081. E-mail: lubinj@mail.nih.gov

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whichever was later (Lee and Fraumeni 1969). The present analysis included 8,014 workers followed through 1989 (Lubin et al. 2000). We determined vital status from the National Death Index (http://www.cdc.gov/nchs/ndi.htm) and other sources, with causes of death recorded from death certificates. A total of 4,930 (62%) workers were deceased.

Following previous analyses of this cohort, we consider respiratory cancer mortality as the primary outcome.

In the 1960s, investigators ranked each work site from 1 to 10 for its potential arsenic exposure. We used the power form of the function $g(x)$.

Table 1. Descriptive statistics for the Montana cohort study of copper smelter workers.

| Characteristic              | All data       | Restricted data |
|----------------------------|----------------|-----------------|
| No. of workers             | 8,014          | 7,887           |
| Person-years               | 256,850        | 144,851         |
| Follow-up years            | 196–1989       |                 |
| Mean cumulative arsenic exposure (mg/m³-year) | 0.35 | 0.36 |
| Mean duration (years)      | 10.3           | 14.9            |
| Respiratory cancer cases   |                |                 |
| No.                       | 446            | 261             |
| Mean cumulative arsenic exposure (mg/m³-year) | 7.0 | 10.4 |
| Mean arsenic concentration (mg/m³) | 0.41 | 0.40 |
| Mean duration (years)      | 17.4           | 26.0            |
| Crude respiratory cancer mortality rate \* 1,000 | 1.74 | 1.80 |

*Person-years in current and recent former (< 5 years) workers and workers with last employment at ≥ 55 years of age. 

Table 2. Summary data, respiratory cancer mortality rates, unadjusted and adjusted SMRs relative to U.S. white males by cumulative arsenic exposure (mg/m³-years) and arsenic concentration (mg/m³) for the Montana cohort study of copper smelter workers.

| Cumulative arsenic exposure (mg/m³-year) | Mean arsenic concentration (mg/m³) |
|----------------------------------------|----------------------------------|
| < 0.75                                  | 0.29                             |
| 0.75–1.99                               | 0.30–0.39                        |
| 2.0–4.9                                 | 0.40–0.49                        |
| 5.0–9.9                                 | 0.50–0.74                        |
| 10.0–14.9                               | 0.80–0.99                        |
| ≥ 15.0                                  | 1.00–1.5                         |
| Cases                                   | 62                               |
| Person-years                            | 71424.0                          |
| Mean                                   | 0.47                             |
| Crude rate x 1,000                      | 0.87                             |
| SMR                                    | 0.97                             |
| 95% CI                                 | 0.8–1.3                          |
| SMR%                                   | 0.84                             |
| 90% CI                                 | 0.6–1.1                          |

*SMRs adjusted for differences by calendar period and country of birth between rates of respiratory cancer in U.S. males and estimated respiratory cancer rates in a hypothetical group of nonexposed workers.

We defined indicator variables $c_i$, $i = 1, \ldots, d$, for $d$ concentration categories where $c_i$ = 1 for intensities within category $i$ and zero otherwise, and modeled disease rate $r(x, d, c)$ as

$$r(x, d, c) = \exp(\alpha^T x) \cdot RR(d, c) \cdot \exp(\gamma^T x) \cdot \exp(\delta^T x) \cdot \exp(\beta^T x)$$

where $d$ is cumulative arsenic exposure and $x$ is arsenic concentration. The vectors of variables $x$ and parameters $\alpha$, $\beta$, $\gamma$, and $\delta$ denote vectors transpose, describe disease rates in nonexposed workers. Within concentration category $i$, RR is linear in $d$; that is, $RR(d, c) = 1 + \gamma_i d$, where $\gamma_i$ is the slope of the linear exposure–response, or ERR/mg/m³-year (ERR, excess relative risk). We used Wald-type confidence intervals (CIs) for $\gamma_i$ after reparameterizing $\gamma_i$ as $\exp(\gamma_i^*)$ to avoid range restrictions. Factoring out $\gamma_i$, we rewrite $RR(d, c)$ as

$$RR(d, c) = 1 + \beta d g(c),$$

which suggested the following model for continuous concentration:

$$RR(d, c) = 1 + \beta d \cdot g(c),$$

where $\beta$ defined ERR/mg/m³-year at $g(c) = 1$. The $g(c)$ function represents the modifying effects of arsenic concentration on the exposure–response relationship. Preliminary analysis suggested using the power form $g(c) = \exp(\phi \ln(c))$, where $\phi > 0$, $\phi = 0$, or $\phi < 0$ denotes a direct (increasing), constant (no variation), or inverse (decreasing) concentration effect, respectively. Model fit did not improve with the addition of $c$ or $\ln(c)^2$.

We extended model 1 to

$$RR(d, c) = 1 + \Sigma \gamma_i d \cdot \exp(\delta_i d)$$
to evaluate departure from linearity, where $\delta_i$ reflects concavity ($\delta_i < 0$) or convexity ($\delta_i > 0$) of the ERRs with cumulative exposure for the $i$th concentration category. The null hypothesis $\delta_i = 0$ specified no departure from linearity. We applied a similar extension to model 2.

Because all workers were exposed, we included the natural logarithm of the age- and year-specific respiratory cancer rates of U.S. males as a fixed offset variable ($x$) to represent rates in nonexposed workers. The model thus represented a regression equation for standardized mortality ratios (SMR) (Breslow and Day 1987). Although model 2 reflected relative SMRs, we refer to quantities as RRs.

Day 1987). Although model 2 reflected relative SMRs, we refer to quantities as RRs. For analyses, we used the Epicure suite of programs (Preston et al. 2004).

Results

The person-year–weighted mean cumulative arsenic exposure was 3.7 mg/m$^3$-years, with a crude respiratory cancer mortality rate of 1.73 per 1,000 person-years, based on 446 total respiratory cancer deaths (Table 1). The SMR for respiratory cancer was 1.56 (95% CI, 1.4–1.7). In the restricted data, the mean cumulative arsenic exposure was 5.4 mg/m$^3$-years, the crude respiratory mortality rate per 1,000 person-years was 1.80, and the SMR was 1.87 (95% CI, 1.7–2.1).

SMRs increased with cumulative arsenic exposure and with arsenic concentration (Table 2). The SMR in the lowest concentration category was significantly elevated, suggesting a difference between respiratory cancer mortality rates for U.S. males and a hypothetical group of nonexposed workers. We fitted model 1 with continuous cumulative arsenic exposure and six categories of arsenic concentration (square symbols, with CIs omitted for clarity), the fitted model 2 using continuous data (solid line), its pointwise 95% CI (dashed lines), and the model for no variation with concentration (model 2 with $\phi = 0$; dotted line). The ERR/mg/m$^3$-year estimate ($\beta$) was $\beta = 0.115$ (95% CI 0.07–0.19) (Table 3), and varied significantly with arsenic concentration ($p < 0.01$). After adjusting for cumulative arsenic exposure, the ERR/mg/m$^3$-year increased with increasing concentration (estimate of $\phi$ was 1.123 (95% CI, 0.41–1.84). Results in the restricted data were similar.

Using model 2, we evaluated time since last arsenic exposure as a modifier of the arsenic exposure–response relationship. We focus on the restricted data, although we show results for all data for completeness. Although variations were not statistically significant, the cumulative arsenic exposure effect ($\beta$) decreased with time since last arsenic exposure by factors of 1.0, 0.8, and 0.2 for < 5, 5–14, and ≥ 15 years since last exposure, respectively (Table 3; change in deviance = 2.6 and $p = 0.27$ comparing models B0-R and T1-R; or change in deviance = 1.2 and $p = 0.55$ comparing models T2-R and T3-R). The arsenic concentration effect ($\phi$) also varied with time since last exposure, but changes in deviance were smaller (Table 3; change in deviance = 1.9 and $p = 0.39$ comparing models B0-R and T2-R, or change in deviance = 0.5 and $p = 0.78$ comparing T1-R and T3-R).

In the restricted data, there was a suggestion of declining arsenic effects with attained age, but no preference for effect modification of age with either cumulative arsenic exposure or arsenic concentration.

Discussion

In our study of copper smelter workers, RRs for respiratory cancer increased linearly with cumulative arsenic exposure within categories of arsenic concentration. In addition, we found a direct concentration effect, whereby the slope of the linear exposure–response relationship increased with arsenic concentration. This pattern implied that for equal cumulative arsenic exposure, the RR of respiratory cancer mortality was greater for cumulative arsenic exposure delivered at higher concentration for shorter duration compared with cumulative exposure delivered at lower concentration for longer duration.

Figure 1. RRs of respiratory cancer mortality by categories of cumulative arsenic exposure (mg/m$^3$-years) and arsenic concentration (mg/m$^3$) relative to U.S. mortality rates for white males, adjusted to nonexposed workers, and fitted linear ERR models for cumulative arsenic exposure: 0.29 mg/m$^3$ (A), 0.30–0.39 mg/m$^3$ (B), 0.40–0.49 mg/m$^3$ (C), and ≥ 0.50 mg/m$^3$ (D). Estimates of the ERR per mg/m$^3$-year and 95% CIs for the four concentration categories were as follows: A, 0.016 (0.005 to 0.041); B, 0.067 (0.024 to 0.119); C, 0.077 (0.017 to 0.198); D, 0.072 (0.043 to 0.107).
duration. The increase in the exposure–response relationship within each arsenic concentration category occurred for the full range of concentrations experienced by smelter workers, suggesting that the direct concentration effect was not rate limited within this range.

One explanation for the impact of arsenic concentration on the association between cumulative arsenic exposure and respiratory cancer may be found in the concentration-dependent ability of cells to methylate and detoxify arsenic. Although human populations differ, most humans exposed to arsenic excrete 10–30% inorganic arsenic, 10–20% monomethylarsonic acid [MMA(V) and MMA(III)], and 60–80% dimethylarsinic acid [DMA(V) and DMA(III)]. The pentavalent metabolites MMA(V) and DMA(V) are generally considered less toxic than inorganic arsenite or arsenate. Trivalent methylated arsenic metabolites are more genotoxic than inorganic arsenite both in vitro and in vivo (Styblo et al. 2002). Although MMA(III) and DMA(III) can be measured in urine, epidemiologic studies to date have not measured trivalent arsenicals because of the preservation techniques required (Aposhian et al. 2000; Le et al. 2000; Mandal et al. 2001; Valenzuela et al. 2005). Epidemiologic studies have used the percent MMA of total inorganic arsenic and the MMA:DMA ratio as surrogate markers of methylation efficiency of ingested arsenic, with increased levels of excreted pentavalent MMA and DMA:DMA ratio in urine indicating reduced methylation efficiency. Studies of arsenic in drinking water conducted in Taiwan, Argentina, Bangladesh, and certain areas of the United States have reported elevated risks of bladder and skin cancers associated with an increased percent MMA in urine, as well as a greater MMA:DMA ratio (Ahsan et al. 2007; Chen et al. 2003a, 2003b; Hsueh et al. 1997; Pu et al. 2007; Steinmaus et al. 2006; Yu et al. 2000). These findings are supported by toxicologic studies showing that methylated arsenicals, particularly MMA(III), have a greater affinity than the nonmethylated forms for protein binding to monothiol, dithiol, and trithiol sites, which can disrupt a number of processes, including gene transcription, glutathione synthesis, DNA methylation, DNA repair, cell division, generation of reactive oxygen species, and signal transduction pathways within cells (Cullen and Reimer 1989; Kitchin and Wallace 1997). Epidemiologic studies to date support only the notion that concentration of exposure has a direct impact on the degree of toxicity and/or DNA damage acquired. Total cumulative arsenic exposure is a function of both concentration and duration of arsenic exposure. Our findings suggest that rates of arsenic biotransformation and excretion are concentration dependent. Toxicologic studies designed to compare cellular and genetic toxicity at a given total cumulative dose delivered at different dose rates are needed to enhance understanding of the mechanistic implications of our results.

Consistent with our findings, two epidemiologic studies have suggested that the toxic effects from cumulative arsenic exposure in drinking water are greater among individuals exposed at higher, as opposed to lower, concentrations. In a case–control study of arsenic-related skin lesions in a screened population in Bangladesh, about 70% of subjects consumed drinking water with arsenic concentrations > 50 μg/L (Rahman et al. 2006). For similar levels of cumulative arsenic exposure, the odds ratios were higher for subjects with older ages at first exposure compared with those younger at first exposure. Because older age at first exposure would reflect shorter duration of exposure, the results suggested higher risks for cumulative exposures with shorter durations and correspondingly higher concentrations, as we observed for lung cancer among smelter workers. In a case–control study of bladder cancer in New Hampshire, odds ratios among smokers increased with higher concentrations of toenail arsenic, with risks being greater among individuals with shorter (< 15 years) compared with longer residence in the current home (Karagas et al. 2004).
A threshold for the carcinogenic effects of arsenic in drinking water at about 150 µg/L, below which there is no risk from exposure, has been suggested (Lamm et al. 2006). Although studies of noncancer outcomes, such as arsenical dermatoses, cardiovascular disease, and cerebrovascular disease, do not support a threshold (Ahsan et al. 2006; Engel et al. 1994; Rahman et al. 2006; Yu et al. 2006), studies of cancer outcomes after relatively low levels of exposure have been limited by low power and potential exposure misclassification (Cantor and Lubin 2007).

Our results may inform the exposure threshold issue. In areas of Taiwan with endemic blackfoot disease, Bates et al. (1992) estimated that consuming drinking water with 470 µg/L arsenic resulted in a lifetime intake of 30,000 mg arsenic. Ingestion of drinking water with 150 µg/L arsenic therefore corresponds approximately to a lifetime intake of 9,600 mg arsenic. Measurement of urinary arsenic and its metabolites serves as a measure of absorption of inhaled arsenic through the respiratory tract, because arsenic excretion occurs mainly through the kidneys (World Health Organization 2001). In a study of smelter workers in Tacoma, Washington, investigators empirically derived the following relationship between inhaled and urinary arsenic levels: airborne arsenic in micrograms per cubic meter = 0.0064 (urine arsenic in micrograms per liter)\(^{1.924}\) (Entenline et al. 1987). In our data, mean airborne arsenic concentrations for the four categories in Figure 1 ranged from 0.29 to 0.65 mg/m\(^3\), and therefore correspond roughly to urinary arsenic levels from 263 to 400 µg/L. Assuming 2 L urine per day, 250 working days per year, no other sources of arsenic and no accumulation of arsenic in the body (Bates et al. 1992), the mean durations of exposure, which ranged from 9.7 to 12.1 years for the four categories, correspond to mean total arsenic intakes of 1,315 (= 263 x 2 x 250 x 10/year/1,000), 1,420, 1,649, and 1,996 mg arsenic, respectively. Thus, cumulative arsenic exposure in the smelter workers corresponded to < 20% of the lifetime arsenic intake at the postulated threshold. Our finding of a linear relationship for the RR of respiratory cancer mortality across the full range of cumulative arsenic exposures within each category of arsenic concentration argues against a threshold at 150 µg/L.

In summary, our cohort study of copper smelter workers revealed a linear relationship between cumulative arsenic exposure and respiratory cancer mortality within categories of arsenic concentration. In addition, we found a direct concentration effect on the exposure–response relationship, indicating that for a fixed level of cumulative arsenic exposure, inhalation of higher concentrations of arsenic over shorter durations was more deleterious than lower concentrations over longer durations.

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