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

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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. Levels often exceed 2 ppm (Kauppinen et al. 1997). SO2 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

SO2-exposed workers showed an increased mortality from lung cancer, but in those studies exposure to SO2 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 sulfate 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 SO2-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 SO2, as well as workers with unknown SO2 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 SO2 exposure status and country is shown in Table 1. Norway provided the largest number of SO2-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 from 5.0 years (New Zealand) to 55.0 years (Sweden).
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 SO₂ 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. SO₂-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 SO₂.

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 SO₂ exposure; the high-exposure group included 2,495 workers, providing 56,902.6 person-years of observation. We constructed several SO₂ 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 SO₂ (< 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 SO₂ exposure and country.

| Country    | Never exposed | Ever exposed | High exposure |
|------------|---------------|--------------|--------------|
|            | 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 | 209880.0 | 185 | 6167.3 |
| France     | 1,361 | 23177.7 | 2,841 | 52441.8 | 19 | 371.9 |
| Japan      | 1,050 | 19294.2 | 1,229 | 22372.7 | 31 | 576.6 |
| New Zealand | 380  | 4138.2 | 5,152 | 53516.5 | 151 | 1754.2 |
| Norway     | 2,384 | 52957.2 | 12,123 | 321390.7 | 1,078 | 280532.2 |
| Poland     | 795  | 13026.5 | 5,317 | 79629.2 | 369 | 62122.2 |
| South Africa | 222  | 4224.5 | 655 | 11704.5 | 4  | 80.3 |
| Spain      | 80   | 1398.5 | 305 | 5177.3 | 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      | 16,309 | 370341.4 | 40,704 | 878699.2 | 2,495 | 56902.6 |

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

### Table 2. Standardized mortality ratios of selected causes by SO₂ exposure.

| Cause of death (ICD-9 classification) | Never exposed | Ever exposed | High exposure |
|---------------------------------------|---------------|--------------|--------------|
|            | SMR | 95% CI | SMR | 95% CI | SMR | 95% CI |
| All causes | 3,224 | 0.91 | 0.88–0.94 | 7,508 | 0.89 | 0.87–0.91 |
| Malignant neoplasms (140–208) | 809 | 0.91 | 0.85–0.97 | 1,756 | 0.91 | 0.87–0.96 |
| Oral cavity, pharynx (140–149) | 15 | 0.77 | 0.69–0.91 | 35 | 0.76 | 0.73–0.80 |
| Esophagus (150) | 18 | 0.83 | 0.89–1.23 | 27 | 0.70 | 0.67–0.73 |
| Stomach (151) | 80 | 0.76 | 0.71–0.82 | 172 | 0.81 | 0.78–0.84 |
| Nose (180) | 3 | 1.09 | 0.23–3.20 | 6 | 0.86 | 0.45–1.65 |
| Larynx (160) | 13 | 1.16 | 0.62–1.98 | 194 | 0.96 | 0.61–1.42 |
| Lung (162) | 194 | 0.92 | 0.79–1.06 | 482 | 1.08 | 0.86–1.18 |
| Bladder (188) | 34 | 1.03 | 0.71–1.43 | 54 | 0.90 | 0.68–1.18 |
| Kidney (189) | 16 | 0.62 | 0.35–1.00 | 58 | 1.04 | 0.79–1.34 |
| Non-Hodgkin lymphoma (200, 202) | 16 | 0.79 | 0.45–1.29 | 45 | 0.94 | 0.68–1.25 |
| Hodgkin disease (201) | 9 | 1.38 | 0.63–2.62 | 13 | 0.94 | 0.54–1.63 |
| Multiple myeloma (203) | 15 | 1.14 | 0.64–1.88 | 29 | 0.97 | 0.58–1.24 |
| Leukemia (204–208) | 18 | 0.60 | 0.35–0.94 | 58 | 0.89 | 0.68–1.15 |
| Disease of circulatory system (390–459) | 1,438 | 0.92 | 0.87–0.96 | 3,660 | 0.94 | 0.91–0.97 |
| Bronchitis, emphysema, asthma (490–493) | 101 | 0.90 | 0.75–1.08 | 142 | 0.90 | 0.67–0.94 |
| Liver cirrhosis (571) | 59 | 1.10 | 0.84–1.43 | 77 | 0.79 | 0.63–0.99 |

Obs, observed. Cohorts from Brazil and South Africa were excluded from the SMR analysis.

High exposure is a subset of ever exposed.
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 SO2. 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 SO2 and other occupational agents on lung cancer mortality are presented in Table 5. There was a suggestion of an interaction between SO2 and welding fumes but not between SO2 and either asbestos or combustion products.

**Discussion**

The main result of this cohort study was an association between SO2 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

| Cause of death                  | RR1 | 95% CI    | RR2 | 95% CI    |
|---------------------------------|-----|-----------|-----|-----------|
| All causes                      | 0.98| 0.93–1.03 | 1.00| 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 SO2.

| WCE (ppm-year) | All neoplasms | Stomach cancer | Lung cancer | Non-Hodgkin lymphoma | Bronchitis, emphysema, asthma |
|----------------|---------------|----------------|-------------|----------------------|-----------------------------|
|                | RR  | 95% CI   | RR  | 95% CI   | RR  | 95% CI   | RR  | 95% CI   | RR  | 95% CI   |
| Ever exposed   |     |          |     |          |     |          |     |          |     |          |
| 0.1–1.99       | 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          | 0.010 | 0.3    | 0.009 | 0.03    | 0.05 |
| High exposure  |     |          |     |          |     |          |     |          |     |          |
| 0.1–13.9       | 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   | 1.4 | 0.4–29   | 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.

*Reference category, which included workers who were never exposed to SO2.
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 SO2 exposure compared with workers in the lowest exposure category. The lack of an association between lung cancer mortality and duration of SO2 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 SO2 exposure in the pulp and paper industry may contribute to lung carcinogenesis.

The evidence of a genotoxic effect of SO2 in experimental systems is limited (IARC 1992). Groups of workers exposed to SO2 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 SO2 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 SO2 carcinogenicity is unclear, Leung et al. (1985) and Menzel et al. (1986) suggested that SO2 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 SO2 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 SO2. In a study of chemical workers exposed to SO2, Bond et al. (1986) reported a significant association between lung cancer mortality and SO2 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 SO2 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 SO2-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 SO2.

We attempted to control for the possible effect of other occupational exposures, such as asbestos. However, similar to SO2 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 SO2-exposed workers. It is possible that the SO2 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 SO2 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 SO2 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-SO2-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 SO2 exposure than that of lung cancer, they suggest that further studies are warranted. Stomach cancer risk was increased in previous studies of pulp and

| Coexposure | Nonhigh SO2 exposure | High SO2 exposure |
|------------|----------------------|-------------------|
|            | 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 SO2 exposure category not exposed to each agent). RR was adjusted for sex, age, employment status, calendar year, and country.

*Individuals who were not exposed to SO2 were excluded from the analysis.
In summary, our findings are compatible with the hypothesis that exposure to SO2 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 SO2 may have a cancer-promoting effect when it occurs in combination with other carcinogens in the pulp and paper industry.

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