Mortality from Lung Cancer in Workers Exposed to Sulfur Dioxide in the Pulp and Paper Industry

Won Jin Lee,[1] Kay Teschke,[2] Timo Kauppinen,[3] Aage Andersen,[4] Paavo Jäppinen,[5] Irena Szadkowska-Stanczyk,[6] Neil Pearce,[7] Bodil Persson,[8] Alain Bergeret,[9] Luiz Augusto Facchini,[10] Reiko Kishi,[11] Danuta Kielkowski,[12] Bo Andreassen Rix,[13] Paul Henneberger,[14] Jordi Sunyer,[15] Didier Colin,[1] Manolis Kogevinas,[15] and Paolo Boffetta[1]

[1]International Agency for Research on Cancer, Lyon, France; [2]University of British Columbia, Vancouver, Canada; [3]Finnish Institute of Occupational Health, Helsinki, Finland; [4]Norwegian Cancer Registry, Oslo, Norway; [5]Stora Enso Oyj, Imatra, Finland; [6]Nofer Institute of Occupational Medicine, Lodz, Poland; [7]Massey University, Wellington, New Zealand; [8]University Hospital Department of Occupational and Environmental Medicine, Linköping, Sweden; [9]Claude Bernard University, Lyon, France; [10]Federal University of Pelotas, Pelotas, Brazil; [11]Graduate School of Medicine, Hokkaido, Japan; [12]National Centre for Occupational Health, Johannesburg, South Africa; [13]Danish Cancer Society, Copenhagen, Denmark; [14]National Institute for Occupational Safety and Health, Morgantown, West Virginia, USA; [15]Municipal Institute of Medical Research, Barcelona, Spain

Our objective in this study was to evaluate the mortality of workers exposed to sulfur dioxide in the pulp and paper industry. The cohort included 57,613 workers employed for at least 1 year in the pulp and paper industry in 12 countries. We assessed exposure to SO_2 at the level of mill and department, using industrial hygiene measurement data and information from company questionnaires; 40,704 workers were classified as exposed to SO_2. We conducted a standardized mortality ratio (SMR) analysis based on age-specific and calendar period-specific national mortality rates. We also conducted a Poisson regression analysis to determine the dose–response relations between SO_2 exposure and cancer mortality risks and to explore the effect of potential confounding factors. The SMR analysis showed a moderate deficit of all causes of death [SMR = 0.89; 95% confidence interval (CI), 0.87–0.96] among exposed workers. Lung cancer mortality was marginally increased among exposed workers (SMR = 1.08; 95% CI, 0.98–1.18). After adjustment for occupational coexposures, the lung cancer risk was increased compared with unexposed workers (rate ratio = 1.49; 95% CI, 1.14–1.96). There was a suggestion of a positive relationship between weighted cumulative SO_2 exposure and lung cancer mortality (*p*-value of test for linear trend = 0.009 among all exposed workers; $p = 0.3$ among workers with high exposure). Neither duration of exposure nor time since first exposure was associated with lung cancer mortality. Mortality from non-Hodgkin lymphoma and from leukemia was increased among workers with high SO_2 exposure; a dose–response relationship with cumulative SO_2 exposure was suggested for non-Hodgkin lymphoma. For the other causes of death, there was no evidence of increased mortality associated with exposure to SO_2. Although residual confounding may have occurred, our results suggest that occupational exposure to SO_2 in the pulp and paper industry may be associated with an increased risk of lung cancer. *Key words:* epidemiology, lung neoplasms, mortality, pulp and paper industry, sulfur dioxide. *Environ Health Perspect* 110:991–995 (2002). [Online 15 August 2002]
http://ehpnet1.niehs.nih.gov/docs/2002/110p991-995lee/abstract.html

Pulp and paper production workers are exposed to a number of hazardous chemicals, and several studies have been conducted that suggest a possible health effect of such exposures. However, previous studies did not usually include an assessment of exposure to specific agents (Toren et al. 1996). Exposure circumstances in pulp and paper mills are complex; it is therefore difficult to identify agents possibly responsible for an adverse health effect from the results of studies based on employment in a given department or mill.

Sulfur dioxide is a common chemical exposure in the pulp production part of the pulp and paper industry, and levels often exceed 2 ppm (Kauppinen et al. 1997). SO_2 is also a major air pollutant suspected to increase mortality from respiratory diseases in the general population (Hoek et al. 2001; Lee et al. 2000; Shinkura et al. 1999; Xu et al. 1994) and to act as a promoter or cocarcinogen (Nisbet et al. 1984). Some early studies (Lee and Fraumeni 1969; Rencher et al. 1977) in SO_2-exposed workers showed an increased mortality from lung cancer, but in those studies exposure to SO_2 occurred together with exposure to known or suspected carcinogens such as arsenic. Previous studies have reported an increased mortality from lung cancer among workers employed in the pulp and paper industry and, in particular, in sulfite pulp manufacture and maintenance (Band et al. 2001; Langseth and Andersen 2000; Szadkowska-Stanczyk and Szymczak 2001; Toren et al. 1991). It was suggested that asbestos, dust, or chlorinated compounds could be among the agents responsible for the increased lung cancer mortality, but no formal attempt was made in these studies to assess exposure to specific agents.

The International Agency for Research on Cancer has coordinated an international cohort study of workers in the pulp and paper industry to investigate patterns of cancer incidence and mortality. Results based on national components of the multicenter cohort have been reported (Andersson et al. 1998; Fassa et al. 1998; Henneberger and Lax 1998; Henneberger et al. 1989; Jäppinen and Pukkala 1991; Jäppinen and Tola 1986; Langseth and Andersen 1999, 2000; Rix et al. 1997, 1998; Sala-Serra et al. 1996; Szadkowska-Stanczyk and Szymczak 2001; Szadkowska-Stanczyk et al. 1997; Wild et al. 1998). Assessment of exposure to specific agents was conducted by an international panel of industrial hygienists (Kauppinen et al. 1997).

In this study we present an evaluation of the mortality of SO_2-exposed workers employed in the pulp and paper industry.

Materials and Methods

We included those workers with at least 1 year of employment in the pulp and paper industry. We excluded countries in which no workers were classified as exposed to SO_2, as well as workers with unknown SO_2 exposure status. A total of 57,613 subjects from Brazil, Denmark, Finland, France, Japan, New Zealand, Norway, Poland, South Africa, Spain, Sweden, and the United States were included in the analysis (51,240 men and 6,373 women); they contributed 1,249,406 person-years of observation from 1945 to 1996. Their distribution by SO_2 exposure status and country is shown in Table 1. Norway provided the largest number of SO_2-exposed workers (29.8%), followed by Finland (16.3%), Poland (13.1%), and New Zealand (12.7%).

Workers were followed up for mortality according to procedures specific to each country. The period of follow-up varied

Address correspondence to P. Boffetta, Unit of Environmental Cancer Epidemiology, International Agency for Research on Cancer, 150 cours Albert-Thomas, 69008 Lyon, France. Telephone: 33-4-72738441. Fax: 33-4-72738320. E-mail: boffetta@iarc.fr

This study was partially supported by grant contracts from the European Commission's Biomed programme (BMH1-CT92-1110 and BMH4-CT95-1100). W.J.L. worked on this study under the tenure of a Special Training Award from the International Agency for Research on Cancer.

Received 27 December 2001; accepted 5 March 2002.

among countries, but in most cases it was between the early 1950s and the mid 1990s. In the whole database, 2% of workers were lost to follow-up and 1% emigrated. Causes of death were either abstracted from death certificates or obtained from mortality registries and coded according to the *International Classification of Diseases,* Revision 9 (ICD-9, 1975).

We reconstructed exposure estimates for SO_2 for each mill and department included in the study and for different time periods, using international industrial hygiene measurement data (both from mills included in the study and from nonparticipating European and North American mills), information from detailed questionnaires about raw materials and production processes submitted by each participating mill, and the experience of the assessment team. SO_2-exposed workers were employed primarily in the following departments: pulp production (sulfite and kraft processes), pulp production from recycled paper, paper and paperboard production, and nonproduction (e.g., maintenance). Workers involved in the manufacture of paper and paperboard products were not exposed to SO_2.

We estimated prevalence and level of exposure for each department in each of the 52 participating mills for every time period in which relevant production conditions appeared to remain constant. The prevalence of exposure referred to the proportion of workers in the department exposed to the agent on an average workday and was categorized as very low (< 5% of workers in the department exposed, coded as 0.025), low (5–50%, coded as 0.25), high (51–95%, coded as 0.75), and very high (> 95%, coded as 0.975). The level of exposure referred to the mean level of exposure at work averaged over the work year among the exposed workers and was categorized as 0 (mean value = 0.15 ppm), 1 (0.5 ppm), 2 (1.5 ppm), and 3 (5 ppm). We defined a group with high exposure as including workers in the two upper categories of both level and prevalence of SO_2 exposure; the high-exposure group included 2,495 workers, providing 56902.6 person-years of observation. We constructed several SO_2 exposure variables, all categorized into quartiles for the statistical analysis: duration of exposure (< 4, 4–12, 13–24, ≥ 25 years), time since first exposure to SO_2 (< 18, 18–28, 29–38, ≥ 39 years), cumulative exposure [Σ level (mean value) × duration; < 23, 23–61, 62–127, ≥ 128 ppm-years], and weighted cumulative exposure [Σ prevalence (code) × level × duration: < 14, 14–38, 39–90, ≥ 91 ppm-years]. Cumulative and weighted cumulative exposures were calculated for all exposed workers as well as for workers in the high-exposure group. Workers with potential exposure but unknown prevalence or level were considered exposed but excluded from the calculation of cumulative exposure.

Standardized mortality ratios (SMRs) were calculated as the ratio of observed to expected deaths. We computed expected deaths by multiplying the person-years in each sex-specific, age-specific, and 5-year calendar period-specific stratum by the national reference rates using the Person Years program (Coleman et al. 1986). National rates were derived from the World Health Organization (WHO) Mortality Database (WHO 2001). Ninety-five percent confidence intervals (CIs) of the SMRs were calculated under the assumption that the observed numbers of deaths follow a Poisson distribution. We performed tests for linear trend in SMRs using a method described by Breslow and Day (1987).

Expected deaths were not available for the South African cohort. In preliminary analyses, the overall SMR in the Brazilian cohort was < 0.5, suggesting possible underascertainment of deaths. These two national components were excluded from the SMR analysis.

We used Poisson regression analysis to examine internal dose–response relations and to explore the effect of potential confounding factors. Rate ratios (RRs) and 95% CIs derived from the analysis were adjusted for

Table 1. Number of workers and person-years included in the study by SO_2 exposure and country.

	Never exposed		Ever exposed		High exposure[a]	
Country	No.	P-Y	No.	P-Y	No.	P-Y
Brazil	10	105.2	2,100	30541.8	9	153.7
Denmark	7,512	174346.6	574	11929.8	388	8452.6
Finland	1,808	53889.7	6,645	209800.6	185	6167.3
France	1,361	23177.7	2,841	52441.6	19	377.9
Japan	1,050	19294.2	1,229	22397.2	31	578.6
New Zealand	380	4138.2	5,152	53516.5	151	1754.2
Norway	2,384	52957.2	12,123	321390.7	1,078	28053.2
Poland	795	13026.5	5,317	79629.2	369	6212.2
South Africa	222	4224.5	655	11704.5	4	80.3
Spain	80	1399.5	305	5171.3	28	359.3
Sweden	1,183	21285.9	3,232	68045.5	129	2257.0
United States	124	2496.2	531	12130.7	104	2456.3
Total	16,909	370341.4	40,704	878699.2	2,495	56902.6

P-Y, person-years.
[a]High exposure is a subset of ever exposed.

Table 2. Standardized mortality ratios of selected causes by SO_2 exposure.

Cause of death	Never exposed			Ever exposed			High exposure[a]		
(ICD-9 classification)	Obs	SMR	95% CI	Obs	SMR	95% CI	Obs	SMR	95% CI
All causes	3,224	0.91	0.88–0.94	7,508	0.89	0.87–0.91	681	0.92	0.85–0.99
Malignant neoplasms (140–208)	809	0.91	0.85–0.97	1,756	0.91	0.87–0.96	161	0.94	0.80–1.10
Oral cavity, pharynx (140–149)	15	0.77	0.43–1.27	35	0.76	0.53–1.06	1	0.29	0.01–1.59
Esophagus (150)	18	0.83	0.49–1.31	27	0.57	0.38–0.83	2	0.54	0.07–1.96
Stomach (151)	80	1.02	0.81–1.26	172	0.81	0.69–0.94	13	0.72	0.38–1.24
Nose (160)	3	1.09	0.23–3.20	6	0.86	0.31–1.87	0	0	—
Larynx (161)	13	1.16	0.62–1.98	24	0.96	0.61–1.42	2	1.09	0.13–3.93
Lung (162)	194	0.92	0.79–1.06	482	1.08	0.98–1.18	58	1.45	1.10–1.87
Bladder (188)	34	1.03	0.71–1.43	54	0.90	0.68–1.18	4	0.62	0.17–1.58
Kidney (189)	16	0.62	0.35–1.00	58	1.04	0.79–1.34	5	0.98	0.32–2.28
Non-Hodgkin lymphoma (200, 202)	16	0.79	0.45–1.29	45	0.94	0.68–1.25	9	2.15	0.98–4.08
Hodgkin disease (201)	9	1.38	0.63–1.62	13	0.84	0.45–1.43	3	2.40	0.49–7.00
Multiple myeloma (203)	15	1.14	0.64–1.88	29	0.87	0.58–1.24	1	0.31	0.01–1.71
Leukemia (204–208)	18	0.60	0.35–0.94	58	0.89	0.68–1.15	9	1.56	0.71–2.96
Disease of circulatory system (390–459)	1,438	0.92	0.87–0.96	3,660	0.94	0.91–0.97	342	0.96	0.86–1.07
Bronchitis, emphysema, asthma (490–493)	101	0.90	0.75–1.08	142	0.80	0.67–0.94	12	0.69	0.35–1.20
Liver cirrhosis (571)	59	1.10	0.84–1.43	77	0.79	0.63–0.99	7	0.98	0.39–2.02

Obs, observed. Cohorts from Brazil and South Africa were excluded from the SMR analysis.
[a]High exposure is a subset of ever exposed.

country, sex, age, calendar period, and employment status (i.e., whether person-years accumulated while workers were employed in the companies included in the study or not). The reference group for each RR was the first level of each variable. Because there was potential confounding among occupational exposures, we also adjusted the RRs for coexposure to other potential carcinogens (acid, asbestos, volatile organochlorine compounds, combustion products, organic dyes, epichlorohydrine derivatives, formaldehyde, pulp and paper dust, reduced organic sulfur compounds, talc, welding fumes, wood dust). In the final models, however, we retained a shorter list of potential confounders. Adjustment for lifestyle factors such as tobacco smoking was not possible.

Results

In this cohort 7,613 deaths occurred among SO_2-exposed workers, including 488 lung cancer deaths. The SMR analysis, based on 7,508 deaths from 10 countries, yielded a deficit (SMR = 0.89; 95% CI, 0.87–0.91) in mortality compared with national rates (Table 2). We also observed a deficit in mortality for all malignant neoplasms (SMR = 0.91; 95% CI, 0.87–0.96; based on 1,756 deaths) and for cancers of the esophagus (SMR = 0.57; 95% CI, 0.38–0.83; 27 deaths) and stomach (SMR = 0.81; 95% CI, 0.69–0.94; 172 deaths). Lung cancer mortality was slightly increased (SMR = 1.08; 95% CI, 0.98–1.18; 482 deaths). The results of the analysis of gender-specific mortality did not reveal any particular feature, with the results among women being based on a relatively small number of deaths (not shown in detail).

Among workers classified in the high-SO_2-exposure group, there was an increased mortality from lung cancer and, although not statistically significant, from non-Hodgkin lymphoma and leukemia (Table 2).

Table 3 shows the results of the comparisons of SO_2-exposed and unexposed workers without and with adjustment for estimated exposure to known or suspected occupational carcinogens. The RRs of bronchitis, emphysema, and asthma were also decreased, whereas those of lung cancer (RR = 1.49; 95% CI, 1.14–1.96) and non-Hodgkin lymphoma (RR = 2.55; 95% CI, 1.06–6.13) increased. Results after further adjustment for exposure to other agents, such as formaldehyde, organochlorine compounds, and pulp and paper dust, were similar to those presented for RR2 in Table 3, although the precision of the RRs was decreased (not shown in detail).

The results on mortality from selected causes of death according to weighted cumulative SO_2 exposure are reported in Table 4. The overall cancer mortality increased significantly with weighted cumulative exposure, no matter whether the analysis included all workers or only those classified in the high-exposure group. A trend was also suggested for mortality from stomach cancer, lung cancer, and non-Hodgkin lymphoma, although it was significant only for the latter two neoplasms when all workers were retained in the analysis. Results on mortality from all cancers combined were driven by the increased mortality from lung cancer. When the latter neoplasm was excluded, the RRs for increasing levels of weighted cumulative exposure were (for the categories reported in Table 4) 1.02 (95% CI, 0.82–1.28), 1.23 (95% CI, 0.98–1.55), and 1.24 (95% CI, 0.98–1.58). Mortality from nonneoplastic respiratory diseases decreased—although not significantly so—with increasing weighted cumulative exposure to SO_2. A similar analysis for other causes of death did not suggest any association. An analysis that did not consider estimated prevalence of exposure (i.e., based on cumulative exposure instead of weighted cumulative exposure) yielded results very similar to those reported in Table 4.

We found no trend between either duration of exposure or time since first exposure and mortality from the causes reported in Table 4 (not shown in detail).

The analyses of the effect of combined exposure between SO_2 and other occupational agents on lung cancer mortality are presented in Table 5. There was a suggestion of an interaction between SO_2 and welding fumes but not between SO_2 and either asbestos or combustion products.

Table 3. Relative risks for selected causes among SO_2-exposed workers.

Cause of death	RR1	95% CI	RR2	95% CI
All causes	0.98	0.93–1.03	1.02	0.95–1.09
All malignant neoplasms	1.01	0.90–1.12	1.01	0.88–1.15
Oral and pharyngeal cancer	1.57	0.70–3.51	1.03	0.40–2.69
Stomach cancer	0.82	0.59–1.14	0.73	0.47–1.12
Lung cancer	1.24	0.99–1.56	1.49	1.14–1.96
Non-Hodgkin lymphoma	1.71	0.77–3.80	2.55	1.06–6.13
Leukemia	2.06	0.98–4.31	2.49	1.13–5.49
Bronchitis, emphysema, asthma	0.77	0.54–1.10	0.67	0.43–1.06
Liver cirrhosis	0.75	0.49–1.13	0.73	0.43–1.22

Abbreviations: RR1, RR adjusted for sex, age, employment status, calendar year, and country; RR2, RR adjusted for sex, age, employment status, calendar year, country, and exposure to asbestos, combustion products, and welding fumes. The reference category included workers who were never exposed to SO_2.

Table 4. Mortality from selected causes by weighted cumulative exposure to SO_2.

	All neoplasms		Stomach cancer		Lung cancer		Non-Hodgkin lymphoma		Bronchitis, emphysema, asthma	
WCE (ppm-year)	RR	95% CI	RR	95% CI	RR	95% CI	RR	95% CI	RR	95% CI
Ever exposed										
0.1–1.9[a]	1.0	—	1.0	—	1.0	—	1.0	—	1.0	—
2.0–5.9	1.0	0.8–1.2	1.0	0.5–2.0	0.9	0.6–1.4	2.6	0.6–11	0.9	0.5–1.7
6.0–20.9	1.3	1.1–1.6	1.6	0.8–3.0	1.6	1.1–2.3	5.3	1.4–21	0.9	0.5–1.8
≥ 21.0	1.3	1.1–1.6	1.3	0.6–2.5	1.5	1.0–2.2	4.4	1.0–18	0.5	0.2–1.1
Trend	0.001		0.3		0.009		0.03		0.05	
High exposure										
0.1–13.9[a]	1.0	—	1.0	—	1.0	—	1.0	—	1.0	—
14.0–38.9	1.0	0.6–1.6	1.4	0.2–11	1.5	0.6–3.4	0.8	0.1–7.1	0.4	0.06–2.9
39.0–90.9	1.1	0.6–1.9	1.8	0.2–18	1.1	0.4–2.9	1.6	0.1–18	0.5	0.07–4.1
≥ 91.0	1.5	0.8–2.7	3.9	0.4–40	1.9	0.7–5.5	1.7	0.1–23	0.2	0.01–3.3
Trend	0.2		0.2		0.3		0.6		0.4	

WCE, weighted cumulative exposure (Σ prevalence × level × duration). RR is adjusted for sex, age, employment status, calendar year, and country. Trend is the *p*-value of the test for linear trend.
[a]Reference category, which included workers who were never exposed to SO_2.

Discussion

The main result of this cohort study was an association between SO_2 exposure and mortality from all neoplastic diseases and lung cancer. In the case of lung cancer, a marginally increased mortality compared with unexposed workers was significantly increased after adjustment for exposures to lung carcinogens. In addition, internal comparisons showed lung cancer mortality elevated 2-fold among workers in the highest category of cumulative SO_2 exposure compared with workers in the lowest exposure category. The lack of an association between lung cancer mortality and duration of SO_2 exposure can be explained by variability in exposure levels across time and country, making duration of exposure a poor indicator of total dose. These findings suggest that SO_2 exposure in the pulp and paper industry may contribute to lung carcinogenesis.

The evidence of a genotoxic effect of SO_2 in experimental systems is limited (IARC 1992). Groups of workers exposed to SO_2 in Sweden (Nordenson et al. 1980) and in China (Meng and Zhang 1990) have been shown to have significantly increased frequency of chromosomal aberrations. Additional nongenotoxic mechanisms through which SO_2 might exert a carcinogenic effect on the lung include slowing of mucociliary clearance, impairment of alveolar macrophage function, and other effects on the immune response such as increased epithelial permeability, which would facilitate absorption of carcinogenic components of particulate matter (Beeson et al. 1998). Even though the molecular basis of SO_2 carcinogenicity is unclear, Leung et al. (1985) and Menzel et al. (1986) suggested that SO_2 may affect the detoxification of xenobiotic compounds by inhibiting the enzymatic conjugation of glutathione and reactive electrophiles. Because glutathione conjugation represents the major pathway of elimination of benzopyrene epoxides in the lung, their results offered a possible explanation for the cocarcinogenicity of SO_2 in combination with polycyclic aromatic hydrocarbons.

Following early observations by Peacock and Spence (1967) of an increased incidence of lung cancer in mice, Ohyama et al. (1999) reported an increased incidence of lung cancer in rats exposed to SO_2. In a study of chemical workers exposed to SO_2, Bond et al. (1986) reported a significant association between lung cancer mortality and SO_2 exposure, for which there was a significant dose–response relationship. Results of two general population studies, the American Cancer Society Study (Pope et al. 1995) and the Adventist Health Study (Abbey et al. 1999; Beeson et al. 1998) suggested a positive association between SO_2 exposure as an air pollutant and increased lung cancer mortality.

An important limitation of the present study is the lack of information on potential lifestyle confounders, chiefly tobacco smoking. Smoking is a well-known potential confounder in studies of lung cancer. Although smoking habits in the cohort are not known, there are indirect approaches to consider whether smoking might be an important confounder in our study. Jäppinen and Tola (1986) surveyed smoking habits in the Finnish component of this study and reported that smoking habits did not differ substantially from those of the national population. According to Axelson (1978), smoking habits in various industrial populations rarely diverge so much that the confounding effect of smoking distorts the risk ratios of lung cancer outside the range of 0.5–1.5. The simple comparisons of risk between SO_2-exposed and unexposed workers were in this range, but the analyses of cumulative exposure gave relative risks above 1.5. In addition, we did not find an increased mortality from smoking-related diseases other than lung cancer, such as chronic bronchitis and bladder cancer. Case–control studies conducted within the pulp and paper industry provided evidence against a confounding effect of smoking (Henneberger and Lax 1998). A further argument against substantial confounding by smoking is the presence of dose–response relationship within the group of workers exposed to SO_2.

We attempted to control for the possible effect of other occupational exposures, such as asbestos. However, similar to SO_2 exposures, these exposures were assessed at the level of department and therefore were likely to be subject to substantial misclassification, leading to possible residual confounding.

The assessment of exposure was carried out by industrial hygienists who were familiar with the pulp and paper industry, although not with all of the mills included in our study. It is likely, therefore, that some misclassification of exposure occurred. Furthermore, work histories were available only at the department level and for the period of employment in the mills under study. If the exposure among workers in a department is not homogeneous, then unexposed workers are classified as potentially exposed (and vice versa), resulting in a tendency to underestimate the risk, if there is one. We addressed the potential misclassification of exposure by repeating the dose–response analysis after restriction of the study population to workers with high exposure.

As in most cohort studies of industrial workers, a deficit in overall mortality was found in our study in the SMR comparisons with the national populations. This is a common occurrence in occupational investigations known as the "healthy worker effect," a combination of several factors associated with employment such as selection of the work force and changes in lifestyle accompanying employment (Monson 1986; Wen et al. 1983).

Death from nonneoplastic respiratory disease was not increased in SO_2-exposed workers. It is possible that the SO_2 exposure is not sufficiently high to cause nonmalignant respiratory diseases that are severe enough to lead to death. In addition, susceptible persons with respiratory disease may not seek employment at the mills or may quit employment because of possible symptoms or disease. Such selection procedures tend to underestimate the risk of nonneoplastic respiratory disease mortality in industrial cohorts. The possible decreased trend with increasing estimated exposure suggests a possible depletion of susceptible individuals from the groups with highest exposures.

Mortality from stomach cancer was nonsignificantly increased among workers with high cumulative SO_2 exposure in the high-exposure group: the lack of a corresponding increase in the SMR analysis suggests a noncausal interpretation (e.g., confounding by another carcinogenic exposure). Because stomach cancer mortality shows important geographical variations, we looked at country-specific SMRs: we could not find an indication of an association with SO_2 exposure in either high-risk countries (e.g., Japan, Spain) or low-risk countries (e.g., United States, Sweden). Mortality from non-Hodgkin lymphoma was elevated among workers classified in the high-SO_2-exposure group but not among other exposed workers. Although the excesses of mortality from non-Hodgkin lymphoma and stomach cancer seem less convincingly related to SO_2 exposure than that of lung cancer, they suggest that further studies are warranted. Stomach cancer risk was increased in previous studies of pulp and

Table 5. Relative risk of lung cancer by coexposure to SO_2 and selected agents.[a]

	Nonhigh SO_2 exposure			High SO_2 exposure		
Coexposure	No. deaths	RR	95% CI	No. deaths	RR	95% CI
Asbestos						
Never	115	1.00	Ref	35	1.54	0.99–2.40
Ever	297	1.09	0.85–1.39	17	1.34	0.80–2.25
Combustion products						
Never	4	1.00	Ref	17	1.34	0.45–4.00
Ever	333	0.55	0.20–1.49	38	0.67	0.24–1.89
Welding fumes						
Never	49	1.00	Ref	39	1.34	0.83–2.14
Ever	247	1.03	0.73–1.47	12	1.66	0.86–3.20

Ref, reference category (workers in the nonhigh SO_2 exposure category not exposed to each agent). RR was adjusted for sex, age, employment status, calendar year, and country.
[a]Individuals who were not exposed to SO_2 were excluded from the analysis.

paper production workers (Rix et al. 1997; Robinson et al. 1986; Wingren et al. 1991).

In summary, our findings are compatible with the hypothesis that exposure to SO_2 in the pulp and paper industry is associated with an increased risk of lung cancer, especially in high-exposure groups. Although confounding, particularly from smoking, may have been occurred, our results are compatible with the notion that SO_2 may have a cancer-promoting effect when it occurs in combination with other carcinogens in the pulp and paper industry.

References

Abbey DE, Nishino N, McDonnell WF, Burchette RJ, Knutsen SF, Lawrence Beeson W, et al. 1999. Long-term inhalable particles and other air pollutants related to mortality in nonsmokers. Am J Respir Crit Care Med 159:373–382.

Andersson E, Nilsson T, Persson B, Wingren G, Toren K. 1998. Mortality from asthma and cancer among sulfite mill workers. Scand J Work Environ Health 24:12–17.

Axelson O. Aspects on confounding in occupational health epidemiology. 1978. Scand J Work Environ Health 4:98–102.

Band PR, Le ND, Fang R, Astrakianakis G, Bert J, Keefe A, et al. 2001. Cohort cancer incidence among pulp and paper mill workers in British Columbia. Scand J Work Environ Health 27:113–119.

Beeson WL, Abbey DE, Knutsen SF. 1998. Long-term concentrations of ambient air pollutants and incident lung cancer in California adults: results from the AHSMOG study. Environ Health Perspect 106:813–823.

Bond GG, Flores GH, Shellenberger RJ, Cartmill JB, Fishbeck WA, Cook RR. 1986. Nested case-control study of lung cancer among chemical workers. Am J Epidemiol 124:53–66.

Breslow NE, Day NE. 1987. Statistical Methods in Cancer Research, Vol II: The Design and Analysis of Cohort Studies. IARC Sci Pub 82.

Coleman M, Douglas A, Hermon C, Peto J. 1986. Cohort study analysis with a FORTRAN computer program. Int J Epidemiol 15:134–137.

Fassa AG, Facchini LA, Dall'Agnol MM. 1998. The Brazilian cohort of pulp and paper workers: the logistic of a cancer mortality study. Cad Saude Publica 14(suppl 3):117–123.

Henneberger PK, Ferris BG Jr, Monson RR. 1989. Mortality among pulp and paper workers in Berlin, New Hampshire. Br J Ind Med 46:658–664.

Henneberger PK, Lax MB. 1998. Lung cancer mortality in a cohort of older pulp and paper workers. Int J Occup Environ Health 4:147–154.

Hoek G, Brunekreef B, Fischer P, van Wijnen J. 2001. The association between air pollution and heart failure, arrhythmia, embolism, thrombosis, and other cardiovascular causes of death in a time series study. Epidemiology 12:355–357.

IARC 1992. Sulfur dioxide and some sulfites, bisulfites and metabisulfites. IARC Monogr Eval Carcinog Risks Hum 54:131–188.

WHO. Manual of the International Statistical Classification of Diseases, Injuries, and Causes of Death. 9th Revision. Geneva:World Health Organization, 1975.

Jäppinen P, Pukkala E. 1991. Cancer incidence among pulp and paper workers exposed to organic chlorinated compounds formed during chlorine pulp bleaching. Scand J Work Environ Health 17:356–359.

Jäppinen P, Tola S. 1986. Smoking among Finnish pulp and paper workers—evaluation of its confounding effect on lung cancer and coronary heart disease rates. Scand J Work Environ Health 12:619–626.

Kauppinen T, Teschke K, Savela A, Kogevinas M, Boffetta P. 1997. International database of exposure measurements in the pulp, paper and paper product industries. Int Arch Occup Environ Health 70:119–127.

Langseth H, Andersen A. 1999. Cancer incidence among women in the Norwegian pulp and paper industry. Am J Ind Med 36:108–113.

Langseth H, Andersen A. 2000. Cancer incidence among male pulp and paper workers in Norway. Scand J Work Environ Health 26:99–105.

Lee AM, Fraumeni JF Jr. 1969. Arsenic and respiratory cancer in man: an occupational study. J Natl Cancer Inst 42:1045–1052.

Lee JT, Kim H, Hong YC, Kwon HJ, Schwartz J, Christiani DC. 2000. Air pollution and daily mortality in seven major cities of Korea, 1991–1997. Environ Res 84:247–254.

Leung KH, Post GB, Menzel DB. 1985. Glutathione S-sulfonate, a sulfur dioxide metabolite, as a competitive inhibitor of glutathione S-transferase, and its reduction by glutathione reductase. Toxicol Appl Pharmacol 77:388–394.

Meng ZQ, Zhang LZ. 1990. Chromosomal aberrations and sister-chromatid exchanges in lymphocytes of workers exposed to sulphur dioxide. Mutat Res 241:15–20.

Menzel DB, Keller DA, Leung KH. 1986. Covalent reactions in the toxicity of SO_2 and sulfite. Adv Exp Med Biol 197:477–492.

Monson RR. 1986. Observations on the healthy worker effect. J Occup Med 28:425–433.

Nisbet ICT, Schneiderman MA, Karch NJ, Siegal DM. 1984. Review and Evaluation of the Evidence for Cancer Associated with Air Pollution: Final Report. EPA-450/5-83-006R. Research Triangle Park, NC:Office of Air Quality Planning and Standards, U.S. Environmental Protection Agency.

Nordenson I, Beckman G, Beckman L, Rosenhall L, Stjernberg N. 1980. Is exposure to sulphur dioxide clastogenic? Hereditas 93:161–164.

Ohyama K, Ito T, Kanisawa M. 1999. The roles of diesel exhaust particle extracts and the promotive effects of NO_2 and/or SO_2 exposure on rat lung tumorigenesis. Cancer Lett 139:189–197.

Peacock PR, Spence JB. 1967. Incidence of lung tumours in LX mice exposed to (1) free radicals; (2) SO_2. Br J Cancer 21:606–618.

Pope CA III, Thun MJ, Namboodiri MM, Dockery DW, Evans JS, Speizer FE, et al. 1995. Particulate air pollution as a predictor of mortality in a prospective study of U.S. adults. Am J Respir Crit Care Med 151:669–674.

Rencher AC, Carter MW, Mekee DW. 1977. A retrospective epidemiological study of mortality at a large western copper smelter. J Occup Med 19:754–758.

Rix BA, Villadsen E, Lynge E. 1997. Cancer incidence of sulfite pulp workers in Denmark. Scand J Work Environ Health 23:458–461.

Rix BA, Villadsen E, Engholm G, Lynge E. 1998. Hodgkin's disease, pharyngeal cancer, and soft tissue sarcomas in Danish paper mill workers. J Occup Environ Med 40:55–62.

Robinson CF, Waxweiler RJ, Fowler DP. 1986. Mortality among production workers in pulp and paper mills. Scand J Work Environ Health 12:552–560.

Sala-Serra M, Sunyer J, Kogevinas M, McFarlane D, Anto JM. 1996. Cohort study on cancer mortality among workers in the pulp and paper industry in Catalonia, Spain. Am J Ind Med 30:87–92.

Shinkura R, Fujiyama C, Akiba S. 1999. Relationship between ambient sulfur dioxide levels and neonatal mortality near the Mt. Sakurajima volcano in Japan. J Epidemiol 9:344–349.

Szadkowska-Stanczyk I, Boffetta P, Wilczynska U, Szeszenia-Dabrowska N, Szymczak W. 1997. Cancer mortality among pulp and paper workers in Poland. A cohort study. Int J Occup Med Environ Health 10:19–29.

Szadkowska-Stanczyk I, Szymczak W. Nested case-control study of lung cancer among pulp and paper workers in relation to exposure to dusts. Am J Ind Med 39:547–556 (2001).

Toren K, Sallsten G, Jarvholm B. 1991. Mortality from asthma, chronic obstructive pulmonary disease, respiratory system cancer, and stomach cancer among paper mill workers: a case-referent study. Am J Ind Med 19:729–737.

Toren K, Persson B, Wingren G. 1996. Health effects of working in pulp and paper mills: malignant diseases. Am J Ind Med 29:123–130.

Wen CP, Tsai SP, Gibson RL. 1983. Anatomy of the healthy worker effect: a critical review. J Occup Med 25:283–289.

World Health Organization. WHO Mortality Database. Available: http://www3.who.int/whosis/whsa/ftp/download.htm [accessed 3 July 2002].

Wild P, Bergeret A, Moulin JJ, Lahmar A, Hours M. 1998. Mortality in the French paper and pulp industry [in French]. Rev Epidemiol Sante Publique 46:85–92.

Wingren G, Persson B, Thoren K, Axelson O. 1991. Mortality pattern among pulp and paper mill workers in Sweden: a case-referent study. Am J Ind Med 20:769–774.

Xu X, Gao J, Dockery DW, Chen Y. 1994. Air pollution and daily mortality in residential areas of Beijing, China. Arch Environ Health 49:216–222.