

ORIGINAL ARTICLE

Cadmium and lung cancer mortality accounting for simultaneous arsenic exposure

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ABSTRACT

Objectives Prior investigations identified an association between airborne cadmium and lung cancer but questions remain regarding confounding by arsenic, a well-established lung carcinogen.

Methods A cadmium smelter population exhibiting excess lung cancer was re-analysed using a retrospective exposure assessment for arsenic (As), updated mortality (1940–2002), a revised cadmium (Cd) exposure matrix and improved work history information.

Results Cumulative exposure metrics for both cadmium and arsenic were strongly associated making estimation of their independent effects difficult. Standardised mortality ratios (SMRs) were modelled with Poisson regression with the contribution of arsenic to lung cancer risk constrained by exposure–response estimates previously reported. The results demonstrate (1) a statistically significant effect of Cd independent of As (SMR=3.2 for 10 mg-year/m³ Cd, $p=0.012$), (2) a substantial healthy worker effect for lung cancer (for unexposed workers, SMR=0.69) and (3) a large deficit in lung cancer mortality among Hispanic workers (SMR=0.27, $p=0.009$), known to have low lung cancer rates. A supralinear dose-rate effect was observed (contribution to risk with increasing exposure intensity has declining positive slope). Lung cancer mortality was somewhat better predicted using a cadmium burden metric with a half-life of about 20–25 years.

Conclusions These findings support an independent effect for cadmium in risk of lung cancer mortality. 1/1000 excess lifetime risk of lung cancer death is predicted from an airborne exposure of about 2.4 $\mu\text{g}/\text{m}^3$ Cd.

INTRODUCTION

Cadmium is present in nickel–cadmium batteries, pigments used in paint and plastics, electronic components and is generated as a fume in some brazing operations. It is an electrochemical and mechanical plating metal for products such as industrial fasteners. A non-ferrous smelter located near Denver, CO, USA, began operation in the mid-19th century producing a variety of non-ferrous metals including lead (1886–1918), arsenic (1918–1925), cadmium (1925–1984) and indium, thallium and selenium.^{1,2} Arsenic production ended in 1925, but arsenic remained at this smelter as a minor component in raw materials originating from bag-house (air filter) dust collections in

What this paper adds

- ▶ Previously reported associations between cadmium exposure and lung cancer were confounded by arsenic.
- ▶ Using prior estimates for the exposure–response for arsenic and lung cancer, the independent effect of cadmium was estimated.
- ▶ Occupational airborne cadmium is a lung carcinogen independent of arsenic.
- ▶ There is suggestion of a negative dose-rate effect and slight diminution of risk with time since exposed.

smelters or processing facilities at other sites of this employer (ASARCO). Previous analyses of lung cancer mortality in these cadmium workers identified excess lung cancer mortality,^{1–3} but questions remain concerning confounding by arsenic.³ One analysis found excess lung cancer mortality only among cadmium workers with high exposure to arsenic.³ Arsenic is a relatively potent lung carcinogen for which several-fold excesses of lung cancer mortality have been observed in copper smelter populations.^{4,5} The current US OSHA permissible exposure limit for cadmium is 0.005 mg/m³ (8 h time-weighted average).⁶ In order to differentiate the effects of cadmium and arsenic on lung cancer risk, a detailed retrospective exposure assessment for arsenic was conducted for this smelter as had previously been performed for cadmium. In addition, a more detailed work history was used and follow-up of vital status was extended through 2002.

METHODS**Study population**

The original smelter cohort consisted of all white male hourly employees and foremen with at least 6 months in a production area between 1 January 1940 and 31 December 1969 ($n=606$).^{1–3} Worker entry into follow-up occurred on the later of 1 July 1940 or 6 months after the date of hire. Previous follow-up until 1984⁵ was extended with a search of the National Death Index⁷ covering the period 1985–2002 for workers known to be alive in 1984. Microfilmed employment records were available for the period 1929–1983; these had been used by Sorahan and Lancashire³ but not in earlier analyses.

These records permitted accounting for workers' proportion of time spent daily in work activities, but actual hours worked each day were not retrieved. Work history after 1983 was unknown (for the 15 workers still active) implying cumulative exposures (lag=5 year) were underestimated for up to 186 person-years of observation (0.8% of total). Smoking information was unavailable.

Exposure assessment

An earlier cadmium (Cd) exposure assessment, based on 173 air samples over the period 1944–1983,^{3 8 9} was revised following further analysis on personal protective equipment (PPE) use (Finley 'Estimating Historical Arsenic Exposures in a Cadmium Smelter', University of Cincinnati, 2003, master thesis). The protection factors for PPE use were developed using parallel air-sampling and urinary Cd concentration data. This effort was an extension of work based on laboratory respirator studies previously reported by Smith *et al.*⁹ The result was a protection factor of 2.0 for the period prior to 1965 and 4.0 for the subsequent years. PPE-adjusted Cd concentrations ranged from 0.001 to 8.5 mg/m³. The resulting exposure matrix consisted of estimated Cd air concentrations for 32 job activities in six time periods: <1950, 1950–1954, 1955–1959, 1960–1964, 1965–1979 and 1980–2002. The few job activities lacking exposure data were assigned the same levels as generic support activities at this smelter.

For the As exposure assessment, there were 165 determinations for airborne arsenic from 44 area and 121 personal samples in the period 1944–1983. It was assumed that the same protection factors applied to both Cd and arsenic (As) exposures. The arsenic exposure matrix was based on models predicting air concentrations of As from (1) total dust measurements, (2) feedstock arsenic levels recorded since 1939 and (3) urinary arsenic measurements (50 samples, all but five from 1974–1975) (Finley 'Estimating Historical Arsenic Exposures in a Cadmium Smelter', University of Cincinnati, 2003, master thesis). This work was blinded to mortality outcomes. The model development followed the general strategy used by Hornung and colleagues¹⁰ in a study of ethylene oxide exposures. The dependent variable was the natural log of airborne arsenic concentrations since the data were highly right skewed, as is typical for occupational exposures. Independent variables included job activity group, calendar year, annual pounds of arsenic in feedstock and sample type. Examination of arsenic concentrations by calendar year revealed that sample year would be the strongest predictor of arsenic concentrations. Consequently, particular attention was paid to modelling for temporal trends in arsenic exposure from 1944 to 1983 in both a parametric form, using either a polynomial model or log of calendar year, as well as a smoothing function using a penalised spline fit.¹¹ The arithmetic mean-concentration was calculated using the relationship: $AM = \exp(\mu + 0.5(\sigma^2))$, where μ is the predicted mean from the model of the log-transformed data and σ^2 is the mean squared error from the model. Arsenic exposure concentrations during 1939 to 1943 were estimated using the feedstock data with the year effect fixed at 1944. The resulting exposure matrix specified As levels yearly from 1939 to 1983 in each of four groups of job activity titles observed to have similar levels. Arsenic exposure levels prior to 1939 (when feedstock data were absent) were assumed to be the same as those estimated for 1939, and those after 1983 were assumed to be the same as those in 1983. Only 12.5% of the study population was hired prior to 1939.

From work histories and the exposure matrices, an exposure history was compiled for each worker consisting of his average Cd and As air concentration in each 10-day period since 1 January 1920. For work in the period prior to 1929 when detailed work histories were unavailable, exposures were assigned as a worker's first known exposure. Cumulative exposures as a function of time of observation were calculated as follows: $cumX(t) = 0.02738 \times \sum_{i=t_1}^t X(i)^p$, where time is in 10-day units, t_1 is time-index at first exposure, t is time-index at observation, $0.02738 = 10/365.25$, X is exposure in mg/m³ and $cumX$ is in mg-year/m³.

To assess possible dose-rate or exposure intensity effects, cumulative exposure to Cd was also computed by summing the exposure intensity (air concentration) raised to some power, p , in the range 0.25–1.5¹²:

$$cumXp(t) = 0.02738 \times \sum_{i=t_1}^t X(i)^p.$$

Another exposure metric in the form of a burden was computed¹³ on the assumption that the biological effect resulting from exposure that creates future cancer risk declines with some half-life, $thalf$:

$$burX(t) = 0.02738 \times \sum_{i=t_1}^t X(i) \exp[(i-t) \ln(0.5)/thalf].$$

Intensity threshold was examined by excluding exposures below thresholds in the range 0.01–0.10 mg/m³ in computing the cumulative exposure.¹² These alternative metrics were examined using profile likelihoods with which a change in deviance ($\Delta[-2\ln L]$) of 3.84 over a specified range of parameter would correspond to a p value of 0.05.¹⁴

Statistical analysis

The rate of lung cancer mortality was modelled using Poisson regression¹⁵ in Epicure¹⁶ with a data set consisting of all person-time jointly classified on (1) age (5-year intervals: 15–19, ..., 80–84, 85+), (2) calendar time (5-year intervals: 1940–1944, ..., 1995–1999, 2000+), (3) Hispanic ethnicity (yes/no), (4) the Cd cumulative exposure metric and (5) As cumulative exposure (~12 000 records). For each 10 days of observation, the Cd and As metrics were jointly classified in 50×50 levels which (for Cd) increased in width logarithmically from 0.22 mg-year/m³ at the lowest level to 1.72 mg-year/m³ at the highest. The person-time weighted cell means of the exposure metric in the classified observations were used as continuous predictors in regression models. Analyses additionally involving classification on duration of Cd exposure were performed from a file consisting of a record for each 10 days of worker observation without joint classification (>800 000 records). To account for delay between an initiating event in carcinogenesis and a resulting death, exposures were lagged 5 years in most analyses, a choice based on the previous study.³

To efficiently control age and calendar time confounding, an offset term was added (with parameter fixed at 1.0) to regression models consisting of the expected number of lung cancer deaths in each stratum of the classification table. This was based on US national rates specific for age and year in white men¹⁷ and produced models of the standardised mortality ratio (SMR). The estimated parameters in these models pertain to ratios of SMRs and can be interpreted as standardised rate ratios (RR) in the absence of an exposure–age interaction (ie, effect modification by age).¹⁸ For this reason, models with an exposure–age interaction were also evaluated.

Several models of SMR were evaluated using various transforms of cumulative exposure and including (1) loglinear and (2) linear relative rate (RR) specifications:

loglinear or exponential form:

$$\exp(a_0 + a_1 \text{Ind}(\text{His}) + a_2 \text{cumX})$$

linear relative rate, linear term:

$$[\exp(a_0 + a_1 \text{Ind}(\text{His}))] \times [1 + a_2(\text{cumX})]$$

linear relative rate, square-root term:

$$[\exp(a_0 + a_1 \text{Ind}(\text{His}))] \times [1 + a_2(\text{cumX})^{0.5}]$$

linear relative rate, power model:

$$[\exp(a_0 + a_1 \text{Ind}(\text{His}))] \times [1 + a_2 \ln(\text{cumX} + 1)]$$

linear relative rate, quadratic terms:

$$[\exp(a_0 + a_1 \text{Ind}(\text{His}))] \times [1 + a_2 \text{cumX} + a_3(\text{cumX})^2]$$

where Ind(His) is an indicator of Hispanic ethnicity.

Relative fit was evaluated by comparing the change in $-2\ln$ (likelihood) with addition of exposure metric terms in the models. The 95% CIs were based on the likelihood ratio test (lrt).

In order to separate the independent contributions of the correlated exposures for Cd and As, models were fit in which the As-associated lung cancer risk was imposed using exposure-response estimates from previous studies.^{4 5} This is a form of 'indirect adjustment' for a confounder¹⁵ that has more often been applied for addressing potential confounding by unknown smoking behaviour.¹⁹ Enterline *et al*⁵ fit power curves for lung cancer SMRs and arsenic exposure at two copper smelters with internal comparisons which produced model forms such as: $\text{SMR} = 1.0 + 0.04897 \text{cumX}^{0.3499}$ (unlagged, in $\mu\text{g-year}/\text{m}^3$). Lee-Feldstein⁴ calculated SMRs in cumulative exposure strata (in $\text{mg-month}/\text{m}^3$) using external US rates at one of the copper smelters analysed by Enterline *et al*, from which a linear exposure-response could be imputed. The specifications for the constrained As effects were derived from the published exposure-response estimates, transformed to cumulative exposure units of $\text{mg-year}/\text{m}^3$ and expressed in a linear RR model design. Some analyses were conducted without applying the PPE protection factor for As because of uncertainty on use of PPE in the published studies reporting the lung cancer-arsenic exposure-response. However, some uniformity in PPE use is plausible as those study sites and the current cadmium smelter were facilities of the same employer. Generalised additive models were not employed because the quality of the exposure data including uncertain protection factors over time would make departures from simple parametric models difficult to interpret.

Attributable cases were calculated by applying the final constrained lung cancer rate model to the observation time of the study population alternately setting Cd, As or neither metrics to 0.0 and then computing the predicted number of lung cancer deaths. Following this procedure in strata of cumulative Cd exposure and then taking differences yields estimated attributable cases.¹⁵

RESULTS

Among qualifying study candidates, five were missing demographic information and were excluded. Within the resulting cohort of 601 workers, a total of 444 deaths were identified, or 74% of the cohort, with 99% ascertainment of vital status. With the update of mortality through the year 2002, there were 36 lung cancer deaths and eight deaths for which cause of death was unknown (1.3%).

Cadmium and arsenic exposures

The PPE-adjusted time-averaged exposures experienced by this cohort for Cd and As were 0.62 and 0.056 mg/m^3 , respectively, and the mean exposure duration was 6.4 year. The mean (lagged) cumulative Cd exposure at end of follow-up was 3.77 $\text{mg-year}/\text{m}^3$ (SD=5.63, max=39.9), and the mean As cumulative exposure was 0.34 $\text{mg-year}/\text{m}^3$ (SD=0.65, max=5.61). The joint distribution of cumulative exposures to Cd and As at the close of follow-up indicated considerable correlation (Pearson $r=0.65$). The pattern of exposure changed over time. In the period 1940–1984, Hispanic workers had slightly higher cumulative Cd exposures (averaged over observation time) than non-Hispanics and slightly lower As exposures, corresponding to their more recent hire.

Lung cancer mortality in relation to Cd and As

The SMR for lung cancer in the updated cohort (adjusted for age and year) was close to expected from national rates (table 1) and, as observed previously, was considerably elevated in non-Hispanic workers (SMR=29/19.9=1.46, 95% CI 0.99 to 2.06) but not in Hispanics (SMR=7/14.1=0.50, 95% CI 0.21 to 0.96) (data not shown). During 1985–2002, the lung cancer SMR for non-Hispanic workers was no longer elevated (SMR=9/9.42=0.96, 95% CI 0.46–1.72). SMRs calculated in strata of traditional, lagged cumulative Cd exposure increase with exposure level, although most are not statistically significant (table 1). In the highest exposure stratum, SMR=8.85 (95% CI 1.47 to 27.3, based on two cases). These SMRs make no adjustment for Hispanic ethnicity or As exposure.

Table 1 Lung cancer cases, SMRs and attributable cases in strata of cadmium cumulative exposure

Cumulative cadmium, $\text{mg-year}/\text{m}^3$		P-Yrs	Obs	Unadjusted for As, ethnicity		Adjusted for As, ethnicity*		Predicted attributable cases†		
Range	Mean			SMR	95% CI‡	SMR	95% CI‡	Cd	As	Cd, As
0.00–0.72	0.23	8545.7	7	0.79	0.34 to 1.54	0.77	0.24 to 1.63	0.36	0.77	1.14
0.73–2.42	1.47	6421.1	8	0.79	0.36 to 1.46	0.94	0.29 to 2.02	1.44	1.19	2.64
2.43–7.81	4.46	5492.4	8	0.81	0.37 to 1.51	0.90	0.21 to 2.06	4.21	1.75	5.96
7.82–16.63	11.13	1782.5	8	2.19	1.00 to 4.07	2.24	0.70 to 4.77	4.47	0.98	5.45
16.76–24.98	19.96	505.5	3	2.53	0.63 to 6.57	2.98	0.21 to 9.05	2.37	0.34	2.71
25.15–39.94	33.08	84.7	2	8.85	1.47 to 27.3	8.93	0.94 to 28.7	1.11	0.09	1.20
Total	3.00	22 832	36	1.06	0.75 to 1.45	1.12	0.76 to 1.58	14.0	5.12	19.1

*SMRs by Poisson regression using an offset based on US lung cancer rates (see text); estimate for white (Anglo) workers, with adjustment for As exposure.

†Based on arsenic-constrained linear RR model in table 3B with cumulative Cd exposure.

‡Profile likelihood-based CI generated by Epicure.

Mean, based on cell means averaged with observation time weighting; P-Yrs, person-years of observation; Obs, observed no. of lung cancer deaths; SMRs, standardised mortality ratios.

Workplace

Table 2 Models of cadmium and arsenic exposure response for lung cancer using traditional cumulative exposures (mg-year/m³, 5-year lag)

Model	Effect*	\hat{a}_i	SMR ₀ †(exp(\hat{a}_0))	RR‡	lrt: χ^2 (df)§	p Value§
1	Intercept (non-Hispanic)	-0.205	0.81			
	Hispanic (0, 1)	-1.130	0.26 ¶	0.32		0.007
	Cumulative cadmium	0.211		3.11	10.2 (1)	0.0014
2	Intercept (non-Hispanic)	-0.005	0.98			
	Hispanic (0, 1)	-1.054	0.35	0.35		0.012
	Cumulative arsenic	1.218		13.2	9.2 (1)	0.0024
3	Intercept (non-Hispanic)	-0.190	0.83			
	Hispanic (0, 1)	-1.098	0.27	0.33		0.009
	Cumulative cadmium	0.125		2.25	2.03 (1)	0.154
	Cumulative arsenic	0.766		8.66	1.00 (1)	0.317
					11.2 (2)**	0.0037

*Model: $SMR = [\exp(a_0 + a_1 \text{Ind}(\text{His}))] \times [1 + a_2(\text{cumCd}) + a_3(\text{cumAs})]$; $a_3=0$ in model 1 and $a_2=0$ in model 2; His = Hispanic ethnicity.

†SMR₀, estimated SMR for unexposed.

‡RR, ratio of SMRs, predicted at 10.0 mg-year/m³.

§ χ^2 to remove exposure term (likelihood ratio test, lrt) and associated p value; for Hispanic term, p value based on Wald statistic.

¶0.26 = $0.81 \times 0.32 = \exp(-0.205) \times \exp(-1.13)$.

**lrt for both exposure terms together.

SMRs, standardised mortality ratios.

With Cd and As cumulative exposures as linear terms in an additive RR model, each exposure alone was a highly significant predictor of lung cancer mortality (table 2, models 1 and 2). Model fit was slightly better for Cd versus As but including both exposure terms did not significantly improve the fit (table 2, model 3). Thus, the cumulative exposures for Cd and As were collinear, and therefore, in modelling the Cd exposure-response, the adjustment for the As effect was unreliable. There was a significant deficit with Hispanic ethnicity (SMR=0.27, p=0.009) (table 2, model 3). These same general findings were observed in models with direct standardisation (no offset), but the effect estimates were smaller and less statistically significant (data not shown). Use of 10-year lagging produced similar results to 5-year lagging.

The form of the exposure-response for Cd (alone, without a term for As) was investigated (table 3A). The simple linear term in the additive RR model appeared to be among the better predictors (lrt=10.21); the square root transformed cumulative exposure produced a somewhat better fit (lrt=10.85) but with a very small intercept (ln(SMR) for unexposed non-Hispanic workers), corresponding in this case to an SMR=0.25 indicating an implausibly strong healthy worker effect. The loglinear

model produced the poorest fit (lrt=8.32) (data not shown). The better-fitting square root Cd metric suggested that the exposure-response curve was supralinear—declining positive slope with increasing cumulative exposure (table 3A). For arsenic alone, traditional cumulative exposure in the additive RR model provided the best fit among the various forms (table 3A).

To separate the contributions of Cd and As to lung cancer risk, models were fit in which the As exposure-response was imposed using prior estimates from other studies.^{4 5} Five different scenarios yielded values at which to fix parameters, b_2 and b_3 , in $1 + b_1(\text{CumCd}) + b_2(\text{CumAs})^{b_3}$. In these constrained models, the Cd effect estimates, b_1 , were similar, in the range 0.181–0.215 (data not shown), corresponding to RRs (at 10 mg-year/m³ Cd) of 2.8–3.2 and likelihood ratio tests of 4.9–7.9 (1 df) (table 4). When the square root transformed Cd cumulative exposure was used as the predictor, slightly stronger effects and better fits (lrt: 5.6–8.4) resulted but again with implausibly small intercepts (SMRs for unexposed workers) and large RRs (table 4). If the intercepts were adjusted to 0.80, a reasonable choice for the healthy worker effect in this cohort, the predicted rate ratios (RR at 10 mg-year/m³ Cd multiplied by SMR(0)/0.80) then fell in the range 3.0–3.3 (table 4). Similarly, adjusted RRs

Table 3 Cadmium (Cd) and Arsenic (As) exposure-responses for lung cancer using alternate model specifications for cadmium or arsenic alone and with constrained arsenic effect

Exposure metric, f(X)	intercept	\hat{a}_2	SMR ₀ (exp(\hat{a}_0))	RR*	lrt: χ^2 (1 df)†	p Value†
A: Cadmium or arsenic alone (lag = 5 years) model: $SMR = [\exp(a_0 + a_1 \text{Ind}(\text{His}))][1 + a_2 f(X)]$						
cumCd‡	-0.205	0.211	0.82	3.1	10.2	0.0014
ln[cumCd+1]	-0.907	2.333	0.40	6.6	10.1	0.0015
sqrt(cumCd)	-1.375	3.062	0.25	10.7	10.9	0.0010
cumAs	-0.0046	1.218	0.99	13.2	9.18	0.0024
ln[cumAs+1]	-0.049	2.099	0.99	6.0	7.75	0.0054
sqrt(cumAs)	-0.296	2.060	0.74	7.5	7.05	0.0079
B: Cadmium with constrained arsenic effect (lag = 5 years (Cd), 0 year (As))§: $SMR = [\exp(a_0 + a_1 \text{Ind}(\text{His}))][1 + a_2 f(\text{Cd}) + 0.5495(\text{cumAs})^{0.35}]$						
cumCd	-0.368	0.215	0.69	3.2	6.3	0.012
ln[cumCd+1]	-1.028	2.476	0.36	5.9	6.2	0.013
sqrt(cumCd)	-1.562	3.632	0.21	11.5	7.0	0.008
durCd¶	-0.376	0.157	0.69	2.6	6.3	0.012

*RR, ratio of SMRs, predicted at 10.0 mg-year/m³; for duration: predicted for 10 years.

†p Value based on likelihood ratio test.

‡cumCd and cumAs: cumulative exposures, in mg-year/m³.

§Constrained As effect derived in table 4.

¶durCd: duration of Cd exposure, lagged 5 years.

SMRs, standardised mortality ratios.

Table 4 Models of lung cancer—cadmium exposure—response, linear and square root, with five estimates for constrained arsenic effect based on previous published work

Fixed cumAs coefficient A ₀	Fixed cumAs power A ₁	SMR ₀ (exp(â ₀))	lrt: χ ² (1 df)	p	RR*	RR † for SMR ₀ =0.8
Linear Cd effect: SMR = [exp(a ₀ +a ₁ ln(His))][1+a ₂ cumCd+A ₀ (cumAs) ^{A₁}]						
0.5495‡	0.350	0.69	6.3	0.012	3.2	2.7
0.8141§	0.408	0.67	4.9	0.027	3.1	2.6
0.5776¶	0.384	0.70	5.9	0.015	3.1	2.7
0.1740** ††	1.0	0.84	6.6	0.010	2.8	2.9
0.0967†† ‡‡	1.0	0.83	7.9	0.005	2.9	3.0
Square root Cd effect: SMR = [exp(a ₀ +a ₁ ln(His))][1+a ₂ sqrt(cumCd)+A ₀ (cumAs) ^{A₁}]						
0.5495‡	0.350	0.21	7.0	0.008	12.5	3.3
0.8141§	0.408	0.20	5.6	0.018	12.7	3.2
0.5776¶	0.384	0.21	6.6	0.010	12.2	3.0
0.1740** ††	1.0	0.31	7.0	0.008	8.4	3.3
0.0967†† ‡‡	1.0	0.28	8.4	0.004	9.3	3.3

*RR, ratio of SMRs, predicted at 10.0 mg-year/m³.

†RR, adjusted to intercept = -0.223 or SMR₀=0.8.

‡Tacoma [5]: SMR=1.0+0.04897cumX^{0.3499} in µg-year/m³; =1.0+0.5495(cumAs)^{0.350} in mg-year/m³.

§...retiree [5]: SMR=1.0+0.04857cumX^{0.4081} in µg-year/m³; =1.0+0.8141 (cumAs)^{0.408} in mg-year/m³.

¶Anaconda [5]: SMR=1.0+0.04062cumX^{0.3843} in µg-year/m³; =1.0+0.5776 (cumAs)^{0.384} in mg-year/m³.

**...hired <1925 [4]: SMR=3.75 for cumX 100–499 in mg-month/m³; =1.0+0.1740 (cumAs)^{1.0} in mg-year/m³ with baseline SMR assumed=0.85.

††Mean value for 100–499 interval estimated as geometric mean of bounds: √(100×499) = 223 mg-month/m³ = 18.6 mg-year/m³; 0.174=(3.75–1.0)/(18.6/0.85).

‡‡...hired 1925–1947 [4]: SMR=2.53 for cumX 100–499 in mg-month/m³; =1.0+0.0967 (cumAs)^{1.0} in mg-year/m³ with baseline SMR assumed=0.85.

SMRs, standardised mortality ratios.

for the constrained linear cumulative Cd models were slightly smaller (2.6–3.0) (table 4).

The different model forms for the Cd–lung cancer response were re-examined, now using models constrained for the As effect, and the results were similar to the univariate results (table 3B vs table 3A). A term for *duration* of Cd exposure (lagged 5 years) was itself a significant predictor and performed as well as Cd cumulative exposure in the constrained model (table 3B).

Testing for an exposure–age interaction by (1) adding a term for age–Indicator (Age≥60)—and then (2) adding the product term—Indicator (Age≥60) × cumCd—to the model along with the exposure main effect produced no improvement in fit: (1) χ²=0.39 (1 df), p=0.53; (2): χ²=0.06 (1 df), p=0.81, implying no important exposure–age interaction and that modelling SMRs was largely unbiased from that cause.

Using the constrained model (As effect based on SMR=1.0+0.04897cumX^{0.35}, the better-fitting model from Enterline *et al*⁵), SMRs were calculated in cumulative Cd exposure strata, but now adjusted for Hispanic ethnicity (which would raise the SMR estimate) and with the imposed As effect (which would lower the SMR estimate), yielding adjusted SMRs that were slightly larger but quite close to the original unadjusted SMRs (table 1).

Attributable lung cancer cases

Assuming no biological interaction in lung cancer risk arising from Cd and As exposures, that is, a case could be attributed to only one of the two exposures, and using the final constrained linear relative rate model (table 3B: cumCd), the numbers of excess lung cancer deaths attributable to Cd or As were calculated (table 1): 14.0 lung cancer deaths are attributable to Cd and 5.1 to As. Thus, 19.1 of the 36 total lung cancer deaths were estimated to be the result of Cd or As exposure. Most of the As-attributed deaths occurred in the four lower strata of Cd cumulative exposure (4.7 of 5.1). The 95% CI for lung cancer deaths attributable to Cd by profile likelihood was 2.57 to 25.6, wider than might be expected from the improvement in model fit with the Cd term (lrt=6.28) possibly because of the constrained As parameter. Using arsenic exposures unadjusted for PPE use produced similar estimates of attributable deaths for Cd and As: 13.6 and 6.3, respectively.

Alternate exposure metrics

If Cd acts as a lung carcinogen through a mechanism by which current exposure concentration has a non-linear effect on future risk, as could occur with inducible pathways, or saturation, in either direction (detoxification or activation), then intensity raised to some power might produce a more appropriate cumulative exposure metric. Models were fit with Cd exposure metrics calculated with intensity raised to powers ranging from 0.25 to 1.5. Modestly improved fits (by profile likelihoods) were observed for exposures raised to the 0.33 power versus 1.0 (Δ(-2lnL)=2.08 to 2.19, table 5). (For the power parameter to be significantly different than 1.0, the Δ(-2lnL) would need to be >3.84.)

The standard cumulative exposure metric also might not be appropriate if there was a repair process, slow elimination of the initiating agent (or toxic metabolite) or depletion of carcinogenic initiation sites. Comparing burden metrics with half-lives ranging from 5 to 40 years (using dose rates based on the 0.33 exponent) suggested improved fit with a half-life of 20–25 years compared with the usual cumulative exposure (which implicitly

Table 5 Alternate cadmium cumulative exposure metrics for cadmium–lung cancer exposure–response with constrained arsenic effect: dose rate and burden half-life

Model*	Change in deviance [Δ(-2lnL)]†					
Cd metric	Dose rate (intensity raised to this power); default=1.00					
	0.25	0.33	0.50	0.80	1.00	1.50
	cumCd	8.09	8.36	8.30	7.11	6.28
ln[cumCd+1]	8.15	8.35	8.25	7.11	6.16	4.20
sqrt(cumCd)	8.26	9.01‡	9.04	7.94	6.96	4.96
Burden half-life (year) (dose rate at 0.33); default=∞	Burden half-life (year) (dose rate at 0.33); default=∞					
	5	10	20	25	40	∞
	cumCd	4.61	7.88	9.30	9.36	9.24
ln[cumCd+1]	6.20	9.97	10.4	10.1	9.63	8.35
sqrt(cumCd)	7.15	10.1	10.7‡	10.2	10.2	9.04‡

*Linear relative rate model: SMR = [exp(a₀+a₁ln(His))][1+a₂f(Cd)+0.5495(cumAs)^{0.35}], f(Cd)=Cd metric.

†Maximum deviance changes across varying parameters displayed in bold font.

‡May be underestimate due to incomplete convergence.

SMRs, standardised mortality ratios.

assumes a burden half-life= ∞) (table 5). Finally, comparing model fit for cumulative exposures calculated with a threshold (below which exposure intensity is ignored) in the range 0.01–0.10 mg/m³ provided little support for a threshold effect in three of the four models and indicated very weak support for a threshold as high as 0.05 mg/m³ using the metric:ln(cumCd +1) (data not shown).

DISCUSSION

Strengths and weaknesses

This study had detailed work history and almost complete mortality ascertainment (1% lost to follow-up). The Cd and As retrospective exposure assessments were based on relatively abundant air-sampling data and, in the case of As, supporting biomonitoring information. If As was the sole causative agent for lung cancer, with Cd present as a non-causative covariate, it would be very unlikely that Cd would show a stronger association with lung cancer, by virtue of confounding, than observed for As alone; the Cd exposure metric would have to be a better representation of true As exposure than the As exposure metric itself. Models with the As effect imposed using prior As exposure–response estimates should largely remove mutual confounding between the Cd and As exposures. Misspecification of the As effect and misclassification of As and Cd exposures could produce small significant estimates of a false Cd effect but not the strong dominant effect observed.

The validity of imposing arsenic exposure–response estimates from copper smelter studies depends on the uniformity of arsenic environmental assessment across sites. The current site was acquired in 1901 by the parent ASARCO, owner of the operations where the As exposure–responses were estimated. Environmental sampling was carried out under the authority of a corporate entity, which has long been active in occupational and environmental health assessment. Other potential carcinogens besides arsenic in the copper smelter environments such as silica, or cadmium, were thought to be present at low levels⁴ but if causing an overestimate of the arsenic exposure–response would result in underestimation of the Cd effect in the present study design.

About one-third of excess lung cancer deaths were attributable to As and more than two-thirds to Cd (table 1). In a sensitivity investigation, increasing the As exposure estimates by a factor of 3 in the constrained linear RR model (using the constraint: 0.5495(cumAs)^{0.35}) resulted in a smaller intercept (SMR₀: 0.69 → 0.64) and a slightly larger Cd effect estimate (b_1 : 0.215 → 0.219) but now less significant (p: 0.012 → 0.020). Using the constraint, 0.1740 (cumAs)^{1.0}, which is more sensitive to changes in cumAs, resulted in the same intercept (SMR₀: 0.84) and a smaller Cd effect estimate (b_1 : 0.181 → 0.141) that was now non-significant (p: 0.010 → 0.06). In both cases, model fit was degraded but a substantial Cd effect remained. Therefore, in order for the stipulated As effect to completely occlude the cadmium contribution to risk, the true As exposures would have to be more than threefold higher than estimated, a large discrepancy. Thun *et al*¹ estimated average arsenic concentrations for this smelter population to be lower than those reported here: 0.10 versus 0.15 mg/m³, respectively, in the absence of respirator use.

The effect observed for duration of Cd exposure, comparable to the Cd cumulative exposure metric itself, implies that after 20-year employment, the risk of lung cancer for any worker would be elevated fourfold (1+20×0.157=4.1, table 3B). Besides As and Cd, there were no other known or suspect lung carcin-

ogens at important air concentrations in this facility including sulphuric acid mist. The Cd exposures may well be poorly characterised over time as is common in occupational cohorts. Improved model fit with modification of the Cd exposure metric for dose-rate (intensity) and time-dependent (burden) effects, compared with duration, supports the inference that Cd is the contributing carcinogen, although these modifications were at best marginally statistically significant.

Models of SMRs are vulnerable to bias arising from exposure–age interaction effects but these effects are generally small,¹⁸ and there was no evidence of interaction in this population. Directly standardised estimates can lose considerable precision when sparse data lead to high instability in the reference stratum rates (see Armstrong,¹⁸ table 3).

In the present analysis, the As effect was imposed using estimated air concentrations adjusted for respirator use. The original studies providing the As exposure–response estimates^{4,5} may not have adjusted for respirator use. Analyses performed here using As exposures unadjusted for PPE use produced slightly smaller and somewhat less precise estimates of Cd effects.

The low lung cancer mortality observed for Hispanic workers is consistent with other studies and is believed to be due to historically low smoking levels.^{20,21} A trend in lung cancer rate ratio was observed for Hispanics living in the Denver area, increasing from 0.40 in 1970 to 0.66 by 1980.²¹ Similarly, the ratio of age-adjusted lung cancer death rates comparing Hispanic with non-Hispanic white men living in New Mexico was 0.34 in 1960, increasing to 0.55 by 1985.²⁰

Comparison with other studies

In a large population of zinc–lead–cadmium smelter workers (n=4393) in the UK, Ades and Kazantzis²² observed significant excess lung cancer (SMR=1.25, 95% CI 1.07 to 1.44), increasing with employment duration. Significantly increasing risk with cumulative exposure was observed for arsenic and lead in univariate models. A less consistent increasing but non-significant trend was seen for cadmium at concentrations (<0.06 mg/m³) considerably lower than in the present study (mean: 0.62 mg/m³). Sorahan *et al*²³ studied workers in two non-ferrous metal production plants that included iron and brass foundries. There were complex exposures including likely hydrocarbon degradation and combustion products and mixed metal exposures. Elevated respiratory disease deaths were observed among copper–cadmium workers but lung cancer, overall, was about as expected (SMR=1.01) without accounting for healthy worker effects. The average Cd exposure of the alloy workers studied was <0.10 mg/m³ (vs 0.62 here). Jarup *et al*²⁴ studied the mortality of Swedish nickel–cadmium battery workers and reported elevated lung cancer that diminished with increasing cumulative exposure to Cd. Exposure levels were <0.10 mg/m³ Cd. Sorahan and Esman²⁵ updated a UK nickel–cadmium battery study and observed a possible lung cancer excess (SMR=1.11, 95% CI 0.81 to 1.48), but analysis of rate ratios in four cumulative exposure strata showed elevation only for the second lowest stratum (0.4–1.2 mg-year/m³) (RR=2.05, 95% CI 1.02 to 4.15). A similar inverse trend at higher exposures was observed for obstructive lung disease. Other exposures, particularly in earlier years, such as nickel, cobalt and sulphuric acid, were not addressed, and the size distribution of cadmium dusts may have differed from that in smelter operations. A recent assessment of lung cancer risk using Cox regression in a region of Belgium with environmental cadmium contamination, observed a HR of 1.57 (95% CI 1.11 to 2.24) for a doubling of cadmium

concentration in the soil.²⁶ Jones *et al*²⁷ analysed lung cancer mortality at a UK tin smelter in relation to arsenic, cadmium, antimony and ²¹⁰polonium. In process areas with the highest As exposures, As levels were 5–10 times greater than the cadmium levels; As levels were three times higher than Cd in the area with the highest Cd exposures. In contrast, in the present study (PPE adjusted), concentrations of Cd on average exceeded As by a factor of 10. The highest Cd exposures in Jones *et al*, in the blast furnace area (0.08 mg/m³), were one-eighth of the average Cd exposure in the present study (0.62 mg/m³). Univariate regression analyses for Cd and lung cancer revealed no association but were probably negatively confounded by the dominant As exposures (the high-As areas were low-Cd areas). Sorahan²⁸ analysed the present (Globe ASARCO) study population with follow-up through 2001 examining only workers who had been assigned to departments with high-As exposures. The SMRs for lung cancer were observed to decline with increasing time since As exposure from which Sorahan concluded that As is a late-stage carcinogen (affecting tumours already advanced and thus manifest soon after As exposure) and interprets these findings as lack of support for a cadmium effect. However, that analysis did not explicitly consider As or Cd levels and could largely reflect the depletion of the high-As exposed population, whose highest exposures occurred prior to 1953. The Sorahan analysis also neglected the strong ethnicity effect observed here.

Best exposure metrics and risk assessment

The best models for lung cancer mortality and cadmium suggest a supralinear dose-rate effect, as might be observed if some protective mechanism was being stimulated or some toxigenic pathway becoming saturated, and risk appears to diminish slowly with time since exposure. These observations, however, are uncertain and wide ranges of dose-rate and half-lives would be consistent with the data. A risk assessment using the Cox regression estimate (0.263) from an earlier analysis of this population concluded that the excess lifetime risk at a Cd exposure level of 0.003 mg/m³ was 1.5/1000² or about 0.002 mg/m³ for 1/1000 excess risk. Using the same excess lifetime risk calculation with the current regression parameter estimate of 0.215 would yield a 1/1000 excess lifetime risk at about 0.0024 mg/m³ (0.002×0.263/0.215) or 2.4 µg/m³ Cd.

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Cadmium and lung cancer mortality accounting for simultaneous arsenic exposure

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