

Enterline 1995

Cancers related to exposure to arsenic at a copper smelter

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Abstract

Objective—This is an update of an earlier study on the relation between exposure to arsenic in air and deaths from respiratory cancer. The purpose was to verify earlier findings of a supralinear dose response relation and to examine relations with other cancers, particularly those reported in studies on drinking water.

Methods—An earlier study of 2802 men who worked at a copper smelter for a year or more during the period 1940–64 and who were followed up for deaths during the period 1941–76 was updated until 1986. Estimates of exposure for the period 1977–1984 were added.

Results and conclusions—The additional follow up confirms the earlier finding that at low doses the increments in death rates for respiratory cancer for a given increment in dose are greater than at high doses. The additional follow up also shows significant increases in cancer of the large intestine and bone, and SMRs >150 for cancer of the buccal cavity and pharynx, rectal cancer, and kidney cancer. There was a positive relation between exposure to arsenic in air and kidney and bone cancer, but none for the other cancers, except respiratory.

(*Occup Environ Med* 1995;52:28–32)

Keywords: arsenic; cancer; dose-response

We (PE, GM) previously reported on the mortality experience of 2802 men who were exposed to arsenic at a copper smelter at Tacoma, WA after a year or more of employment during the period 1940–64.^{1,3} These reports showed an excess in deaths from respiratory cancer during the period 1941–76 with the excess related to cumulative airborne exposure to arsenic. In the most recent report, the respiratory cancer dose-response curve at lower exposures was much steeper than at higher exposures so that the dose-response curve was supralinear (concave downward). This was true for the relative as well as the absolute response, and for follow up that started at entry into the study, or follow up that started at the end of exposure.³ Thus, in

tional 10 years of follow up, until 1986. The purpose is to verify our previous findings and to explore an additional question, and that is whether inhaled arsenic is related to internal cancers as well as to respiratory cancer.

The copper smelter where workers in this study were exposed to arsenic started operations in 1913 and at one time was the largest in the United States, producing about 10% of the refined copper in the entire country. For many years it was the source of all of the arsenic commercially produced in the United States. Further information about this smelter is contained in an earlier paper.²

Methods

For the entire cohort of 2802 men who worked for a year or more during the period 1940–64 it was possible to determine vital status at the end of 1986 for 98.5%. An additional 522 deaths were identified, which increased the total from 1061 in the last report to 1583. Of 1583 known deaths, death certificates were obtained for 1530 or 96.6%. The additional 522 deaths were traced through the United States Social Security Administration, the United States National Death Index, and by personal phone contacts. Death certificates were obtained from state Health Departments and coded by a nosologist to the underlying cause of death according to the revision of international classification of causes of death in effect at the time of death. For malignant neoplasms expected numbers of deaths were based upon the mortality of the population of the State of Washington.⁴ These are available for the entire follow up period 1941–86 for malignant neoplasms but only from 1960 for other causes of death. Thus, for this report follow up for non-malignant disease only starts in 1960 whereas follow up for malignant disease starts in 1941.

In the calculation of expected deaths only mortality of white men was used as all the 2802 workers in the study were men and nearly all were white. Expected deaths were also calculated with death rates for Pierce County, the county where the smelter is located.⁴ Results were about the same as when Washington state rates were used. Because of larger numbers of deaths and more stable rates only Washington state rates are used in

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Expected deaths are age-time specific death rates of white men for the state of Washington multiplied by person-years lived by the cohort in five year age-time intervals. The SMRs were calculated with the computer program OCMAP.⁵

Exposure to arsenic was estimated from departmental measurements of arsenic in air contained in company annual reports that started in 1938, and measurements of urinary arsenic identified by department and worker started in 1948. We combined these data to allow an analysis of the relation between the concentrations of arsenic in air and various cancers.

Measurements of arsenic in air were mostly confined to departments in which arsenic was thought to be a problem. Measurements of urinary arsenic, on the other hand, were offered to all workers, and they represent all departments of the smelter. The conversion of data of urinary arsenic to air arsenic was made by the identification of departments and years for which data from both air and urinary arsenic were available and by the determination of the mathematical relation between the two. Although a total of 34 pairs of data were available, six pairs were deleted, one pair because the value of arsenic in air was based on only one sample and the other five pairs because notations in the annual reports indicated that the measurements of arsenic in air were not representative of normal working conditions. The remaining 28 pairs of data represented 11 of the 33 departments at the smelter.

Average concentrations of arsenic in air were weighted to reflect as closely as possible actual exposures of workers. Before 1971, data of arsenic in air came from spot samples and tape samples. As far as possible these were weighted for hours per shift at the sam-

ple location, numbers of men at that location per shift, and frequency of operation (for samples that reflected exposure from a particular operation). Starting in 1971, data for arsenic in air were based on readings from personal samples. These seem to be representative of personal exposure for particular departments.

From these data an exposure matrix of arsenic in air was developed by department and year from 1938 up to the time the smelter closed in 1984. Combined with job histories for each worker cumulative exposure was calculated and expressed as $\mu\text{g}/\text{m}^3/\text{y}$. For years before 1938 the exposure data for 1938 were used. Additional details on the method used in estimations of exposure are contained in an earlier report.³

RESULTS FOR CANCER

Table 1 shows the mortality experienced for selected malignant neoplasms in total and by time since first exposure. Overall, there were significant excesses for all malignant neoplasms taken together, cancer of the large intestine, cancer of the respiratory system, and bone cancer. When there were <20 years since first exposure the only significant excess is for respiratory cancer. For ≥ 20 years since first exposure SMRs are generally higher but those that are significant are the same as for the total cohort.

As well as the cancers that were significantly in excess in table 1 there are three sites for which there were 10 or more deaths and for which the SMRs were >150 but were not significant. For cancer of the buccal cavity and pharynx the SMR was 168.7 based on 12 deaths. For rectal cancer the SMR was 176.0 based on 15 deaths, and for kidney cancer there were 11 deaths and the SMR was 163.5. Ten of the 11 deaths from kidney cancer occurred ≥ 20 years after first exposure.

Table 1 Observed (O) and expected (E) deaths and SMRs for selected cancers by years since first exposure, Tacoma copper smelter

Cancer site	Total			Exposure <20 y			Exposure ≥ 20 y			CI
	O	E	SMR (CI)	O	E	SMR	O	E	SMR	
All malignant neoplasms:	395	276.06	143.1**	43	36.10	119.1	352	239.95	146.7**	
Buccal cavity and pharynx	12	7.12	168.7	2	1.14	175.8	10	5.98	167.3	
Digestive organs and peritoneum:	95	79.08	120.1	11	10.94	100.6	84	68.14	123.3	
Oesophagus	7	6.08	115.2	0	0.64	—	7	5.44	128.8	
Stomach	18	16.43	109.6	2	2.79	71.8	16	13.64	117.3	
Large intestine	38	23.48	161.8**	2	2.61	76.8	36	20.87	172.5**	
Rectum	15	8.52	176.0	4	1.33	299.9	11	7.19	153.0	
Biliary passages and liver	1	4.72	21.2	0	0.58	—	1	4.13	24.2	
Pancreas	14	16.26	86.1	2	2.19	91.5	12	14.07	85.3	
All other digestive	2	3.59	55.7	1	0.80	125.0	1	2.79	35.8	
Respiratory system:	188	89.65	209.7**	17	9.66	176.0*	171	79.99	213.8**	
Larynx	3	3.17	94.7	0	0.42	—	3	2.75	109.2	
Bronchus, trachea, lung	182	85.03	214.1**	17	9.04	188.1*	165	75.99	217.1**	
All other respiratory	3	1.46	205.4	0	0.20	—	3	1.26	238.1	
Breast	0	0.46	—	0	0.10	—	0	0.36	—	
Prostate	28	25.62	109.3	2	1.23	163.2	26	24.39	106.6	
Testes and other male genital organs	1	1.31	76.6	1	0.70	143.2	0	0.61	—	
Kidney	11	6.73	163.5 (6-19)	1	1.04	95.9	10	5.69	175.9 (0.8-3.2)	
Bladder and other urinary organs	8	9.61	83.2	1	0.94	106.7	7	8.67	80.7	
Malignant melanoma of skin	1	2.56	39.1	0	0.55	—	1	2.00	49.9	
Eye	1	0.28	361.6	0	0.04	—	1	0.23	428.1	
Central nervous system	5	8.15	61.4	0	1.98	—	5	6.16	81.1	
Thyroid and other endocrine glands	1	1.00	99.9	0	0.24	—	1	0.76	131.7	
Bone	5	1.10	455.6*	0	0.28	—	5	0.82	610.2**	
All lymphatic, haematopoietic:	24	27.21	88.2	7	5.16	135.5	17	22.05	77.1	
Lymphosarcoma and reticulosarcoma	3	5.36	55.9	0	1.21	—	3	4.15	72.3	
Hodgkin's disease	2	2.91	68.8	2	1.20	166.4	0	1.70	—	
Leukemia and aleukemia	9	11.28	79.8	2	2.04	97.8	7	9.24	75.8	
All other lymphopoietic tissue	10	7.66	130.5	3	0.70	426.8	7	6.96	100.6	

populations. We looked for skin cancers in the smelter population of Tacoma and found no excess.²¹ These are rarely fatal and could only be found at work, not very long after the onset of exposure. Skin cancer related to arsenic in drinking water does not usually appear until after the age of 30 and the incidence rises rapidly with age.²² Thus, the latent period for skin cancer and perhaps other cancers related to ingested arsenic could be very long, so perhaps this is the reason these were not seen in the smelter worker population of Tacoma. It may also be that, as noted by Bates *et al*, in comparison with populations exposed to arsenic in drinking water the exposure of our population, and perhaps other populations exposed to arsenic in air is relatively low.¹⁹

One cancer with an apparently short latent period in this study is respiratory cancer. As table 1 shows, a significant excess (SMR = 203.3) occurred in <20 years. The SMR remained around 200 in successive 10 year periods and was 151.9 $\geq$ 50 years since first exposure. We are not aware of published studies of other workers from copper smelters that report increments in respiratory or lung cancer by time from first exposure. Ott *et al* reported no deaths from respiratory cancer in a population occupationally exposed to insecticides containing arsenic <15 years from first exposure (0.4 expected), but did report excesses for the subsequent time since first exposure categories.¹¹ In a study by us (PE, GM) of workers at a copper smelter at Salt Lake City, UT where there was exposure to arsenic the SMR for respiratory cancer <20 years since first exposure was 170.0 (11 deaths) and $\geq$ 20 years 107.8 (39 deaths).^{12,23} Perhaps a short latent period is somehow related to the way exposure occurs in the lung as inhaled arsenic seems to be retained in the lung for long periods.²⁴ On the other hand, perhaps the lung has a particular susceptibility. One curious finding in studies of arsenic in drinking water is a dose related excess in mortality from lung cancer—an excess surpassed only by an excess in urinary cancer.¹⁹ We are not aware of any other ingested substance that may cause lung cancer.

The dose-response relation between airborne arsenic and respiratory cancer found in this study is unusual. As noted in our earlier report, this could be because air measurements are not good measures of biological dose.³ The relation is not likely to be due to confounding, but this needs further study. Smoking can be an important confounder in respiratory cancer and data on the histories of the study population for smoking are being collected. These will be modelled along with other covariates in a future publication.

The excess we found in bone cancer has not, to our knowledge, been reported in other studies. As arsenic is stored in the bone, however, this may be an important finding.^{25,26} Of the five deaths coded by our nosologist to

information on the death certificate indicated that these may not have been the primary sites. If we had recoded these, however, it would have invalidated our comparison with the external control population.

This research was supported in part by the US Environmental Protection Agency. (Agreement No CR811173.)

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