The Incidence of Respiratory Symptoms and Diseases Among Pulp Mill Workers With Peak Exposures to Ozone and Other Irritant Gases*

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Objectives: **Pulp mills in Sweden started to use ozone as a bleaching agent in the early 1990s. The goal of this study was to investigate whether the incidence of selected respiratory outcomes was associated with peak exposures to ozone or other irritant gases (*ie*, chlorine dioxide [ClO_2] or sulfur dioxide [SO_2]) used in these mills.**

Methods: **Bleachery workers (n = 245) from three pulp mills where ozone was used participated in surveys in the mid- to late-1990s. Comparison workers (n = 80) were from two adjacent paper mills. The person-time at risk was calculated for each participant, covering the period of employment when ozone was used. Data were collected by questionnaire, and a peak exposure was defined as a self-reported exposure to an irritant gas resulting in acute respiratory symptoms. The outcomes analyzed were self-reports of physician-diagnosed asthma, attacks of wheeze, and chronic bronchitis (*ie*, chronic cough with phlegm). Participants also reported when the peak exposures and outcomes occurred.**

Results: **Based on proportional hazards regression (controlling for gender, age, cigarette smoking, atopy, and peak irritant exposures that occurred before follow-up), workers who reported both ozone and ClO_2/SO_2 peak exposures had elevated hazard ratios (HRs) for all three outcomes. Those who reported only ozone peak exposures had elevated HRs of 6.5 (95% confidence interval [CI], 1.2 to 36.3) for asthma and 3.3 (95% CI, 1.1 to 10.2) for attacks of wheeze but no increase in risk for chronic bronchitis. Workers with only ClO_2/SO_2 peak exposures had elevated HRs for attacks of wheeze (HR, 7.5; 95% CI, 1.9 to 29.3) and chronic bronchitis (HR, 22.9; 95% CI, 4.5 to 118.2) but not for asthma.**

Conclusions: **These findings suggest the need for additional efforts to prevent peak exposures in pulp-bleaching operations.** ***(CHEST 2005; 128:3028–3037)***

Key words: asthma; irritant gases; occupation; ozone

Abbreviations: CI = confidence interval; Cl_2 = chlorine; ClO_2 = chlorine dioxide; HR = hazard ratio; ppb = parts per billion; RADS = reactive airways dysfunction syndrome; SO_2 = sulfur dioxide

Respiratory symptoms and diseases associated with chlorine bleaching agents used in pulping operations were first reported in the medical literature in the mid-1800s.[1] The adverse effects of chlorine (Cl_2), chlorine dioxide (ClO_2), sulfur dioxide (SO_2), and other irritant gases on pulp and paper workers continue to be documented in the medical literature.[2–6] Only a few investigators have calculated the incidence, rather than prevalence, of asthma among pulp mill workers who have experienced peak exposures to these irritant gases. For example, in a large study[3] of workers from 62 pulp and paper plants in the United States, workers with peak exposures had an elevated rate of asthma compared to workers not exposed to irritant gases, but the difference was not statistically significant. In contrast, investigators in Sweden observed a statistically significant elevation in the asthma incidence rate for bleachery workers with peak exposures, compared to paper mill workers.[2]

In the early 1990s, several Swedish pulp mills replaced Cl_2 compounds with ozone to bleach pulp.[1]

Ozone is a respiratory irritant that can lead to increased airway responsiveness and inflammation.[7] Controlled exposure chamber studies[8] of humans indicate that acute respiratory symptoms are associated with ozone exposure, and ambient levels of ozone contribute to the exacerbation of existing asthma.[9–12] In addition, longitudinal studies[13–15] of adults suggest that the development of asthma is associated with long-term exposure to ambient ozone. In a study by McDonnell et al,[15] the relative risk for asthma among men was 2.1 for each increase of 27 parts per billion (ppb) in ambient ozone concentration, which ranged from 0 to 74.9 ppb (mean, 46.5 ppb).

In order to bleach pulp, levels of ozone are as high as 90,000,000 ppb within the enclosed process. Bleachery employees who work around ozone are subject to low-level background exposures and occasional high-level peak exposures due to process or equipment failures.[16] Levels were measured in two pulping operations in Sweden with stationary monitors in the ozonator and mixing rooms, where accidental exposure of workers to leaks were most likely. Over 366 days of monitoring, levels were $>$ 900 ppb ozone on 6 days. In one of the mixing rooms, ozone levels $>$ 300 ppb were recorded on approximately one third of the days.[16] With such high-level exposures, it seems that exposed workers would have an increased risk for asthma. However, this has not always been observed. A medical survey was conducted in 1995 and 1996 at the two Swedish pulp mills where ozone was measured, and the prevalence of adult-onset asthma was not increased for bleachery workers with or without a history of ozone peak exposures.[16] There was an additional survey at these two mills and another mill in 1998 and 1999, at which time the prevalence of adult-onset asthma was increased for those bleachery workers who reported at least four ozone peak exposures that had resulted in acute symptoms.[17] A consistent finding from the surveys was an increase in adult-onset wheeze associated with bleachery work and ozone peak exposures.[16–18]

Several aspects of these studies suggested the need for additional data analyses to examine the relationships between respiratory symptoms and diseases and ozone exposures in pulp-bleaching operations. First, with the exception of an analysis of wheeze based on the 1995-to-1996 data,[16] prevalence was used to measure frequency. Incidence provides a more accurate estimate of risk and could be calculated with data available from these surveys. Second, when prevalence was calculated, cases were counted if they occurred at any time after age 15 years. It was possible to limit analyses to those cases with onset while ozone was being used, thus providing a more accurate estimate of the effect of this exposure. Third, chronic bronchitis, defined as chronic cough with phlegm, had not yet been investigated using these data.

To address these limitations, we conducted additional analyses of data from the two surveys of pulp mill workers in Sweden. The focus of our analysis was whether the incidence of asthma, attacks of wheeze, and chronic bronchitis among pulp mill workers was associated with peak exposures due to ozone, to other irritant gases (ClO_2 or SO_2), or to both.

Methods and Materials

Subjects and Person-Years of Follow-up

The participants in the current investigation were selected from two surveys that were conducted in Swedish pulp and paper mills. The Local Ethical Committee at Göteborg University reviewed and approved the protocols for these studies. In each survey, eligible people received a mailed questionnaire that inquired first about work experience and exposures, then about respiratory symptoms and diseases, and finally about smoking history. These questions were based on items from the 1978 American Thoracic Society respiratory questionnaire[19] and the European Community for Coal and Steel questionnaire on respiratory symptoms.[20]

For the 1995-to-1996 survey, the researchers invited all the process, maintenance, and laboratory workers from the bleaching departments ("bleacheries") in two Swedish sulfate pulp mills and the process workers from two adjacent paper mills.[16] These pulp mill/paper mill combinations are identified in this article as mills B and C. A survey was also conducted at another pulp mill (mill A) in 1995, but that was before ozone was introduced, so no data were used from that survey.[2] The researchers used the same methods at all three mills in from 1998 to 1999.[2,17] Participation was 90% of eligible workers at mills B and C from 1995 to 1996 and 87% at mills A, B, and C from 1998 to 1999. Thirty-seven workers participated only in 1995 to 1996, 172 participated in both surveys, and 119 participated only in 1998 to 1999, yielding a total of 328 workers who participated in at least one of the surveys. For participants from mills B and C, we preferentially used data from the later survey to maximize the number of

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person-years of follow-up (see below). Three workers who participated only from 1998 to 1999 were deleted: one worker was missing data for all outcomes, and the other two workers had data missing for smoking. Another person from the last survey had data missing on smoking, but we were able to substitute his data from the 1995-to-1996 survey. The paper mill workers should not have been at risk for peak exposures to irritant gases. However, one of the paper mill workers who participated in both surveys reported gassing events between the two surveys, so we used his earlier data to maintain the paper mill workers as a reference group that was unexposed during follow-up. We retained paper mill workers who reported peak exposures that had occurred prior to the period of follow-up. At final count, the total number of participants for the current analysis was 325, with data from the 1995-to-1996 survey for 39 workers and from the 1998-to-1999 survey for 286 workers. Figure 1 summarizes the distribution of workers by participation in the two surveys, with numbers presented separately for the 245 bleachery workers and 80 paper mill workers. For each of the three outcomes, additional people were excluded either because they had experienced onset of the illness or symptom prior to the start of follow-up or because information about the outcome was missing.

Since times of onset for respiratory outcomes and peak exposures were reported in years, follow-up was also calculated in years. The start of follow-up (when the accumulation of person-years of risk started) was the year in which the facility first used ozone or the individual's first full year of employment, whichever was later. The conclusion of follow-up (when the accumulation of person-years of risk stopped) was either at the time of the survey or the onset of the outcome, whichever was earlier.

Exposures in the Mills

The two paper mills where reference participants were selected produced printing paper. Measurements of exposures in similar paper mills have identified relatively low dust levels of approximately 0.5 mg/m^3.[21] In each of the three pulp mills, Cl_2 and/or ClO_2 was used as a bleaching agent starting in the 1950s. The switch to ozone as a bleaching agent occurred in 1995 at mill A, 1993 at mill B, and 1992 at mill C. However, bleachery workers were potentially exposed to other irritant gases after the introduction of ozone. For example, SO_2 has continued to be used in one of the pulping operations at mill A. Also, hypochlorite was produced at mill A and used to clean production water. As a result, workers were potentially exposed to chlorine gas until hypochlorite production was stopped in 1998. At mill B, ClO_2 is still used in one of the bleachery lines, and SO_2 is used in the production of the ClO_2. Both of these compounds were used at mill C until 1995.

Exposure Variables

Peak irritant exposures were counted if they were reported to have occurred during the period of follow-up and before or in the same year as the outcome of interest. The questionnaires in both the 1995-to-1996 and 1998-to-1999 surveys included the following questions: "Have you ever been exposed to ozone resulting in coughing, wheezing, breathlessness, or pain in thorax as a result? If yes, when did this occur?" Study participants were considered to have experienced a peak ozone exposure if they answered "yes" to the question about ozone exposure with respiratory symptoms.

We also used information from the questionnaire to construct variables for peak exposures due to other irritant gases. From the 1995-to-1996 survey questionnaire, the relevant questions about peak exposures to ClO_2 were: "Have you been exposed to chlorine dioxide resulting in coughing, breathlessness, or wheezing? If yes, when did this occur." A similar pair of questions was used to identify participants with a history of peak exposures to SO_2. The 1998-to-1999 survey questionnaire used the same questions, except they were framed to ascertain responses only about the preceding 3 years. These reports were summarized into a single indicator variable that was positive if the person had experienced a peak exposure of either ClO_2 or SO_2 during follow-up.

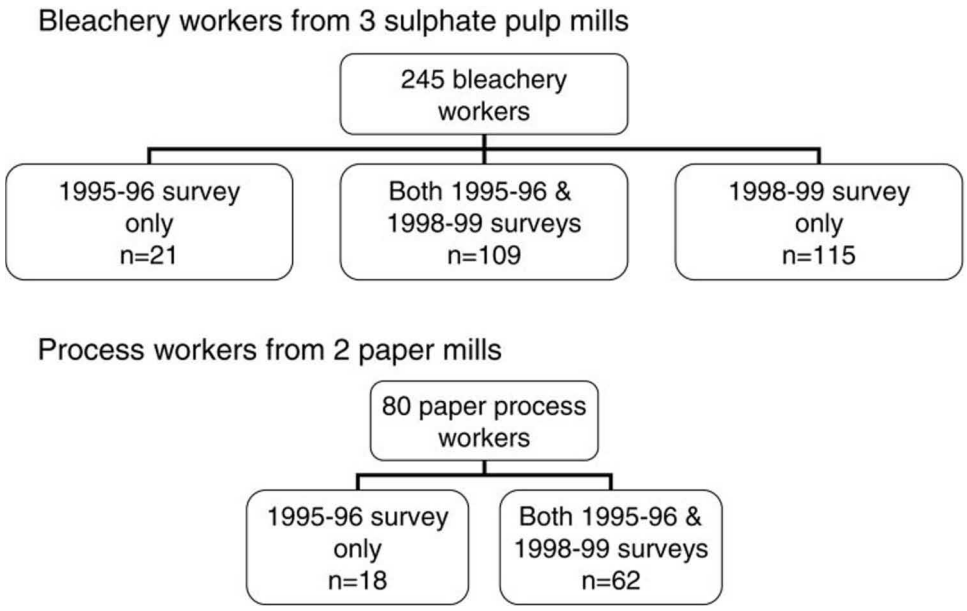

FIGURE 1. Origin of the data for the 325 workers who participated in one or both of two medical surveys. For workers who participated in both surveys, data were used from the latter survey (1998 to 1999).

Outcome Variables

The three respiratory outcomes were all self-reported on the survey questionnaires and included physician-diagnosed asthma, attacks of wheeze, and chronic bronchitis. The latter was defined as a report of chronic cough with phlegm that lasted at least 3 months a year and for at least 2 years in a row. The specific questions are presented in the Appendix. Chronic bronchitis corresponds to stage 0 of COPD as defined by the Global Initiative for Chronic Obstructive Lung Disease.[22] The year of onset was reported for each outcome, and we used it in several ways. First, we excluded participants from data analysis if the year of onset preceded the year in which they started follow-up. Second, for cases that occurred the same year as the start of follow-up or later, we stopped accumulation of person-years at onset. Third, for subjects who reported irritant peak exposures, we established if these exposure events occurred before or during the year of onset.

We originally planned to use the paper mill workers as the comparison group. However, these 80 workers had no cases of asthma, only one case of chronic bronchitis, and two cases of wheeze. In order to have a larger comparison group, we combined the paper mill workers and pulp mill workers without peak exposures.

Potential Effect Modifiers and Confounders

We investigated whether certain variables modified or confounded the relationships between peak exposures and the outcomes of interest. These variables included gender, age, cigarette-smoking status, atopy, and peak exposures to irritant gases (Cl_2, ClO_2, and SO_2) that occurred prior to the start of follow-up. Atopy was defined as a positive inhalant allergy test result (Phadiatop; Pharmacia & Upjohn Diagnostics; Uppsala, Sweden).

Statistical Analysis

We calculated crude incidence rates for all participants and by peak exposure status by dividing the number of cases by the person-years of risk. Statistical analyses were performed using statistical software (SAS for Windows; SAS Institute; Cary, NC). Tests for statistical significance were accomplished using Fisher exact test or continuity-corrected χ^2 test for categorical variables, and Student t test for continuous variables.[23] We investigated the potential for effect modification by testing the homogeneity of odds ratios while stratified by covariates for gender, age, former smoking, current smoking, atopy, and peak exposures before the start of follow-up. There were two instances in which the test of homogeneity had a $p < 0.10$, but each involved small numbers with zero cells in two-by-two tables, and the data did not suggest substantial effect modification that should be accommodated in the analyses.

We used the PHREG procedure (SAS Institute) to implement Cox regression analysis. Non-time–dependent potential confounders included in each model were gender (female vs male), age in years (at birthday in the first year of follow-up), atopy (yes vs no), and peak exposures before the start of follow-up (yes vs no). There were two time-dependent cigarette-smoking variables, one each for former and current smokers, with never-smokers as the common comparison group.

Results

Characteristics of the 325 Survey Participants

Only a small percentage of all 325 survey participants were women (n = 24, 7%). Age during the first year of follow-up ranged from 20 to 60 years (mean ± SEM, 39.6 ± 0.51 years; median, 40 years). One fourth (n = 81) of the participants had evidence of atopy, and approximately one half (n = 154, 47%) had ever smoked, including 18% (n = 60) who smoked at some time during the period of follow-up. There were 126 participants (39% of 325 subjects) who reported a peak exposure to an irritant gas that had occurred prior to the period of follow-up. These pre–follow-up exposures were reported by 11 of the 80 paper mill workers (14%) and 115 of the 245 pulp mill workers (47%).

A total of 110 participants (45% of the 245 pulp mill workers) reported some peak irritant exposure had occurred during the period of follow-up. Seventy-five of the pulp mill workers (31%) reported an ozone peak exposure, 63 workers (26%) reported a peak exposure due to ClO_2/SO_2, and 28 workers (11%) who reported both types of peak exposures. The two types of irritant peak exposures were not strongly correlated, with a Spearman correlation coefficient of $r = 0.25$. The 215 participants who reported no peak exposures included 135 of the pulp mill workers (55%) and all 80 paper mill workers.

There was little difference in gender, age, atopy, and smoking status between workers with and without peak exposures during follow-up. The most notable difference was that the pulp mill workers with peak exposures due only to ClO_2 or SO_2 were somewhat younger (mean, 37.2 ± 1.14 years) during the first year of follow-up than the pulp and paper workers who experienced no peak exposures (mean, 40.2 ± 0.62 years) [$p < 0.05$]. Also, the 110 pulp mill workers with peak exposures during follow-up were more likely than the 215 other survey participants to have experienced peak exposures before follow-up started (65% vs 25%, $p < 0.0001$).

Person-Years of Follow-up by Outcome

The number of participants and person-years included in the data analysis for the three outcomes are presented in Table 1. Wheeze had the greatest number of deletions due to onset before the period of follow-up (n = 56), and chronic bronchitis had the fewest (n = 7). All three outcomes had an average of approximately 5.5 person-years of follow-up per participant.

Crude Incidence Rates of Respiratory Symptoms and Diseases by Peak Exposures

The total crude incidence rates for the three outcomes, in descending order, were 14.5×10^{-3} person-years for wheeze, 7.5×10^{-3} person-years for chronic bronchitis, and 4.7×10^{-3} person-years for asthma (Table 2). Among the three categories of

Table 1—*Participants and Person-Years of Follow-up by Outcome

Variables	Asthma	Wheeze	Chronic Bronchitis
Total survey participants	325	325	325
Exclusions			
Onset prior to follow-up	19	56	7
Missing outcome	3	4	7
Participants included in analysis	303	265	311
Person-years of follow-up			
Total	1,699	1,446	1,723
Mean	5.6	5.5	5.5

*Data are presented as No.

those with peak exposures during follow-up (*ie*, only ozone, only ClO_2/SO_2, both), the only ozone category consistently had the greatest number of person-years (Table 2). In general, the rates were greater for participants who reported ozone and/or ClO_2/SO_2 peak exposures than for participants who reported no peak exposures. The one exception was for those who reported only ClO_2/SO_2 peak exposures, who had no cases of asthma, vs three cases (2.4×10^{-3} person-years) in the no-peak exposure group (Table 2).

Proportional Hazards Regression Models

Hazard ratios (HRs) from the proportional hazards regression models are presented in Table 3. We fit three different models for each outcome, with variables to control for gender, age, former smoking, current smoking, atopy, and peak irritant exposures before follow-up. The exposure variable in model 1 was for any peak irritant exposure during follow-up, which was associated with a statistically significant increase in risk ($p \leq 0.05$) for each of the three outcomes. In model 2, we included separate variables for ozone and ClO_2/SO_2 peak exposures in order to assess the effect of each while controlling for the other. Statistically significant ($p \leq 0.05$) elevations in HRs were observed for ozone peak exposures with asthma and for ClO_2/SO_2 peak exposures with wheeze and chronic bronchitis. Model 3 in Table 3 included three peak exposure variables (only ozone, both ozone and ClO_2/SO_2, only ClO_2/SO_2) that allowed us to determine whether each type of peak exposure was a risk factor in the absence of the other. The only-ozone peaks variable was associated with asthma and wheeze, while the only-ClO_2/SO_2 peaks variable was associated with wheeze and chronic bronchitis. Workers who reported both ozone and ClO_2/SO_2 peak exposures had statistically significant increased HRs for all three outcomes.

Among the potential confounders, age was more positively associated with asthma and chronic bronchitis ($p \leq 0.05$) than with wheeze ($p > 0.10$ to ≤ 0.20). The HRs for atopy were positive in all the regression models with $p < 0.10$, except in model 1 for chronic bronchitis ($p = 0.26$). Chronic bronchitis was more common among women ($p \leq 0.01$). Peak exposures prior to follow-up were positively associated with wheeze but not at the level of statistical significance ($p > 0.05$ to ≤ 0.20).

There was overlap among the participants who reported an onset of respiratory outcomes during follow-up. In particular, there were three workers who reported all three outcomes during follow-up, one who reported both asthma and wheeze, and five who reported both wheeze and chronic bronchitis. That is, almost one fifth of the workers with wheeze

Table 2—*Crude Incidence Rates for Selected Respiratory Symptoms and Diseases for All Participants and by Peak Exposure Status

	Peak Exposures			No Peak Exposures			
Variables	Only Ozone	Both Ozone and ClO_2/SO_2	Only ClO_2/SO_2	Pulp Mill	Paper Mill	Subtotal	Total
Asthma							
Cases	3	2	0	3	0	3	8
Person-years of follow-up	216	102	116	826	439	1,265	1,699
Rate per 1,000 person-years	13.9	19.2	0	3.6	0	2.4	4.7
Wheeze							
Cases	6	4	4	5	2	7	21
Person-years of follow-up	172	75	94	700	405	1,105	1,446
Rate per 1,000 person-years	34.9	53.3	42.6	7.1	4.9	6.3	14.5
Chronic bronchitis							
Cases	1	2	5	4	1	5	13
Person-years of follow-up	208	94	121	850	450	1,300	1,723
Rate per 1,000 person-years	4.8	21.3	41.3	4.7	2.2	3.8	7.5

*Data are presented as No.

Table 3—*Relative Risk of Ozone Peak Exposures and Other Peak Exposures for Selected Respiratory Symptoms and Diseases

Proportional Hazards Regression Models†	Asthma	Wheeze	Chronic Bronchitis
Model 1			
Any ozone or ClO_2/SO_2 peak	4.9 (1.05–23.1)	4.8 (1.8–12.4)	4.7 (1.3–16.6)
Model 2			
Ozone peak exposures	7.8 (1.5–40.2)	2.3 (0.9–5.6)	0.5 (0.1–1.9)
ClO_2/SO_2 peak exposures	1.2 (0.2–7.5)	4.7 (1.6–14.2)	17.5 (3.9–78.4)
Model 3			
Only ozone peak exposures	6.5 (1.2–36.3)	3.3 (1.05–10.2)	1.1 (0.1–10.1)
Both ozone and ClO_2/SO_2 peak exposures	10.4 (1.2–90.5)	9.5 (2.3–38.3)	7.7 (1.1–52.8)
Only ClO_2/SO_2 peak exposures	0	7.5 (1.9–29.3)	22.9 (4.5–118.2)

*Data are presented as HR (95% CI).

†Each model included variables (not shown) to control for gender, age in first year of follow-up, former smoker, current smoker, atopy, and peak irritant exposure before start of follow-up.

(4 of 21 subjects) and almost one fourth of the workers with chronic bronchitis (3 of 13 subjects) also reported new asthma. We reanalyzed both wheeze and chronic bronchitis after deleting everyone who reported onset of asthma either before or during follow-up. This impacted the estimates of relative risk for peak exposures based on the regression models (not shown). For wheeze, the only loss of statistical significance was in model 3 with the variable "only-ozone peak exposures." With chronic bronchitis, statistical significance was lost for "any ozone or ClO_2/SO_2 peak exposures" in model 1 and for "both ozone and ClO_2/SO_2 peak exposures" in model 3. In summary, with recent and past asthma cases deleted, both wheeze and chronic bronchitis were associated with ClO_2/SO_2 peak exposures but not ozone peak exposures at the $p \leq 0.05$ level of statistical significance.

Workers With Incident Asthma

Characteristics of the eight cases of asthma are summarized in Table 4. Five subjects had never smoked cigarettes, and only one subject smoked during follow-up. They tended to be older, with a mean age during the first year of follow-up of 44.5 years, vs 38.3 years for the other 295 participants ($p = 0.12$, *t* test). Also, 50% of the patients with asthma were atopic, which was greater than the 21% for other participants ($p = 0.08$).

Discussion

Why Do the Findings Differ for Peak Exposures due to Ozone vs ClO_2/SO_2?

Ozone peak exposures were a risk factor for asthma but not chronic bronchitis, and ClO_2/SO_2 peak exposures were a risk factor for chronic bronchitis but not asthma. If exposure levels are high enough, a variety of gases can penetrate deeply in the lungs. Nevertheless, the difference in water solubility for ozone vs ClO_2 and SO_2 might help to explain the differences in relative risk for asthma and chronic bronchitis. Specifically, ozone is less water soluble than ClO_2 and SO_2 and more likely to impact

Table 4—*Characteristics of the Eight Workers With Onset of Asthma During Follow-up*

Patient No.	Gender	Age, yr	Atopy	Smoked Cigarettes: Ever	Smoked Cigarettes: During Follow-up Period	Year of Asthma Onset	Year of Earliest Peak Exposure During Follow-up: Ozone	Year of Earliest Peak Exposure During Follow-up: ClO_2/SO_2
1	Male	50	Yes	Yes	No	1993	1992	
2	Male	43	No	Yes	No	1995	1993	
3	Male	46	Yes	No	No	1998	1996	
4	Male	58	No	No	No	1998	1995	1997
5	Male	34	No	No	No	1999	1999	1997
6	Female	41	Yes	No	No	1994		
7	Male	34	No	No	No	1995		
8	Male	50	Yes	Yes	Yes	1995		

* FU=follow-up period

Table 5—*Selected Findings From Related Studies of Pulp Mill Workers Exposed to Ozone and Other Irritant Gases at Three Mills in Sweden*

Variables	Olin et al[18]	Olin et al[16]	Andersson et al[2]	Olin et al[17]	Current Study		
Mills	C	B, C	A	A, B, C	A, B, C		
Survey years	1996	1995, 1996	1995	1998, 1999	1995, 1996, 1998, 1999		
Participants							
Pulp mill workers at risk, No.							
Irritant exposures	56	129	89	228	227 (asthma)	194 (wheeze)	233 (chronic bronchitis)
Paper mill workers	39	80	210	63	76 (asthma)	71 (wheeze)	78 (chronic bronchitis)
Total	95	209	299	291	303 (asthma)	265 (wheeze)	311 (chronic bronchitis)‡
Self-reported peak exposures	O_3 ,ClO_2	O_3, ClO_2, SO_2	Cl_2, ClO_2, SO_2	O_3, ClO_2	O_3, ClO_2, SO_2		
Self-reported outcomes*							
Asthma	Not available	No change in prevalence with any exposure	Incidence increased if bleachery or any peaks, but not if only Cl_2/ClO_2 peaks	Prevalence increased if ≥ 4 O_3 peaks	Incidence increased if any peaks or O_3 peaks		
Wheeze	Prevalence increased if bleachery; not worse in bleachery if O_3 or ClO_2 peaks	Prevalence increased if bleachery, any peaks, or O_3 peaks; incidence increased 1992–1995 if bleachery	Incidence increased if any peaks or if only Cl_2/ClO_2 peaks	Prevalence increased if bleachery or ≥ 4 O_3 peaks	Incidence increased if any peaks, O_3 peaks, or ClO_2/SO_2 peaks		
Cough with phlegm	Not available	No change in revalence with any exposure	Not available	Not available	Not available		
Chronic bronchitis (chronic cough with phlegm)	Not available	Not available	Not available	Not available	Incidence increased if any peaks or ClO_2/SO_2 peaks		

*The prevalent cases of asthma, wheeze, and cough with phlegm in the three studies by Olin and colleagues[16–18] included survey participants who reported onset of these outcomes at any time after age 15 years. Incidence of wheeze was measured during years of ozone use based on data from the 1995-to-1996 survey in Olin et al.[16] All measurements of frequency in the current study were incidence during years of ozone use.

smaller airways, while the other two gases are more likely to impact larger airways.[24]

Comparisons to Findings From Prior Studies of Subsets of the Current Cohort

The bleachery workers in this study were potentially exposed to several irritant gases, including ozone, ClO_2, and SO_2. It was important to determine the effect of ozone because it was the most recently introduced irritant gas in the mills. The findings from prior studies of subsets of the current cohort, along with findings from the current study, are presented in Table 5. The current finding that attacks of wheeze are associated with ozone and ClO_2/SO_2 peak exposures is consistent with the results of nearly all of the prior studies. That is, attacks of wheeze appear to be a common result of high irritant gas exposures, regardless of the agent. The findings for asthma are more mixed across the different studies. The current finding of an increased incidence of asthma associated with ozone gassings is similar to the finding based on the prevalence of adult-onset asthma using only the from 1998-to-1999 data.[17] While the use of prevalence led to the same general conclusion, our calculation of incidence and focus on the period when ozone was used provide more accurate estimates of risk and relative risk.

Unlike the findings for ozone, ClO_2/SO_2 peak exposures alone were not associated with asthma in the current study. This contrasts with findings from the earlier study of workers from mill A, in which the incidence of asthma was associated with peak exposures to any irritant gas, based on cases with onset prior to the current period of follow-up.[2]

A prior analysis based on the from 1995-to-1996 data from mills B and C examined the prevalence of cough with phlegm and identified no association with bleachery work or any peak irritant exposures.[16] We defined chronic bronchitis as cough with phlegm lasting for at least 3 months a year and for at least 2 years in a row, which had not been an outcome of interest in any of the prior studies. We found that chronic bronchitis was strongly associated with ClO_2/SO_2 peak exposures but not ozone peak exposures (models 2 and 3 in Table 3). Since the symptoms had to have lasted at least 2 years, some of the gassing events occurred too late in the period of follow-up for this requirement to be fulfilled by the time of interview. We were concerned that the low relative risk associated with ozone peak exposures might be an artifact of this phenomenon. However, when we examined the dates of peak exposures for the 311 participants whose data were used in the analysis of chronic bronchitis, the median year of peak exposure was actually earlier for ozone (1993) than for ClO_2/SO_2 (1996).

Possible Mechanisms of Asthma Following Peak Exposures

The occurrence of asthma following peak exposures to irritant gases raises the possibility that some of the cases might have fulfilled the criteria for reactive airways dysfunction syndrome (RADS).[25] RADS is characterized by onset of symptoms shortly after a very high-level exposure. In the current study, peak exposures were counted if they resulted in acute respiratory symptoms, suggesting a RADS-like pattern of onset. Some cases might have had onset after repeated high exposures rather than after a single exposure event. Peak irritant exposures might also have put workers at greater risk for subsequent sensitization to allergens and the development of associated allergic asthma.[26]

Asthma in the Comparison Group

In the current study, the participants without any peak exposures were overwhelmingly male (91%), had a mean age of approximately 40 years in the first year of follow-up, and an incidence of 2.4×10^{-3} person-years for self-reported asthma. This rate was somewhat greater than published incidence rates based on questionnaire studies of Swedish residents. For example, from one study[27] conducted in Sweden, the incidence of self-reported asthma among male adults by age category was: 1.5×10^{-3} person-years (21 to 30 years), 1.1×10^{-3} person-years (31 to 40 years), and 1.6×10^{-3} person-years (41 to 50 years). The somewhat higher rate of asthma based on the current cohort might reflect the influence of their background (*ie*, non-peak) occupational exposures to irritant gases, which are higher on average than what is experienced by the general public. In fact, all three asthma cases among participants without peak exposures occurred in pulp mill workers who experienced background exposures to irritant gases.

Limitations of the Current Analysis

In general, we had a relatively small number of participants and person-years of follow-up, which meant our findings are not as conclusive as we would have liked. The deletion of those who had experienced onset of outcomes of interest prior to the period of follow-up accounted for a substantial number of survey participants. For example, deletions due to earlier onset numbered 56 for wheeze (Table 1). This reduction in the number of cases was

justified by the increased validity of the current analyses relative to earlier analyses in which any outcome in adulthood was counted, regardless of temporal relationship to exposure. A major consequence of these exclusions was that the number of study subjects reporting outcomes was a maximum of 21 for wheeze and only 8 for asthma (Table 2). As a result, several of the HRs had broad confidence intervals (CIs) [Table 3]. With this in mind, it will be important to see whether these findings are replicated in studies of other workers who have similar exposures. Also, it would be advantageous in future studies to have greater numbers of study participants, years of follow-up, and cases.

Since we depended on subjects to report peak exposures, there was the opportunity for underreporting and overreporting. Some workers might have failed to report peak exposures that actually did occur. This misclassification would have introduced exposed individuals into what we had identified as the unexposed comparison group. Other workers might have overreported peak exposures, resulting in unexposed participants being classified as exposed. If there were an effect of exposure and the misclassification of exposure were nondifferential with respect to the outcomes, then our effect estimates would have been biased to the null.

Misclassification of exposure might have introduced bias away from the null, especially if participants with a discernable health problem were more likely to report peak exposures. If there had been such a bias, we would have expected to observe elevated risk ratios for both types of peak exposures with all outcomes, but we did not. Also, those with onset of one of the three outcomes before the start of follow-up were not more likely to report a peak exposure during the study period (data not shown). While we cannot conclusively rule out bias, these observations argue against a consistent differential reporting of peak exposures based on respiratory disease/symptom status.

For participants who reported a peak exposure in the same year that they reported onset of asthma or symptoms, we do not know for sure if the outcome followed the peak. For asthma, this uncertainty about the order of events applied to only one of the eight cases.

Self-reporting via questionnaire is a standard method for identifying respiratory symptoms such as cough, phlegm, and wheeze[19,20] but has the potential for introducing misclassification. A very high specificity is desirable in a study of risk, since false-positive outcomes can quickly overwhelm true-positive outcomes with even a modest decline in the specificity. Self-reporting of asthma is likely to have a high specificity and low sensitivity for ascertainment of this condition. For example, the specificity was 0.99 and sensitivity was 0.57 for self-reported asthma when the "gold standard" was the decision of a physician who conducted a telephone interview.[28]

Additional Analysis

The Global Initiative for Chronic Obstructive Lung Disease criteria for stage 0 COPD is intended to identify people at risk for the development of chronic airflow limitation.[22] Epidemiologic studies[29,30] published in the 1990s support the concept that people with chronic cough and phlegm are at risk for an accelerated decline in FEV_1. A more recent study[31] questioned whether stage 0 is really a good predictor of subsequent airflow limitation. Asthma has also been identified as a risk factor for chronic airflow limitation in some studies.[32,33] Given our findings that asthma is associated with ozone peak exposures and chronic bronchitis is associated with ClO_2/SO_2 peak exposures among pulp mill workers, obstructive changes in spirometry might be associated with both types of high-level exposures. The participants in the current investigation completed spirometry as well as a questionnaire. We plan to conduct statistical analysis of these cross-sectional and longitudinal spirometry data to investigate whether obstructive changes are associated with peak exposures to ozone and other irritant gases in these pulp mill workers.

Conclusion

The findings suggest that peak irritant exposures continue to pose a risk for respiratory symptoms and diseases among pulp mill workers. In particular, we observed elevated risks for asthma and wheeze associated with ozone peak exposures, and elevated risks for wheeze and chronic bronchitis associated with ClO_2/SO_2 peak exposures. Based on these observations, additional efforts are needed to prevent high-exposure events in pulp bleaching operations.

Appendix

Questions for Respiratory Symptoms and Diseases

Asthma: Have you been diagnosed as having bronchial asthma by a physician? If yes, in what year?

Wheeze: Have you at any time after 15 years of age had an attack of wheezing, whistling, or a noisy sound in your chest when breathing? If yes, in what year did you first notice it?

Chronic bronchitis (or chronic cough with phlegm): Do you cough up phlegm, or do you have phlegm in your chest that you have difficulty getting up? If yes, have you coughed like this daily for at least 3 months for 2 years in a row? If yes, in what year did you first notice it?

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