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Mortality from lung cancer in an acetylene and phthalic anhydride plant

A case-referent study

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RIBOLI E, BAI E, BERRINO F, MERISI A. Mortality from lung cancer in an acetylene and phthalic anhydride plant: A case-referent study. *Scand j work environ health* 9 (1983) 455–462. The study tested the hypothesis that an excess of lung cancer observed in a small town of the Milano Province in Italy was attributable to occupational exposures in a chemical plant (SISAS) producing mainly acetylene, phthalic anhydride, and their derivatives. Exposures included a large number of chemicals, some of which are known or suspected carcinogens such as soot and phthalates. The local register of deaths was the source of the cases and referents. The cases (N = 43) were the male residents in the town who had died from lung cancer from 1976 to 1979. The referents were a sample of residents from the same town who had died during the same four-year period from causes other than respiratory cancer. Causes of death were validated through clinical data and relatives' reports. Information for a complete occupational history and on smoking habits was collected in interviews of the next of kin of each study subject. After control for age and smoking, the risk of dying from lung cancer for the subjects previously employed at the SISAS plant relative to those never occupationally exposed was 5.6 (95 % confidence limits 1.9–16.2). The risk for exposure to lung carcinogens in work environments other than SISAS was 1.7 (95 % confidence limits 0.9–3.5). On the whole, occupational exposure to chemical carcinogens accounted for about one-third of the total number of lung cancer deaths that occurred in the area during the study period. The results call for further investigation of specific chemicals, mainly soot and phthalates, in the etiology of lung cancer.

Key terms: attributable risk, occupational exposures, phthalates, smoking, soot.

In 1978 the public health officer of Pioltello, a town located in the Milano Province of the Lombardy Region (Italy), reported a crude lung cancer mortality rate of 91.3 per 100,000 person-years for the male residents of the town in the period 1974–1978. From the figures for the whole Lombardy Region, one would have expected a crude rate of 53.3 deaths per 100,000 person-years, a figure leading to a standardized mortality ratio of 1.72 (95 % confidence limits 1.30–2.23). The

rate remained stable at about the same high value over a five-year period.

Most of the Pioltello residents affected by lung cancer and other serious diseases were diagnosed and treated in general hospitals of the Milano metropolitan area so that a systematic misdiagnosis restricted to Pioltello residents seemed unlikely. Potential etiologic factors included environmental exposure to specific carcinogenic stimuli and/or a particular pattern of smoking, such as the presence of a high proportion of smokers among the male residents of Pioltello.

Pioltello is a town located 6 km east of the city of Milano; it had a population of 30,000 in 1980. Previously a rural area, Pioltello experienced rapid industrial development beginning in the 1950s.

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A number of chemical plants and machinery factories are located in the town and its surroundings. The largest one is the SISAS (Società Italiana Serie Acetica Sintetica) chemical factory, in operation since 1947; its main production has been acetylene and phthalic anhydride. The company employed about 700 workers during the 1960s and about 500 during the 1970s. Most former and present SISAS workers live in Pioltello. Preliminary technical data collected by the occupational health service in the local health unit suggested that SISAS workers could have been exposed to chemicals that are known or suspected carcinogens, such as soot and phthalates.

Soot carcinogenicity has been suspected since the observation of an increased frequency of scrotal cancer among chimney sweeps was published in 1775 by Sir Percival Pott (18). More recent experimental animal data, short-term tests (4, 7, 9, 17), and epidemiologic studies on humans (2, 3, 5, 6, 7, 9, 10, 19) have supported earlier observations.

Phthalates have been found to cause tumors in experimental animals in bioassays conducted for the National Toxicology Program of the National Cancer Institute in the United States (8).

On the basis of these preliminary considerations, we hypothesized that occupational exposures to soot and phthalates in the SISAS plant contributed to the reported excess of lung cancer above and beyond tobacco smoking and perhaps other occupational exposures. A case-referent study was designed to test this hypothesis. The study also sought to validate the diagnosis reported on the death certificates through alternative sources of information, such as clinical records and reports of relatives.

Exposure at the SISAS plant

Two basic production processes occur in the SISAS plant, an acetylene cycle and a phthalic anhydride cycle. Additional cycles, in which acetylene and phthalic anhydride derivatives are produced, depend on the two main processes.

The acetylene production is accomplished through the partial combustion of methane with oxygen, followed by

rapid quenching of the reaction products with water (the BASF system). The resulting gases, "air gas" and acetylene, are washed with water and then filtered on granular coke. The water from the quenching and gas washing are decanted, cooled in a natural draft cooling tower (Balke tower), and then recirculated in the plant.

Large quantities of soot are obtained as a by-product of the partial combustion of methane. The soot has been stored for 30 years in the SISAS factory yard, and by 1980 approximately 500,000 m³ had accumulated. Soot powders coming from the plant are wet, and they are dried by the sun during storage in the factory yard. Soot dust thus can be spread in and around the factory by the wind. After about one year of storage, the soot is covered with grass, which reduces the air dispersion.

Acetylene, after separation from the "air gas," may be sold as such or used as an intermediate for acetaldehyde production, involving mercury ions as a catalyst. Acetaldehyde is utilized in the production of ethyl acetate (by reaction with aluminum alcoholate) and in the production of acetic acid (by oxidation in the presence of manganese acetate). Acetylene is also used with acetic acid for the production of vinyl acetate and its polymers.

The phthalic anhydride cycle starts from o-xylene, which is subjected to catalytic oxidation in a tube-west reactor. Phthalic anhydride is separated by sublimation and is also utilized to produce some phthalates, such as n-butyl-phthalate, isobutyl-phthalate, di-(2ethyl-exil)-phthalate, and butylbenzyl-phthalate, which are used as plasticizers in rubber and plastics manufacturing.

Until 1976 the daily production of acetylene and derivatives was about 130 t. In 1977 the acetylene production was reduced to 12 t/d, while the phthalic anhydride and plasticizer production was increased.

Subjects and methods

Source of subjects

The register of deaths of the Pioltello municipality was the source for both the

case and the reference series. Notification of death being compulsory by law in Italy, the register is considered to be complete. Name, date of birth, last address, and date and cause of the death of residents are recorded in the register. The cause of death was not available for a few subjects who died out of town. For each of these subjects we obtained the cause of death from the municipality where death occurred. Male subjects whose death was attributed to lung cancer on the death certificate and whose death occurred between 1 January 1976 and 31 December 1979 were selected as the cases; 53 subjects met these criteria. The referents were selected from the register as the first two persons listed, after each case, whose age was within five years of that of the case and whose death certificate did not mention respiratory cancer. Through this procedure we selected 106 referents with a distribution for age and date of death comparable to the cases.

Assesment of exposures

The next of kin of each study subject was interviewed at home by two physicians (EB & AM). Most of the interviews were conducted with the widow, less frequently with other relatives. Smoking habits were inquired into with questions on age at start, average number of cigarettes smoked per day in adulthood, and age at stopping. An effort was made to collect a complete occupational history. For each job we asked the main duty, period of employment, and the name and address of the company. A further question specifically asked whether the subject worked at the SISAS plant, his specific duty, and the work period. The interviewers also investigated the diagnosis told to the patient's family by clinicians.

We were not able to trace 6 of 53 (11.3 %) cases and 7 of 106 (6.6 %) referents either because the subject's family had moved or because he had no relatives living in the town.

Validation of death diagnosis

The diagnosis reported on a death certificate has more limited reliability than

a diagnosis based on clinical data. Metastatic lung cancer, for example, may be reported on a death certificate as primary lung cancer, while lung cancer may be erroneously omitted as the main condition underlying another immediate cause of death. The first type of error would lead to an overestimation of the lung cancer death rate, and the inclusion of subjects without lung cancer in the case series would weaken any casual association. The second type of error would lead to an underestimation of the death rate, but the inclusion of cases in the reference series would still bias the estimate of the exposure effect towards the null, even if the amount of bias could be negligible for a rare disease.

To validate the death certificate diagnoses for the Pioltello residents, we searched for the study subjects in the files of the Regional Discharge Diagnosis Information System, operating in Lombardy since the end of 1975. The system provides a patient's identification data, summary of final diagnosis coded according to the eighth revision of the International Classification of Diseases (21), and type of treatment for each hospitalization.

We identified 41 out of the 53 cases originally included in the study. For 38 patients the death diagnosis of primary lung cancer was confirmed by clinical data. The other three patients were reported on clinical records as having other primary cancer with lung cancer metastasis. Relatives reported lung cancer as the cause of death for 11 out of the 12 remaining cases and laryngeal cancer with lung metastasis for one subject.

Neither the Regional Discharge Diagnosis Information System nor the family raised the possibility of a diagnosis of lung cancer for any of the referents. The final study size was 43 cases (38 confirmed by clinical data and 11 confirmed by relatives minus 6 not traced by interviewers) and 99 referents.

Categorization of exposures

The evaluation of the collected information and the subject classification according to exposure status was done by two of us (ER & FB) without knowing whether the subject was a case or a referent. We

considered three main exposures as follows:

SISAS plant (S+): We classified as exposed 18 subjects who worked at the plant for 2 to 20 years. Among them, 15 were employed directly by the factory, while three were employees of other companies in charge of maintenance and repair at the SISAS plant. The one subject, a referent, who worked just one month at SISAS as a bricklayer in structural building repairs, was classified as nonexposed.

Other occupational exposures (E+): The subjects were classified according to the likelihood of past exposure to chemicals known to be lung carcinogens in humans. In the E+ category we placed all the subjects who had ever held a job associated with definite or probable exposure to any of the following substances or activities, regarded as lung carcinogens in humans by the IARC-WHO expert committee in 1979 (9): arsenic and certain compounds containing arsenic; asbestos; bis(chloromethyl)ether; chlor(methyl)ether; chromium and certain chromium compounds; underground mining of hematite; mustard gas; nickel refining; soots, tars and mineral oils; and vinyl chloride.

No occupational exposure (E-): The subjects who never held a job which may have exposed them to any of the chemicals or activities listed for the S+ or E+ exposure were considered nonexposed.

In addition to classifying the subjects according to their occupational history, we also divided them according to their smoking habits (ie, average number of cigarettes smoked per day during adulthood) for the analysis. Because of the small number of persons who had never smoked, we put them and the light smokers (less than 10 cigarettes/d) in a single group.

Statistical methods

The chi square for association was computed for several fourfold tables, along with the point estimates of the odds ratio,

according to the methods described by Mantel & Haenszel (11).

The computation of the chi square for trends over the categories of exposures was based on the Mantel extension of the Mantel-Haenszel test (12).

For estimating the etiologic fraction, the test-based confidence limits, and the standardized risk ratio, we followed the methods outlined by Miettinen (14, 15, 16). Analysis of the data was done using the programs written by Rothman & Boice (20).

Results

Table 1 shows the cases and referents stratified by age and smoking and divided by occupational history and exposure.

The crude risk of lung cancer associated with employment at the SISAS plant relative to no occupational exposure to lung carcinogens was 4.1.

The Mantel-Haenszel point estimate after control for age and smoking was 5.6 (95 % confidence limits 1.6-19.9). The difference between the crude and the Mantel-Haenszel odds ratio results mainly from controlling for confounding by tobacco.

The etiologic fraction due to SISAS was 82 % for the exposed and 17 % for all cases.

Altogether occupational exposures in the SISAS plant or in other work environments may account for about one-third of the cases that occurred in the Pioltello population during the study period. This percentage roughly corresponds to the excess mortality which gave rise to the study, and about half of it could be explained by SISAS alone.

As was already noted, due to the small number of cases who never smoked, one of the categories used to evaluate the effects of smoking is defined as those who never smoked plus those who smoked less than 10 cigarettes/d. The specific crude odds ratios for each level of smoking and occupational exposure are reported in table 2. The comparison category consists of the cases with no occupational exposure at the lowest smoking level. The risks associated with tobacco for the mild and heavy smoker categories are

Table 1. Distribution of the cases of lung cancer and the referents into categories of occupational exposure.

Cigarettes per day	Occupational Exposure ^a			All
	S+	E+	E-	
<i>Subjects < 60 years of age</i>				
0-9				
Cases	1	1	0	2
Referents	3	2	5	10
10-19				
Cases	2	2	3	7
Referents	2	7	10	19
≥ 20				
Cases	2	7	3	12
Referents	0	6	4	10
<i>Subjects ≥ 60 years of age</i>				
0-9				
Cases	2	0	1	3
Referents	1	7	14	22
10-19				
Cases	0	5	4	9
Referents	1	8	18	27
≥ 20				
Cases	2	3	5	10
Referents	1	3	7	11
<hr/>				
All				
Cases	9	18	16	43
Referents	8	33	58	99
<hr/>				
Crude odds ratio	4.1	2.0	1	
Standardized odds ratio ^b	5.2	1.8	1	
Mantel-Haenszel chi square	7.02	1.44	—	
Mantel-Haenszel odds ratio				
Point estimate	5.6	1.7	1	
95 % confidence interval	1.6-19.9	0.7-4.1	—	
Etiologic fraction %, exposed	82.1	31.4	—	
95 % confidence interval	36.1-95.0	0-63.0	—	
Etiologic fraction %, population	17.2	16.6	—	
95 % confidence interval	4.8-28.0	0-38.0	—	

^a S+ = employed by SISAS at one time, E+ = never employed by SISAS but probably exposed to lung carcinogens in work for another company, E- = never employed by SISAS and never occupationally exposed.

^b The standard is the age and smoking distribution of the E- category.

Table 2. Crude odds ratios and 95 % confidence intervals for death from lung cancer among different categories of occupational exposures, according to the level of smoking.

Cigarettes per day	Occupational exposure ^a		
	S+	E+	E-
0-9			
Crude odds ratio	14.3	2.1	1
95 % confidence interval	1.6-126.9	0.1-37.5	—
10-19			
Crude odds ratio	12.7	8.9	4.8
95 % confidence interval	1.2-133.8	1.3-62.8	0.6-36.2
≥ 20			
Crude odds ratio	76.0	21.1	13.8
95 % confidence interval	7.5-765.8	3.4-132.0	2.1-92.1

^a S+ = employed by SISAS at one time, E+ = never employed by SISAS but probably exposed to lung carcinogens in work for another company, E- = never employed by SISAS and never occupationally exposed.

likely to be underestimated because the categories are compared to an "unclean" category. Nevertheless the risk due to smoking is quite evident and dose-related for the E- and E+ categories, with chi squares for trend equal to 5.31 ($p = 0.021$) and to 7.77 ($p = 0.005$), respectively. The dose response for smoking is less evident for the S+ category (chi square for trend = 1.86, $p = 0.243$).

It should be stressed that the odds ratio estimates for SISAS exposure were based on a very small number of exposed cases in each smoking level so that the variability of each estimate is quite large, as indicated by the wide confidence intervals.

Discussion

The major result of this study is the finding of a lung cancer risk 5.6 times higher for subjects with employment at the SISAS factory in comparison to those with no occupational exposure.

Of the biases that could affect our findings, selection should not be an issue because the subjects' recruitment was performed without any knowledge of exposure status.

Observation bias could have occurred at the time of information gathering since the interviewers were aware of the subjects' death diagnoses and had to get confirmation from relatives. In addition the SISAS plant was widely considered by the population as polluted and unhealthy, a factor raising the issue of differential recall for the occupational history. On the other hand, observation and recall biases are unlikely to account for our results because

prior employment in the largest plant of a town as small as Pioltello is a clearly defined event, well known by the workers' wives and close relatives. Thus it seems unlikely for employment history to have been misreported by the interrogated subjects or subjectively interpreted by the interviewers.

Major confounding factors could be age, smoking, and other occupational exposures. Age was taken into account in the study design by the recruitment of referents with the same age distribution as the cases and by conditional stratified analysis.

Smoking was found to be negatively associated with employment at SISAS, non-exposed referents including a higher proportion of mild and heavy smokers than the exposed ones (table 3). In fact, after standardization for the smoking and age of the nonexposed referents, the adjusted odds ratio of 5.2 for SISAS exposure is higher than the crude one (4.1), the component of the crude odds ratio due to smoking being 0.78. The same value can be obtained with Axelson's theoretical formula for estimating the possible effect produced by a confounder (1). We are aware that controlling smoking over only three strata may leave some residual confounding. Nevertheless in our data the confounding is towards the null, and a more complete control would probably enhance the risk estimate.

A few subjects in the S+ exposure category may have been exposed to lung carcinogens while working for other companies. If this situation had occurred more frequently than among subjects never employed by SISAS, the observed risk associated with SISAS employment might have been at least partially due to confounding by other occupational exposures. Because of the limited size of the studied population it was not feasible to analyze the data conditionally on other occupational exposures. Nevertheless we could estimate the effect of the possible confounding factor by comparing the SISAS exposed category with the "other occupational exposures" category. The corresponding odds ratio after control for age and smoking was 3.0. This is the minimum estimated risk associated with SISAS employment on the conservative assumption

Table 3. Percentage of subjects who smoked more than nine cigarettes per day during adulthood among different categories of occupational exposures.

	Occupational exposure ^a		
	S+	E+	E-
Cases	66.7	93.8	94.4
Referents	50.0	72.7	67.2

^a S+ = employed by SISAS at one time, E+ = never employed by SISAS but probably exposed to lung carcinogens in work for another company, E- = never employed by SISAS and never occupationally exposed.

that all SISAS workers were also exposed to carcinogens in other factories.

The subjects employed by SISAS included two clerks belonging to the reference series, while the exposed cases were all employed in production. As many workers had several duties in two or more production cycles, we could not relate the risk to any specific type of work.

In SISAS, exposures probably included a large number of chemicals, such as raw materials, final products and by-products, but for only a few of them are data available on carcinogenicity. At the time the study was done, soot seemed the most likely substance involved in the hypothesized carcinogenic effect of the SISAS work environment. A number of arguments supported our reasoning. First, there was already evidence that soot can be a lung carcinogen in humans. Contrary results (13) may be explained by the variable content of polycyclic aromatic hydrocarbons and by the size of the particles. Second, the period since production, which started in the late 1940s, was long enough to make it compatible with the usual latency period between occupational exposure to polycyclic aromatic hydrocarbons and death from lung cancer. Third, the soot was produced in very large quantities and stored in a way that made exposure likely in and around the plant.

It may be of interest to note that, while all the referents lived in the town, upwind of the plant, two cases with no occupational exposure lived close to the factory. One was a farmer who cultivated the land around the SISAS plant and whose brother also died of lung cancer six years before. The other was the graveyard keeper, who worked downwind of the factory just across the road, where the Pioltello cemetery is located. Thus environmental exposure from the SISAS plant could account for a proportion of lung cancer mortality larger than the estimated excess. Unfortunately the design of our study does not allow evaluation of that aspect.

Phthalates have been found to cause tumors in animals. Di(2-ethylexil)phthalate caused liver tumors in both rats and mice, and butylbenzylphthalate induced leukemia in female rats. These findings raise a serious public health issue, given the large use of the substances as plasti-

cizers in the manufacture of food-packaging materials and the consequent wide exposure among the general population. Phthalates are blended at the usual level of 50 % to polyvinyl chloride and vinyl copolymer resins for the production of plastic films. Phthalates migrate from plastic packaging films to food under storage conditions and have been found at concentrations ranging from 0.04 mg/kg to 68.0 mg/kg according to the type of food (8). Di(2-ethylexil)phthalate and butylbenzylphthalate have been produced for about 15 years by SISAS, along with other phthalates. Few subjects in our study worked in phthalate production, but the data are too scanty to draw any specific conclusions.

Given the presented considerations and the limited size of our study, any etiologic interpretation should be cautious. Nevertheless the results do suggest the need for further investigations (i) to clarify the possible etiologic roles of specific chemicals, (ii) to monitor the impact of recent changes in production cycles, and (iii) to assess improvements in environmental work conditions.

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