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Key terms: arsenic; arsenic exposure; cancer; interaction; lung; lung cancer; occupational arsenic exposure; occupational exposure; smelter; smoking; sulfur dioxide

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On the interaction between occupational arsenic exposure and smoking and its relationship to lung cancer

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PERSHAGEN G, WALL S, TAUBE A, LINNMAN L. On the interaction between occupational arsenic exposure and smoking and its relationship to lung cancer. *Scand j work environ health* 7 (1981) 302–309. The interaction between occupational arsenic exposure and tobacco smoking and its relationship to lung cancer mortality among 228 deceased Swedish copper smelter workers was studied with the case-referent technique. Arsenic exposure was assessed via detailed company records, and information on smoking habits was gathered from the next of kin. The age standardized rate ratio for death from lung cancer was 3.0 for arsenic-exposed nonsmokers and 4.9 for smokers without occupational arsenic exposure in relation to nonarsenic-exposed nonsmokers. For arsenic-exposed smokers the rate ratio was 14.6, indicating a multiplicative effect of the two exposures. Eighty-five percent of all deaths from lung cancer among the smelter workers could be “explained” by arsenic exposure and/or smoking. The interaction between arsenic and smoking suggests that a strong preventive effect on lung cancer incidence could be obtained by decreasing either one of the exposures or by disaggregating them.

Key terms: smelter, sulfur dioxide.

Exposure to inorganic arsenic compounds has been associated with an increased mortality from lung cancer among copper smelter workers (12, 25, 33), pesticide production workers (9, 15, 21), and vintners (8, 29). In several of the studies positive dose-response relationships were indicated. Investigations on Swedish copper smelter workers have revealed an increased risk of lung cancer (23), especially among workers exposed to arsenic (2, 34).

The interaction between tobacco smoking and occupational exposures can sometimes be fit to a multiplicative model, in which the effect, eg, increase in lung can-

cer incidence, on workers who are smokers can be estimated by the multiplication of effects in nonexposed smokers and exposed nonsmokers. This type of interaction has been observed in asbestos factory and insulation workers (4, 31), and in uranium ore miners (1). In other instances the multiplicative model is not applicable, eg, among zinc-lead miners (3) and workers exposed to chloromethylethers (35). Two studies on American copper smelter workers exposed to arsenic did not give evidence of a positive interaction between smoking and smelter employment (not further specified) on lung cancer mortality (25, 26). However, no detailed analysis of the arsenic-tobacco smoking interaction was performed.

A peculiarity with arsenic carcinogenicity is the discrepancy between epidemiologic and experimental data. Animal carcinogenicity tests have been negative except for some preliminary data indicating a role of arsenic in the development of lung cancer (10) and leukemia (20). Arsenic is not mutagenic in bacterial tests (13, 28).

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On the other hand, there are indications, from different experimental systems, that arsenic may interfere with deoxyribonucleic acid (DNA) repair, and therefore a cocarcinogenic effect is possible (11, 27).

The purpose of the present investigation was to elucidate the arsenic-tobacco smoke interaction among workers from a large Swedish copper smelter. It was anticipated that the results would give practical guidance for minimizing the risks associated with occupational exposure to arsenic, as well as provide insight into the mechanisms of arsenic carcinogenicity.

Methods

Source of subjects

The study was performed according to the case-control or case-referent technique within a cohort. The cohort included all male workers employed at least three months at the Rönnskärsverken copper smelter since the start of operations in 1928 until 1 January 1967 (34). It consisted of 3,958 subjects who were followed until 1 January 1977, and all but 1 % were traced. Data on the causes of death among the 953 workers who had died before this date were obtained from the National Register on Causes of Death. This register contains information from death certificates, which have been shown to be of high validity for most diagnoses (6).

The cases constituted all men who had died from cancer of the trachea, bronchus, or lung (International Classification of Diseases 162, eighth revision), ie, a total of 76 subjects. Two referents were chosen for each case among deceased workers in the cohort who had not died from cancer of the trachea, bronchus, or lung. The referents were matched to the cases according to year of birth. Altogether the group of cases and referents included 228 subjects.

Source of exposure information

The information on occupational exposure was gathered from company records, which had been kept since the start of

operations at the smelter in 1928. The records contained detailed information on the time spent in various workplaces at the smelter by each worker (34).

The assessment of arsenic exposure was based on a safety engineer's estimations of exposure levels in each department during different time periods (19). Exposure to sulfur dioxide (SO_2), which often occurred together with arsenic, was assessed in a similar way. Actual measurements were few however; in 1954 it was reported that the average concentrations of airborne arsenic ranged from 0.06 to 2 mg/m³, while those of SO_2 ranged from 15 to 300 mg/m³ at the roasters and copper furnaces and in the converter hall (14). The workers were classified into different categories according to their estimated exposure to arsenic and SO_2 , and the time trend in exposure levels was also taken into account:

- a. Roaster workers: More than six months of work in the gas purifier or roaster departments. Both arsenic and SO_2 exposure was high for this group.
- b. High arsenic: More than six months of work in the arsenic metal, arsenic refining, arsenic salt, building, electric, machine, or selenium departments, excluding roaster workers. The arsenic exposure was high in this group, but lower than for the roaster workers, and the SO_2 exposure was substantially lower than for the roaster workers.
- c. High SO_2 : More than six months of work in the anode furnace, converter, copper furnace, or sulfur departments, excluding roaster workers and workers in the high arsenic category. The SO_2 levels were as high in these workplaces as at the roasters, but the arsenic levels were substantially lower.

Arsenic exposure primarily occurred at the workplaces included in the roaster worker, high arsenic, and high SO_2 exposure categories. Consequently, the workers in these categories were grouped together in the "arsenic exposed" category. The major remaining worksites at the smelter, where subjects in the reference category (no arsenic exposure) had worked, included the battery factory, central laboratory, coal crusher, copper foundry, deliv-

Table 3. Tobacco consumption among smoking smelter workers in different exposure categories.^a

Exposure category	Number	Daily tobacco consumption ^b (g)	
		Mean	Standard deviation
No arsenic exposure			
Cases	24	12.3	9.7
Referents	49		
High sulfur dioxide exposure			
Cases	9	10.9	13.3
Referents	21		
High arsenic exposure			
Cases	18	14.7	8.7
Referents	19		
Roaster workers			
Cases	17	11.5	10.0
Referents	11		

^a For 11 of the 168 subjects reported to be daily smokers for at least 2 a, it was not possible to get data on consumption.

^b Computed by adding cigarettes (assuming 1 g tobacco/cigarette) and pipe tobacco (calculated from data on weekly consumption).

Fig 1. Etiologic fraction of lung cancer cases among smelter workers exposed to arsenic and/or smokers.

Fig 2. Etiologic fraction (EF) of deaths due to lung cancer associated with arsenic (As) exposure and smoking. Bars indicate approximate 95 % confidence intervals.

etiologic fraction of 67 %, ie, 4.7 out of the total of 7 lung cancer cases in this group. Similarly, for a total of 24 cases of lung cancer among the smokers not exposed to arsenic, 19.2 may be attributed to smoking, and the etiologic fraction of 93 % of the arsenic-exposed smokers corre-

sponds to 41 out of 43 cases. Altogether this makes 64.9 "etiologic" cases ie, which not would have occurred in the absence of exposure.

Fig 2 shows the relative importance of arsenic exposure and smoking for the whole population of smelter workers.

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