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Mortality Patterns Among Workers Exposed to Arsenic, Cadmium, and Other Substances in a Copper Smelter

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Objective *To evaluate the long-term mortality experience of workers exposed to arsenic, cadmium, and other substances at a copper mine and smelter in Copperhill, Tennessee studied earlier as part of an industry-wide study.*

Methods *Subjects were 2,422 male workers employed three or more years in the smelter or mill between 1/1/46 until the plant strike and scale-down of operations in April 1996. Vital status was determined through 2000 for 99.4% of subjects and cause of death for 91.3% of 878 deaths. Historical exposures were estimated for lead, SO_2, arsenic, cadmium, dust, and cobalt. We computed standardized mortality ratios (SMRs) based on U.S. and local county rates and modeled internal relative risks (RRs).*

Results *We observed overall deficits in deaths based on national and local county comparisons from all causes, all cancers and most of the cause of death categories examined. We found limited evidence of increasing mortality risks from cerebrovascular disease with increasing duration and cumulative arsenic exposure, but no evidence of an exposure–response relationship for cadmium exposure and bronchitis.*

Conclusions *Our limited evidence of an association between inhaled arsenic exposure and CVD is an exploratory finding not observed in other epidemiology studies of more highly exposed occupational populations. Possible alternative explanations include chance alone and uncontrolled confounding or effect modification by co-exposures or other factors correlated with arsenic exposure and unique to the Copperhill facility.*
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KEY WORDS: cohort study; mortality; copper smelting; arsenic; cadmium; cerebrovascular disease; bronchitis; copper; lead; SO_2; dust; cobalt

BACKGROUND

The Copper Basin area of southeastern Tennessee is the site of a copper mining, milling, and smelter facility in the town of Copperhill, TN. Copper smelting began in the Copper Basin in the mid-19th century and was conducted at the Copperhill site from 1901 to 1986. Due to the high sulfur content of the local ore, the facility also produced a variety of sulfur products during its history. These activities continued until April 1996 when a strike occurred and production activities were scaled down considerably. The Copperhill facility was one of the eight smelters included in an

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epidemiology study of U.S. copper and zinc smelter workers conducted by the University of Pittsburgh, Department of Biostatistics in the 1980s [Enterline et al., 1986, 1987b] and funded by the former Smelter Environmental Research Association (SERA).

Overall, the original SERA copper smelter worker study found no evidence of elevated mortality from all causes of death combined, all cancers combined, and from most of the specific cause of death categories examined. The only notable findings from the study were an association between arsenic exposure and lung cancer in a southwestern U.S. smelter that used a high arsenic content ore (a previously known association), and an association across all study sites between emphysema mortality and sulfur dioxide (SO_2) exposure considered an exploratory finding of unknown significance. No adverse mortality risks were reported among workers from the Copperhill facility [Enterline et al., 1986, 1987b].

In 2000, community concerns about possible adverse health effects stemming from the Copperhill facility prompted residents and union officials to contact the National Institute for Occupational Safety and Health (NIOSH) and request a health hazard evaluation (HHE). Because of the methodological difficulties associated with studying long-term health effects in a community-at-large, the HHE was aimed at an updated and expanded evaluation of mortality among former workers of the Copperhill facility, many of whom were included in the previous epidemiology study and were current residents of the Copper Basin area. As part of the NIOSH HHE, NIOSH commissioned two of the current authors (G. Marsh and N. Esmen), who were co-investigators of the earlier epidemiology study, to perform the updated and expanded study of the Copperhill workforce. A non-technical summary of our findings is provided in the NIOSH HHE Report [NIOSH, 2007]. We report here the detailed results of our study.

METHODS

Cohort Enumeration and Validation

The Copperhill cohort comprised 2,422 male workers employed three or more years in smelter, mill, or sulfur operations between 1/1/46 and 4/30/96. Subjects were identified from the original study cohort file (workers employed three or more years between 1/1/46 and 12/31/76) and by an updated, comprehensive review of hard copy and electronic personnel files maintained at the facility. The completeness of the cohort was verified by an independent cross-check of union contract books provided by union representatives.

Cohort Follow-Up

We used our standard vital status tracing protocol to identify deaths among cohort members with unconfirmed vital status (not known from company-held records to be alive as of the study end date) [Schall et al., 1997, 2001]. This protocol relies on national-scale sources, such as the Pension Benefit Information Company and the National Death Index, to focus on the complete and accurate identification of deaths among persons unconfirmed as alive and assumes that persons not identified as deceased using these rigorous and accurate sources are alive. Deaths were coded by a National Center for Health Statistics (NCHS) trained nosologist to the underlying cause of death using the International Classification of Diseases (ICD) rules in effect at time of death. We identified 961 subjects or 39.7% of the cohort as deceased and obtained cause of death for 878 or 91.3%. Only 14 or 0.6% of the cohort remained untraced due mainly to missing or incorrect Social Security number.

Exposure Assessment

We estimated job and time-specific exposures to six agents: lead, SO_2, arsenic, cadmium, dust, and cobalt, using a modification of the process-based projection of exposure measurements, first described in detail by Esmen [1979] and later further developed by others [Stewart et al., 1986; Dodgson et al., 1987; Yu et al., 1990; Schneider et al., 1991]. The process information gathered in the original Copperhill study [Enterline et al., 1986, 1987b] was augmented by additional documentation provided by the company and interviews with 49 knowledgeable former Copperhill employees to obtain full details of the processes and process changes over the extended period of the study. An independent check on the recall of the interviewees was attempted by including, when possible, several questions on process and task descriptions which could be compared to company records or descriptive field notes from the previous study. The responses to these questions were better than 90% correct. These results, while not formally administered or analyzed, suggested that the interviewee recall of tasks and processes was sufficiently accurate for exposure estimation purposes.

Company recorded job titles were used to generate a job dictionary and the job dictionary was used to generate a job/exposure matrix based on the relative exposure intensities as these intensities changed over time. While the task involved in some job titles resulted in a very broad distribution of exposures, the personnel assigned to these tasks could not be specifically identified, resulting in high exposure potential for some subgroups in the job classes. An example of this difficulty is shown in the Figure 1, which compares measured exposures of workers assigned to blending (mean = 13.54, median = 4.8, range 0.28–92.4 $\mu g/m^3$) with measured exposures of other operators with the same job title in the copper system (mean = 1.54, median = 0.6, range 0.0–8 $\mu g/m^3$). Because tasks were not reported to be rotating, blenders in the copper system job class had

exposures about one order of magnitude higher than other workers in the copper system who had the same job titles. While this inherent deficiency may hinder comparison with the results of other studies from the exposure level perspective, the ranking of the exposures for this study was not affected. The difficulties associated with the inability to identify imbedded high exposure classes of workers occur frequently in occupation and environment studies. Esmen et al. [2007] provide a discussion of and potential solution to these difficulties.

From individual worker job histories and job/exposure matrix-based exposure estimates, we computed for each subject three time-dependent summary measures of exposure for each of the six exposure agents considered: duration of exposure (Dur) = the sum of the days spent in jobs with non-zero exposure (in years); cumulative exposure (Cum) = the product of the number of days in each job and the estimated average daily exposure, summed across all jobs (in ppm for SO_2 or mg/m^3-years); and average intensity of exposure (AIE) = the ratio of Cum to Dur (in ppm for SO_2 or mg/m^3). These summary measures are expressed as Agent_DurX, Agent_CumX, and Agent_AIEX, where X represents the number of exposure categories.

Statistical Methods

General mortality patterns

We examined the total and cause-specific mortality experience of the Copperhill cohort from January 1, 1949 to December 31, 2000 using a modified life table procedure from the Occupational Cohort Mortality Program (OCMAP-Plus) [Marsh et al., 1988b]. Person-years at risk contributed by each study member were jointly classified by race, age group, calendar time, duration of employment (DOE), and the time since first employment (TSFE). To account for the 3-year minimum employment cohort entrance criterion, person-year counts began on July 1, 1949 for study members hired before 1946 and three years after the date of hire for members hired in 1946 or later. For workers lost-to-follow-up, person-year counts stopped at the last date of known vital status, which was employment termination date. Person-years for subjects of unknown race were assigned to white or non-white categories in proportion to the person-year distribution of study members with known race using the proportional allocation method (PAM) algorithm in OCMAP-Plus. We applied this approach separately to assign race to observed deaths of unknown race.

We computed expected numbers of deaths based on both the total U.S. and the local three-county area in which Copperhill workers largely resided (Polk Co., TN, Fannin Co., GA, Cherokee Co., NC). Population-weighted county mortality rates were obtained from the Mortality and Population Data System (MPDS) maintained by the University of Pittsburgh [Marsh et al., 2004]. While U.S. mortality rates were available for the entire 1949–2000 study period, MPDS mortality rates for all deaths combined and non-malignant cause of death categories were available only from 1962–2000. Thus, expected numbers of total and non-cancer deaths were limited to 1960–2000 (with 1962–1964 rates applied to 1960–1964 person-years). MPDS cancer mortality rates were available from 1950–2000 and 1950–1954 rates were applied to 1949–1954 person-years. Because local death rates usually provide the most valid external mortality comparisons (as they help to adjust for the social, cultural, and economic factors related to disease), our analysis of general mortality patterns focused primarily on the local county comparisons.

Mortality excesses and deficits were expressed as standardized mortality ratios (SMRs) along with their 95% confidence intervals (CI). We computed SMRs for the total cohort and subgroups defined by work area within the Copperhill facility (smelter, acid, mill/mine, and mixed areas), race (white, non-white), year of hire, DOE, and the TSFE.

Mortality in relation to occupational exposure

SMRs were computed for subgroups of the cohort defined by two categories of exposure to each of six exposure agents (lead, SO_2, arsenic, cadmium, dust, and cobalt). For each agent, we dichotomized exposure as ''unexposed'' and ''exposed'' and person-year counts in the unexposed baseline category included the observation time of workers before their first exposure. Using the results of this two-category analysis, we selected for further exploratory analysis any cause of death category that revealed a 50% or greater (SMR $\geq$ 150) mortality excess in the ''exposed'' category and a corresponding baseline or deficit mortality experience (SMR $\leq$ 100) in the ''unexposed'' category. An additional screening criterion was that the total number of observed deaths in the ''exposed'' category must be six or greater to permit a reliable, finer breakdown of the ''exposed'' category. We used this ''screening'' procedure to focus on the most biologically plausible findings and to mitigate the multiple statistical comparisons problem that can lead to many false positive findings.

Cause of death categories satisfying the screening algorithm described above for a particular exposure agent were further analyzed by three exposure metrics (duration of exposure, average intensity of exposure, and cumulative exposure). For each metric we formed an unexposed category and two exposed categories, with exposure cutpoints chosen to approximately dichotomize the corresponding observed number of deaths. This three exposure-level analysis provided a rough assessment of a possible exposure–response relationship within any of the 18 exposure metric/exposure agent

combinations considered. As we did not design our analyses of general mortality patterns and mortality in relation to occupational exposure to test specific *a priori* hypotheses regarding possible associations with exposure and particular mortality outcomes, we considered them exploratory in nature and interpreted results accordingly. Our analysis of mortality in relation to occupational exposure was based both on external mortality comparisons (i.e., with the local multi-county population) via SMRs and on internal comparisons of cohort rates via relative risks (RRs).

For internal comparisons, we used RR regression modeling to investigate the dependence of the internal cohort rates (modeled as time to death) on the categorical exposure measures with adjustment for potential confounding factors. For cause of death categories satisfying the screening algorithm, we explicitly constructed risk sets from the cohort data file with age as the primary time dimension, using the RISKSET program module in OCMAP-Plus [Marsh et al., 1988b]. Risk sets were matched further on year of birth (±5 years) to account for cohort effects. Time-dependent exposures were evaluated for each individual at each event time they were at risk. We fit multiplicative RR models of the form $\lambda(t) = \lambda_0(t) \exp\{x(t)\beta\}$ to the internal cohort rates [Cox, 1972, 1975; Breslow and Day, 1987]. The conditional logistic regression program in STATA [Stata Corp, 2003] was used to estimate β. The overall statistical significance and linear trend of each main exposure effect (expressed as a global and trend *P*-value, respectively) was assessed with a likelihood ratio statistic.

We first considered potential confounding factors univariately as categorical variables to identify patterns of univariate associations with the outcome and sparse data problems. The following study factors were considered as potential confounders: race (white, non-white, and unknown), year of hire, work area (smelter, acid, mill/mine, and mixed), DOE, and TSFE. If warranted by the univariate associations, possible exposure-disease associations were then evaluated using a forward-stepwise approach to adjust for possible confounders. All tests on SMRs and RRs were done at the 0.05 significance level with no adjustment made for multiple comparisons.

TABLE I. Distribution of Copperhill Cohort by Selected Demographic and Work History Factors

Factor	Number	%
Persons	2,422	100.0
Person-years	79,501	100.0
Work area		
Smelter	1,312	54.2
Acid	12	0.5
Mill/mine	28	1.1
Mixed	1,070	44.2
Race		
White	1,719	71.0
Non-white	229	9.4
Unknown	474	19.6
Year of birth		
<1910	364	15.0
1910–1919	361	14.9
1920–1929	510	21.1
1930–1939	386	15.9
1940–1949	547	22.6
1950+	254	10.5
Year of hire		
<1940	356	14.7
1940–1949	717	29.6
1950–1959	280	11.6
1960–1969	550	22.7
1970–1973	386	15.9
1974+	133	5.5
Duration of employment		
<5	112	4.6
5–9	276	11.4
10–19	629	26.0
20–29	579	23.9
30+	826	34.1
Time since first employment		
<10	16	0.7
10–19	85	3.5
20–29	570	23.5
30+	1,751	72.3

RESULTS

Characteristics of the Cohort

The extended Copperhill cohort includes 2,422 subjects who contributed a total of 79,501 person-years of observation during the updated 1949–2000 study period (Table I). This is nearly three times the size of the original cohort (840 subjects, 28,189 person-years). About one-half (54.2%) of subjects had been employed only in the smelter and most of the remaining subjects had mixed employment in the smelter, acid plant, or mill/mine. Of the 1,948 subjects with known race, 71% were white. Fifty-eight percent of subjects worked at the facility for 20 or more years and 95.8% of subjects were followed 20 or more years from their hire date.

General Mortality Patterns

Mortality from all causes combined

Table II shows for the total Copperhill cohort during the entire study period, observed deaths and SMRs based on the U.S. and local county comparisons. During the 1949–2000 study period, we observed 961 deaths in the total cohort,

TABLE II. Observed (Obs) Deaths and SMRs for Selected Causes of Death[†]

		U.S.		Local county	
Cause of death (9th revision ICD codes)	**Obs**	**SMR**	**95% CI**	**()[a] SMR**	**95% CI**
All causes of death (001–999)	961	81**	76–86	(907) 79**	73–84
All cancer (140–208)	228	82**	71–93	84**	73–96
Buccal cavity and pharynx (140–149)	5	71	23–166	126	41–294
Digestive organs and peritoneum (150–159)	51	70**	52–92	83	62–109
Esophagus (150)	5	59	19–138	60	20–141
Stomach (151)	7	60	24–123	78	31–160
Large intestine (153)	20	84	51–129	110	67–170
Rectum (154)	4	68	19–175	160	44–410
Biliary passages and liver primary (155, 156)	5	77	25–180	76	25–178
Pancreas (157)	7	50	20–103	46*	19–95
All other digestive (152, 158, 159)	3	127	26–372	160	33–466
Respiratory system (160–165)	93	96	77–117	86	69–105
Larynx (161)	3	81	17–238	104	21–303
Bronchus, trachea, lung (162)	88	95	76–117	84	67–104
All other respiratory (160, 163, 164, 165)	2	206	25–744	354	43–1279
Prostate (males only) (185)	17	60*	35–95	71	41–113
Kidney (189.0, 189.1, 189.2)	4	62	17–159	76	21–195
Bladder and other urinary organs (188, 189.3, 189.4, 189.8, 189.9)	5	67	22–157	110	36–257
Malignant melanoma of skin (172)	5	141	46–328	114	37–265
Eye (190)	1	628	16–3497	540	14–3007
Central nervous system (191, 192)	11	171	85–305	139	69–248
Thyroid gland and other endocrine glands and related structures (193, 194)	1	128	3–714	92	2–511
Lymphatic-hematopoietic tissue (200–208)	21	83	51–127	73	45–112
Non-Hodgkin's lymphoma (200, 202.0, 202.1, 202.8, 202.9)	8	91	39–180	80	35–158
Leukemia and aleukemia (204–208)	8	81	35–160	70	30–139
All other lymphopoietic tissue (202.2, 202.3, 202.4, 202.5, 202.6, 203)	5	101	33–235	75	25–176
All other malignant neoplasms (171, 173, 195–199)	14	66	36–110	71	39–119
Benign neoplasms (210–239)	5	101	33–235	(4) 114	31–292
Diabetes (250)	9	41**	19–77	(9) 46*	21–88
Cerebrovascular disease (430–438)	72	93	73–117	(68) 107	83–136
All heart disease (390–398, 402, 404, 410–429)	326	73**	66–82	(314) 76**	68–85
Rheumatic (390–398)	2	34	4–121	(2) 74	9–266
Ischemic (410–414)	272	79**	70–89	(262) 80**	70–90
Chronic disease of endocardium and other myocardial insufficiency (424, 428)	9	56	26–107	(9) 58	27–111
Hypertension with heart disease (402, 404)	6	37**	13–80	(5) 67	22–157
All other heart disease (415–417, 420–423, 425–427, 429)	37	59**	41–81	(36) 61**	43–84
Hypertension w/o heart disease (401, 403, 405)	2	36	4–129	(2) 49	6–175
Non-malignant respiratory disease (460–519)	68	74*	58–94	(65) 59**	46–76
Influenza and pneumonia (480–487)	17	51**	30–82	(16) 47**	27–77
Bronchitis, emphysema, and asthma (490–493)	18	87	52–138	(17) 58*	34–93
Other non-malignant respiratory disease (460–466, 470–478, 494–496, 500–519)	33	88	61–124	(32) 69*	47–97
Ulcer of stomach and duodenum (531–533)	5	96	31–223	(4) 55	15–141
Cirrhosis of liver (571)	10	41**	20–76	(10) 48*	23–88
Nephritis and nephrosis (580–589)	8	70	30–137	(8) 80	35–158
All external causes of death (E800–999)	63	68**	53–87	(57) 50**	38–64
Accidents (E800–949)	47	80	59–106	(42) 57**	41–77
Suicides (E950–959)	11	55*	28–98	(10) 53*	26–98
Homicides and other external (E960–978, E980–999)	5	37*	12–87	(5) 22**	7–51
Unknown causes		83		(66)	

[†]Observation period is 1960–2000 for all causes combined and non-malignant causes of death based on local county comparison.
[a]Observed number of deaths during truncated 1960–2000 study period.
*$P < 0.05$.
**$P < 0.01$.
Total Copperhill Cohort, U.S. and Local County Comparisons, 1949–2000

yielding a statistically significant 19% deficit in total mortality compared with the general U.S. population. A similar statistically significant 21% deficit in total mortality based on 907 deaths was observed using the local county comparison during the truncated 1960–2000 study period (Table II). We observed deficits in total mortality in all the cohort subgroups examined and many of these were statistically significant (data not shown). We also observed a decreasing trend in the all cause SMRs by year of hire and increasing trends by DOE and TSFE reflecting the gradual reduction in the healthy worker survivor effect as the cohort was followed through time (data not shown).

Mortality from all malignant neoplasms combined

During the 1949–2000 study period, we observed 228 cancer deaths in the total cohort, yielding statistically significant 18% and 16% deficits in total cancer mortality compared with the general U.S. and local county experience, respectively (Table II). We observed deficits in total cancer mortality in all the cohort subgroups examined and many of these were statistically significant. Similar to all cause mortality, we observed a decreasing trend in SMRs by year of hire and increasing trends by DOE and TSFE (data not shown).

Cancer site-specific mortality

Table II reveals no evidence of any important excesses in cancer site-specific mortality among the total Copperhill cohort. Most of the excesses observed were based on five or fewer observed deaths and were not statistically significant. A 39% excess in cancer of the central nervous system was observed based on 11 deaths, but this was not statistically significant. Our subgroup analyses revealed no patterns or trends in cancer site-specific SMRs suggesting an association with occupational factors (data not shown).

Mortality from non-malignant diseases and external causes

None of the many non-malignant disease and external cause of death categories examined among the total cohort during the truncated 1960–2000 study period (Table II) revealed evidence of elevated mortality risks. Besides a few small, not statistically significant excesses in deaths, most of the categories examined revealed deficits in deaths and many of these were statistically significant. Further, our subgroup analyses revealed no patterns or trends in non-malignant disease or external cause of death suggesting an association with occupational factors (data not shown).

Mortality in Relation to Occupational Exposure

Characterization of exposures

We characterized and compared relevant summary statistics for each of the three metrics of exposure (duration, average intensity, and cumulative) and the time since first exposure calculated for each of the six agents considered individually for exposed workers only (lead, SO_2, arsenic, cadmium, dust, and cobalt) (data not shown). Overall, historical average exposure levels to lead and SO_2 were closest to current professional guideline exposure levels (e.g., 2005 TLVs); exposures to the other four agents were considerably less than the current TLVs. The only agent present in each employment group was SO_2. The median average intensity of SO_2 exposure among subjects in the ''acid only'' (5.00 ppm) group was 1,00 times higher than those among subjects in the ''smelter only'' group (0.05 ppm). Exposure to the other five agents occurred only among workers employed in the ''smelter only'' and ''mixed employment'' group.

We also examined the patterns of multiple exposures to two or more of the six characterized agents. SO_2 was, by far, the most common exposure agent and this exposure usually occurred alone. In fact, 37,740 or 66.5% of the total exposed person-years (to all agents) were accrued by subjects having exposure only to SO_2. The only other exposure to occur alone was dust and only 24 subjects (83 person-years) had this single exposure. Exposure to four agents (lead, arsenic, cadmium, and cobalt) never occurred alone in any job. A total of 262 subjects (1,259 person-years) worked in jobs with no exposures to any agent. As for joint exposures, 647 subjects (3,786 person-years) were exposed at some time to jobs involving all six agents. Of the various combinations of two to five agents, the largest number of subjects (644 subjects; 5,017 person-years) were exposed to four: lead, SO_2, cadmium, and dust (data not shown).

Exploratory mortality analysis

Table III shows the key results of our exploratory analysis of mortality in relation to occupational exposure to each of the six agents considered separately and dichotomized in a time-dependent fashion as ''unexposed'' and ''exposed.'' From the hundreds of comparisons made, our screening procedure resulted in the selection of only two exposure/cause of death subgroups, both of which involved a non-malignant cause of death category: (1) arsenic exposure and cerebrovascular disease and (2) cadmium exposure and bronchitis.

Table IV shows the results of our exposure–response analysis for arsenic exposure and cerebrovascular disease using the three exposure metrics duration, cumulative, and

TABLE III. Key Results of Exploratory Analysis* of Mortality in Relation to Occupational Exposure, Total Cohort, 1960–2000, Observed Deaths and SMRs, Local County Comparison

		Unexposed			Exposed		
Cause of death	**Agent**	**Obs**	**SMR**	**95% CI**	**Obs**	**SMR**	**95% CI**
Cerebrovascular disease	Arsenic	43	93	67–125	25	152	99–225
Bronchitis	Cadmium	1	23	1–126	6	168	62–365

*Exploratory screening procedure = exposure and COD selected if (SMR in unexposed $\leq$100) and (SMR exposed $\geq$150 and number of observed deaths $\geq$6).

average intensity of exposure. For the duration and cumulative exposure metrics, we categorized exposure into two (Grouping 1) and four (Grouping 2) approximately equal groups based on the corresponding number of observed deaths. The exposure category-specific SMRs in Table IV were limited to the 1960–2000 period; the RRs shown in Table IV pertain to the full 1946–2000 period.

For duration and cumulative exposure (Grouping 1) and average intensity of exposure, none of the potential confounders evaluated in univariate models was a statistically significant predictor of cerebrovascular disease, and thus were not included as covariates in the RR models. Table IV shows that cerebrovascular disease SMRs increased with increasing duration, cumulative and average arsenic

TABLE IV. Copperhill Cohort Study, Cause of Death Category and Exposure Selected by Exploratory Screening Algorithm*, SMRs (Local County Comparison) and RRs for Cerebrovascular Disease by Arsenic Exposure Metric, Total Cohort

	External comparisons (1960–2000)[a]			Internal comparisons (1946–2000)[b]			
Arsenic exposure metric	**Obs**	**SMR**	**95% CI**	**Obs**	**RR**	**95% CI**	**Global (trend) *P*-value**
Duration of exposure (years) (Grouping 1)							
Unexposed	43	93	67–125	47	1.00		
>0–6.535	13	133	71–227	13	1.36	0.72–2.55	0.176
6.536+	12	181	94–317	12	1.84	0.96–3.52	(0.062)
Duration of exposure (years) (Grouping 2)							
Unexposed	43	93	67–125	47	1.00		
<0.902	6	101	37–220	6	1.07	0.45–2.53	0.333
0.902–6.53	7	180	72–371	7	1.77	0.79–3.98	(0.062)
6.54–14.43	6	239	88–521	6	2.19	0.92–5.20	
14.44+	6	146	53–317	6	1.59	0.67–3.77	
Cumulative exposure ($\mu g/m^3$-years) (Grouping 1)							
Unexposed	43	93	67–125	47	1.00		0.166
>0–0.414	13	133	71–228	13	1.34	0.72–2.51	(0.058)
0.415+	12	180	93–315	12	1.87	0.98–3.56	
Cumulative exposure ($\mu g/m^3$-years) (Grouping 2)							
Unexposed	43	93	67–125	47	1.00		
<0.046	6	102	37–222	6	1.08	0.46–2.52	0.093
0.046–0.413	6	155	57–337	6	1.46	0.62–3.46	(0.065)
0.414–0.721	7	404**	162–832	7	3.70**	1.65–8.30	
0.722+	6	122	45–265	6	1.33	0.56–3.13	
Average intensity ($\mu g/m^3$)							
Unexposed	43	93	67–125	47	1.00		
Exposed (all cases but one with AIE = 0.05)	25	152	99–225	25	1.46	0.89–2.41	0.146

*Exposure and COD selected if (SMR in unexposed $\leq$100) and (SMR exposed $\geq$150 and number of observed deaths $\geq$6).
[a]Time period restricted to 1960–2000 due to MPDS rate limitations.
[b]Full observation period (1946–2000) used for RRs.
**$P < 0.01$.

exposure, but none of the SMRs was statistically significant. Because all but one of the observed deaths had an average intensity of exposure of 0.05 μg/m^3, only one exposed category was formed for this metric. Similarly, RRs increased with increasing levels of each exposure metric, and none of the category-specific RRs was statistically significant. In the internal comparisons, none of the exposure metrics was a statistically significant predictor of cerebrovascular disease mortality (global *P*-values less than 0.05). The increasing trends in RRs for duration of exposure and cumulative exposure were marginally statistically significant (trend $P = 0.062$ and 0.058, respectively).

Moving from two to four exposed categories for duration and cumulative exposure (Grouping 2) produced less evidence of an upward gradient in SMRs or RRs although the trend *P*-values for both metrics remained marginally statistically significant (trend $P = 0.062$ and 0.065, respectively). For cumulative arsenic exposure, the sole category 0.414–0.721 μg/m^3-years produced a statistically significantly elevated SMR (SMR = 404, 95% CI = 162–832) and RR (RR = 3.70, 95% CI = 1.65–8.30).

The top portion of Table V shows the results of our exposure–response analysis for cadmium exposure and bronchitis using the three-exposure metrics duration, cumulative, and average intensity of exposure. None of the potential confounders evaluated in univariate models was a statistically significant predictor of bronchitis, and thus were not included as covariates in the RR models. SMRs for bronchitis revealed no evidence of an association with increasing duration of cadmium exposure or cumulative cadmium exposure; whereas SMRs were elevated similarly in both exposed categories of average intensity of exposure. The SMR for workers in the lower non-baseline category of duration of exposure was statistically significant (three observed deaths, SMR = 493, CI = 102–1442). Similarly, RRs for bronchitis revealed no evidence of an association with increasing duration or cumulative cadmium exposure. RRs for two isolated exposure categories were statistically significant, (duration of

TABLE V. SMRs (Local County Comparison) and RRs for Cadmium Exposure and Bronchitis and COPD by Exposure Metric, Total Cohort

		External comparisons (1960–2000)[a]			Internal comparisons (1946–2000)[b]			
Cause of death	**Cadmium exposure metric**	**Obs**	**SMR**	**95% CI**	**Obs**	**RR**	**95% CI**	**Global (trend) *P*-value**
Bronchitis	Duration of exposure (years)							
	Unexposed	1	23	1–1326	1	1.00		
	>0–1.837	3	493*	102–1442	3	14.80*	1.17–7.88	0.056
	1.838+	3	100	21–293	3	3.83	0.30–202.6	(0.302)
	Cumulative exposure (μg/m^3-years)							
	Unexposed	1	23	01–126	1	1.00		
	>0–13.374	3	443	92–1296	3	14.77*	1.17–7.84	0.056
	13.375+	3	102	21–299	3	3.81	0.30–201.6	(0.302)
	Average intensity (μg/m^3)							
	Unexposed	1	23	1–126	1	1.00		
	>0–5	3	163	34–476	3	6.51	0.52–345.2	0.232
	5.01+	3	176	36–514	3	5.74	0.46–303.2	(0.180)
COPD	Duration of exposure (years)							
	Unexposed	9	56	26–106	9	1.00		
	>0–14.668	5	62	20–144	5	1.06	0.28–3.57	0.730
	14.668+	6	104	38–226	6	1.57	0.45–5.07	(0.483)
	Cumulative Exposure (μg/m^3–years)							
	Unexposed	9	56	26–106	9	1.00		
	>0–73.334	5	79	26–184	5	1.42	0.37–4.78	0.834
	73.334+	6	79	29–173	6	1.19	0.34–3.79	(0.796)
	Average intensity (μg/m^3)							
	Unexposed	9	56	26–106	9	1.00		
	>0–5	7	92	37–191	7	1.56	0.49–4.80	0.665
	5.01+	4	63	17–161	4	0.99	0.22–3.57	(0.891)

[a]Time period restricted to 1960–2000 due to MPDS rate limitations.
[b]Full observation period (1946–2000) used for RRs.
*$P < 0.05$.

exposure >0–1.837 years: RR = 14.80, 95% CI = 1.17–7.88; cumulative exposure >0–13.374 μg/m^3-years: RR = 14.77, 95% CI = 1.17–7.84).

Because the small number of bronchitis deaths and possible ambiguities of death certificate classification (e.g., overlap with emphysema) complicate data interpretation, we performed additional exposure–response analyses of the larger, combined category of ''chronic obstructive pulmonary disease (COPD).'' As for bronchitis, none of the potential confounders evaluated in univariate models was a statistically significant predictor of COPD, and thus were not included as covariates in the RR models. The bottom portion of Table V shows the results our exposure–response analysis for cadmium exposure and COPD using the three exposure metrics duration, cumulative, and average intensity of exposure. With the exception of a very small 4% excess in deaths among subjects in the highest duration of exposure category, none of the exposure category-specific SMRs were greater than 100. Due mainly to the low SMRs observed in the baseline categories of each exposure metric, RRs are elevated in most of the non-baseline categories of exposure for the three metrics, although none of these elevations is statistically significant and there is little evidence of a trend with increasing exposure.

DISCUSSION

The general mortality patterns observed in this expanded and updated study of the Copperhill cohort indicated statistically significant reduced mortality risks from all causes combined, all cancer sites combined and for many specific malignant and non-malignant disease categories examined. This generally favorable mortality experience is influenced in part by the ''healthy worker effect,'' a relative absence of deleterious health risks in relation to employment, and the effects of continuing employment with its many benefits, such as improved health care and quality of life.

Of the exposure agents considered, exposure levels were relatively the highest and potentially the most problematic for lead and SO_2. A major finding of the original SERA cohort study [Enterline et al., 1986, 1987b] was an association with SO_2 exposure and mortality from emphysema across the eight copper smelter study sites combined, but we saw no evidence of this association in the current Copperhill study. This was not an unexpected finding as the SO_2 exposures at Copperhill were much lower than those in some other copper smelters examined in the SERA study.

Our analysis of mortality in relation to occupational exposure identified only two exposure agent/cause of death categories for further, more detailed exploratory analysis: arsenic exposure and cerebrovascular disease, and cadmium exposure and bronchitis. High levels of ingested inorganic arsenic in drinking water have been linked to arsenical dermatosis and to elevated risks of cancer of the skin, bladder, kidney, liver, and lung [Bates et al., 1992], as well as to diabetes mellitus [Lai et al., 1994; Rahman et al., 1998] and cardiovascular disease, including, carotid atherosclerosis, peripheral vascular ischemic heart disease, and cerebrovascular disease [Wu et al., 1989; Engel et al., 1994; Hertz-Picciotto et al., 2000; Lubin and Fraumeni, 2000; Wang et al., 2007]. Recent literature reviews concluded that while epidemiological studies conducted in general populations strongly support chronic arsenic exposure as a risk factor for various cardiovascular diseases, studies of occupational populations are inconclusive due to methodological limitations, including lack of adjustment for the healthy worker effect [National Research Council, 1999, 2001; Navas-Acien et al., 2005; Wang et al., 2007]. A U.S. study found that after adjustment for the healthy worker effect, the association between arsenic and ischemic heart disease became stronger and the increasing trend was statistically significant [Hertz-Picciotto et al., 2000].

Despite the biological plausibility that arsenic can be toxic to the cardiovascular system, cerebrovascular disease has not been implicated in studies of persons with much higher occupational inhalation exposures than those encountered by Copperhill workers [e.g., Hertz-Picciotto et al., 2000; Lubin et al., 2000]. In fact, Hertz-Picciotto et al. [2000] and Lubin et al. [2000] observed that most occupational studies of arsenic, in which inhalation is the primary route of exposure, have shown excesses only for respiratory cancer. The arsenic exposures observed in this study are at the low end of those reported in other studies of occupational exposures in smelters [Enterline and Marsh, 1982; Enterline et al., 1987a,b], and, in general, are lower than the highest arsenic exposures reported in environmental studies [Lubin et al., 2007]. However, as discussed above, there is a subcohort embedded in the job-classes associated with the copper production unit that had exposures that are comparable to the exposures observed in environmental studies of persons exposed to contaminated drinking water [Chiou et al., 1997; Chowdhury et al., 2000; Lubin et al., 2007]. Although this sub-cohort cannot be individually identified from the work records, their exposures were as high as 90 μg/m^3 (Fig. 1). Based on the physical work rate and the hours worked, this high level may correspond to a dose of 230–630 μg/day which is similar to a daily dose of 230–630 μg/L. As concentration in drinking water. Therefore, the experience of this sub-cohort is arguably similar to the experience of those subjects in the medium dose range of the environmental studies. Table VI shows a sample of epidemiological and environmental studies to illustrate this point.

Our exploratory finding for cerebrovascular disease revealed increasing SMRs and RRs with increasing duration, cumulative and average arsenic exposure, and the trends in RRs relative to two metrics (duration and cumulative exposure) were marginally statistically significant. Given the absence of an established risk in studies of more highly

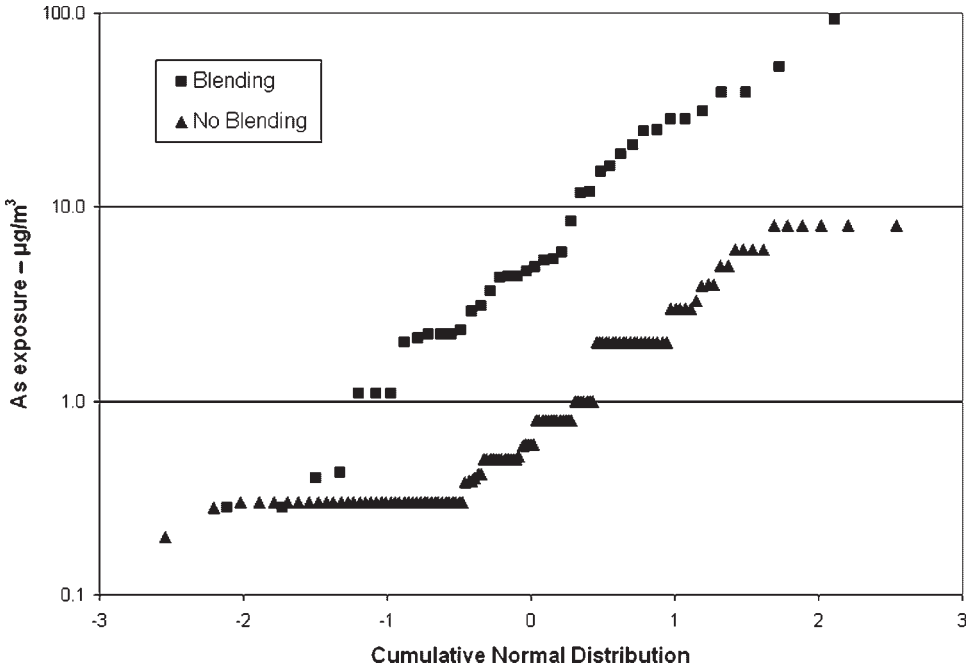

FIGURE 1. Arsenic Exposures for Cranemen and Feedermen in Copperhill Facility.

exposed subjects (both occupational and environmental), it is possible that the apparent trends in cerebrovascular disease mortality risk with increasing exposure may be a reflection of uncontrolled confounding or effect modification by one or more co-exposures or other factors that were correlated with arsenic exposure and unique to the Copperhill facility. Also, chance alone may explain our findings for arsenic and cerebrovascular disease, as none of the exposure category-specific SMRs or RRs were statistically significant.

A British cohort study of male workers employed in several plants involving cadmium processes found a statistically significant overall excess of deaths due to bronchitis and evidence of an association with both duration and intensity of cadmium exposure [Armstrong and Kazantzis, 1983, 1985; Kazantzis et al., 1988]. Although cadmium exposure levels were not reported in the British study, the levels of exposure in the cadmium processing plants studied were probably much higher than those encountered at the Copperhill facility, especially for British

TABLE VI. Comparison of Copperhill High Exposures With Some Reported Environmental Exposures Under the Assumption of 3–6 m^3/Day Inhalation and 1 L/Day Water Consumption

Locale	Mean (µg/day)	98th percentile (µg/day)	Source	Comments
Copperhill	55–110	230–630	This work	Estimated from a fitted lognormal distribution
West Bengal	~90	400	Chowdhury et al. [2000]	Estimated from a figure in the source
Bangladesh	~210	1100	Chowdhury et al. [2000]	Estimated from a figure in the source
Argentina (High)	~180	—	Hopenhayn-Rich et al. [1998]	Estimated using non-censored values-likely over-estimate
Argentina (Medium)	~120	—	Hopenhayn-Rich et al. [1998]	Estimated using non-censored values-likely over-estimate
Finland		<70	Kurtio et al. [1999]	
Maryland		<15	Ryan et al. [2000]	
CA, NE, UT, AK, etc.		<75	Lubin et al. [2007]	
Northern Mexico		<(160–740)	Lubin et al. [2007]	
Chile (1955–1969)	570		Smith et al. [1998]	
Chile (1970–1974)	270		Smith et al. [1998]	
Chile (1975–1979)	180		Smith et al. [1998]	
Chile (1990–1994)	40		Smith et al. [1998]	

men who worked in jobs with ''high'' exposures where the largest bronchitis mortality excesses occurred. Historical air monitoring samples from the Copperhill facility showed that only maintenance work in the copper system had reasonable potential for cadmium exposure.

In our exploratory analysis of bronchitis mortality in relation to cadmium exposure, we observed no or little evidence of an association with increasing duration or average intensity of cadmium exposure although the small number of bronchitis deaths observed in our study ($n = 7$) precluded a more definitive exposure–response relationship for cadmium. In addition, the possibility that uncontrolled confounding by cigarette smoking and/or co-exposures to one or more of the other agents considered in our study (e.g., SO_2 or dust) may have played a role in our findings for bronchitis cannot be ruled out. Only three of the six cadmium-exposed decedents were exposed for periods longer than two years, and the average intensity of cadmium exposure was relatively high for only one of three exposed workers (data not shown). Based on these findings, we conclude that our exploratory finding for bronchitis mortality most likely does not represent a causal association. This conclusion was supported by our analysis of the larger, combined category of COPD, which revealed little evidence of an association with cadmium exposure.

A limitation of the Copperhill cohort study is the absence of complete information on lifetime smoking history. While we sought to collect smoking data from personnel records to enable the evaluation of potential confounding by smoking, we found these data to be unavailable for about 40% of the total cohort. This is a common shortcoming of occupational cohort studies that rely on company-held records as a source of smoking history data. We did not view this as a critical limitation, however, given the absence of elevated mortality risks or exposure–response relationships for smoking-related diseases. Further, considering that we observed large *deficits* in deaths for the major smoking-related diseases (respiratory system cancer, non-malignant respiratory disease, heart disease, etc.), it is unlikely that the absence of elevated risks was the result of negative confounding by smoking.

Because we examined cancer mortality in the Copperhill cohort using a very detailed breakdown of cancer sites, many sites, especially among the cohort subgroups, included only a few observed deaths. This resulted in imprecise measures of comparative mortality as reflected by the very wide confidence intervals around the SMRs. This feature of the analysis should be considered carefully when interpreting very large or very small SMRs based on small numbers of deaths. A related limitation is the small numbers of subjects and observed deaths (and the attendant low statistical power to detect possibly important mortality excesses) in many cohort subgroups and exposure groups examined. Statistical power was not a central issue in this study, however as the study was deemed exploratory and no specific *a priori* hypotheses were tested.

The Copperhill cohort study has many methodological strengths, including: long observation period; large percentage of subjects employed and observed for extended periods of time; excellent mortality follow-up and death certificate ascertainment rates; the use of both a U.S. and local county comparison; an historical reconstruction of exposure to six agents that enabled an analysis of mortality in relation to occupational exposure; and the application of an objective screening algorithm to mitigate false positive findings from the large number of comparisons in the exposure–response analysis.

CONCLUSIONS

Our limited evidence of an association between inhaled arsenic exposure and cerebrovascular disease is an exploratory finding not observed in other epidemiology studies of more highly exposed populations. Possible alternative explanations include chance alone and uncontrolled confounding or effect modification by co-exposures or other factors correlated with arsenic exposure and unique to the Copperhill facility.

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