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Incidence of asthma among workers exposed to sulphur dioxide and other irritant gases

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ABSTRACT: The aim of the present study was to investigate whether repeated peak exposure (gassings) to sulphur dioxide (SO_2) and other irritant gases increases the risk of new-onset asthma. A questionnaire was sent to 4,112 sulphite workers, of whom 1,919 completed the questionnaire and 396 completed the short-form questionnaire, which was sent out as a last reminder. A sample of 130 nonrespondents completed a telephone interview using the short-form questionnaire.

The incidence of adult-onset, physician-diagnosed asthma during employment duration was analysed in relation to exposure to SO_2 and gassings giving rise to respiratory symptoms. Incidence rates, as well as incidence rate ratios with 95% confidence interval (CI), were calculated. Further Cox regression models were used allowing assessment of hazard ratios (HR) stratified for sex and adjusted for atopy, smoking habits and age.

The incidence rate for asthma among sulphite mill workers reporting gassings of SO_2 was 6.2 out of 1,000 person-yrs, compared with 1.9 out of 1,000 person-yrs among subjects unexposed to SO_2 and any gassings (HR (95% CI) 4.0 (2.1–7.7)). Among males reporting gassings to SO_2, the HR (95% CI) for asthma was 5.8 (2.6–13) compared with unexposed males.

In conclusion, repeated peak exposure to sulphur dioxide increased the incidence of asthma during work in sulphite pulp mills, which supports the hypothesis of irritant-induced asthma.

KEYWORDS: Gassings, irritant-induced asthma, occupational asthma, pulp and paper industry, sulphur dioxide

Over the last 10 yrs, several questionnaire-based studies on the incidence of asthma have been published, showing an incidence of about 1–3 cases per 1,000 person-yrs [1–3]. About 15% of all incident cases of asthma among adults are due to exposure in the workplace [4], and it is a well-described fact that many allergens (sensitisers) can induce occupational asthma. However, regarding exposure to irritants, such as sulphur dioxide (SO_2), ammonia and chlorine (Cl_2), the current knowledge is limited. Vast clinical experience has taught that high accidental exposures to irritants can induce asthma [5, 6]. There is a need for better knowledge regarding the clinically important issue as to whether recurrent episodes of irritant gassing exposure (low to medium) increase the risk for asthma [7]. However, a few epidemiological studies have been published, mainly dealing with occupational exposure to Cl_2/chlorine dioxide (ClO_2) and new-onset asthma [8, 9]. In none of these studies has the relationship between exposure to SO_2 and asthma been investigated.

Regarding this research issue, case reports are of limited interest because the temporal relationship is hard to evaluate. Studies have to be designed in such a way as to make it possible to assess whether exposure increases the risk for new-onset asthma. Another problem is that exposure to irritants, such as SO_2, Cl_2 or ammonia, is spread over many different occupations, making it difficult to study sufficiently large groups. However, in the pulp and paper industry, large occupational groups are exposed to SO_2, ClO_2 and ozone. In sulphite mills, where wood is pulped using an acidic method, large groups of workers are exposed to SO_2. In addition to SO_2, the workers may also infrequently be exposed to other irritant gases. In a previous study, sulphite mill workers were observed to have an increased mortality due to asthma, probably caused by accidental exposures to SO_2 [10].

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Consequently, the aim of the present study was to investigate the incidence of adult-onset asthma in association with repeated peak exposures to SO_2 by comparing exposed and unexposed workers within a cohort of sulphite mill workers.

MATERIALS AND METHODS

The entire cohort was identified by searching through all personnel files from four Swedish sulphite mills, where the production of pulp started in 1900, 1903, 1869 and 1960, respectively. All employees who were employed for $\geqslant$6 months at any time between 1940 and 2000 were registered. This resulted in a cohort of 10,041 subjects. For all included subjects, information about employment time was obtained from the personnel files.

Workers employed between January 1, 1980, and July 1, 2000, and alive at the last date were eligible for this retrospective questionnaire study (n=4,279). Of these, 34 could not be located, 13 died during the survey and 120 were excluded because they were aged >80 yrs. This left 4,112 workers eligible for the study.

In 2001, a comprehensive questionnaire titled ''Work conditions and health in the pulp industry'' was mailed to the 4,112 subjects. The questions had been used in previous studies [8, 11]. A last reminder included a short questionnaire, comprising the most important items. The key items from both questionnaires are listed in table 1. The comprehensive questionnaire was answered by 1,919 subjects (47%), whereas 396 subjects responded to the short version, giving a total response rate of 56%. Among the subjects responding to the comprehensive questionnaire, 111 subjects were excluded due to incomplete answers, resulting in a population of 1,808 subjects. Basic data about the study subjects are given in table 2.

TABLE 1 Key items used in the short questionnaire taken from the comprehensive questionnaire answered by sulphite mill workers

About exposures at your work	
4a	Have you been exposed to sulphur dioxide?
4b	If ''yes'', during which years?
5	Have you ever been exposed to sulphur dioxide resulting in coughing, breathlessness, wheezing or pain in the chest?
8	Have you ever been exposed to chlorine/chlorine dioxide resulting in coughing, breathlessness, wheezing or pain in the chest?
About your health	
20a	Have you been diagnosed by a physician as having asthma?
20b	If ''yes'', give the year of diagnosis?
23a	Have you at any time since age 15 yrs had an attack of wheezing or whistling in your chest?
23b	If ''yes'', in which year did you first notice it?
19b	Have you ever had hay fever?
About tobacco	
48	Have you ever smoked daily for at least 1 yr?
49, 50	If so, during which years?

Definitions

In the present study, asthma was defined as self-reported physician-diagnosed asthma with reported onset from the age of 16 yrs. Atopy was defined as a positive response to the questions about allergy in childhood and/or hay fever. In the short questionnaire, atopy was defined as ever hay fever. Smoking was defined as daily smoking for $\geqslant$1 yr. According to the status at follow-up, smokers were divided into current, former and never-smokers. The years of starting and stopping smoking were also obtained and used for time-dependent analysis.

Exposure to SO_2 was defined as an affirmative answer to item 4a (table 1), and gassing to SO_2 was defined as reported peak exposure giving rise to respiratory symptoms (item 5; table 1). Any gassings was defined as gassings to SO_2, Cl_2/ClO_2 or gassings with any other irritant chemicals.

Unexposed subjects were those not reporting exposure to SO_2 and, in addition, not reporting gassings to SO_2, Cl_2/ClO_2 or any other irritant chemicals. Hence, the cohort was divided into three groups: group one, consisting of subjects exposed to SO_2 (including those subjected to SO_2 gassings); group two, consisting of subjects not reporting exposure to SO_2, but reporting gassings other than with SO_2; and group three, which contained unexposed subjects.

Workers employed in the digester department, where the pulping process takes place, were the most likely to be exposed to SO_2. Therefore, a separate analysis on subjects reporting that they worked in a digester department was performed.

Nonrespondents

A sample of nonrespondents (n=316) was randomly chosen for a telephone interview based on the short questionnaire. Of these, 130 could be reached for the interview.

Statistical methods

For all items, subjects not answering were excluded from that analysis. The main analyses were performed on the subjects answering the comprehensive questionnaire (n=1,808).

Data on the year of diagnosis of asthma, time of employment and episodes of gassings allowed calculation of the incidence of asthma (during employment time plus 1 yr) in relation to gassings and other exposure variables. Person-yrs were calculated from each employment period (according to the personnel files) or until the year of reported diagnosis for cases. Incidence rate ratios (IRR) for asthma were calculated comparing gassed or exposed workers with unexposed workers and 95% test-based confidence intervals (CI) were outlined [12]. To assess the impact of selection bias, additional analyses were performed with information from short questionnaires and nonrespondents included.

Hazard ratios (HR) from Cox regression models were calculated, after stratifying for sex and adjusting for atopy, time-dependent smoking status (never/former/current) and time-dependent age $\geqslant$50 yrs.

The attributable fraction of gassings to SO_2 on incident asthma among employees in sulphite pulp mills was calculated using the formula HR–1/HR.

TABLE 2 Basic data for 1,808 sulphite mill workers employed during the period of 1980–2000

	Subjects n	Age yrs	Atopy %	Smoking habits %		Exposed to SO_2	Gassings to SO_2 n	Asthma %
				Never-smokers	Current smokers			
CQ								
Males	1548	48.4±13.8	16.8	47.6	12.5	656 (42.4)	429	5.6
Females	260	42.3±11.2	30.4	57.7	18.1	47 (18.1)	24	7.3
Short Q								
Males	332	46.9±13.6	24#	48	7	149 (45)	96	4
Females	52	44.8±13.1	17#	54	12	7 (14)	5	2
Nonrespondents interview								
Males	116	42.6±12.7	19#	49	16	34 (29)	23	5
Females	14	40.2±16.7	14#	57	7	2 (14)	1	0

Data are presented as n, mean±SD, % or n (%). CQ: comprehensive questionnaire; Q: questionnaire. #: atopy defined as ever hay fever.

RESULTS

In total, 142 subjects reported physician-diagnosed asthma, 78 of which were excluded. The reasons for exclusion were onset of asthma before 16 yrs of age (n=36) and onset of asthma before (n=25) or after (n=17) employment. These exclusions left 1,730 subjects for analysis, of whom 1,489 were male. In the final population, 64 cases of asthma (54 males) had onset of asthma during employment time.

The incidence rate for asthma among sulphite mill workers exposed to SO_2 was 4.4 per 1,000 person-yrs (n=35) as compared with 1.9 per 1,000 person-yrs (n=15) among subjects classified as unexposed (HR (95% CI) 2.7 (1.4–5.1); table 3). The risk further increased among subjects reporting gassings to SO_2 (4.0 (2.1–7.7)) and even further among those with frequent SO_2 gassings (6.8 (3.1–15)). The subgroup of workers with gassings only to SO_2 also had a high risk (5.8 (2.8–12)). The group with gassings to other irritants had also an increased risk for asthma (4.6 (2.1–10.0)).

When a Cox regression model including different kinds of gassings, atopy, smoking and age, and stratified for sex, was applied to all subjects (exposed, other gassings and unexposed), the risk for asthma in relation to SO_2 gassings was still high (HR (95% CI) 4.3 (2.3–8.2)). The risk for asthma among those with ''other gassings'' was 2.8 (1.3–5.9). To evaluate interaction, the incidence and risk was assessed in different strata according to atopy and ever-smoking (table 4). The highest risk for asthma occurred among never-smoking workers with atopy reporting gassings.

Working in the digester area, regardless of reported irritant gas exposure, was also associated with a significant increased risk for asthma (HR (95% CI) 4.2 (1.9–9.1)). The attributable fraction of incident asthma among sulphite mill workers due to exposure to SO_2 was 63% and 75% for gassings to SO_2.

Restricting the analysis to males increased the risks. Among males reporting gassings to SO_2, the HR for asthma was 5.8 (2.6–13) compared with unexposed males.

The interview with nonrespondents was completed by 130 subjects (12.5% of nonresponders). Analysing the complete and short questionnaires, together with the interview with nonrespondents, gave an HR for gassings to SO_2 of 3.0 (1.8–5.1). The incidence rate among nonrespondents reporting exposure to SO_2 was 10.6 per 1,000 person-yrs.

DISCUSSION

The most important result extracted from the present study is that repeated events of peak exposure to an irritant gas, such as SO_2, causes a three-fold increased incidence of asthma.

TABLE 3 Adult-onset asthma during the employment period of 1980–2000# plus 1 yr comparing different irritant exposure to unexposed in a sulphite mill cohort

	Subjects n	Person-yrs	Cases n	Incidence¶	IRR (95% CI)	HR+ (95% CI)
Exposed to SO_2	674	8028	35	4.4	2.4 (1.3–4.2)	2.7 (1.4–5.1)
Gassings to SO_2	430	5338	33	6.2	3.3 (1.9–5.9)	4.0 (2.1–7.7)
Frequent gassings to SO_2	167	2252	20	8.9	4.8 (2.6–8.8)	6.8 (3.1–15)
Other gassings	207	2087	14	6.7	3.6 (1.8–7.1)	4.6 (2.1–10)
Unexposed	849	8086	15	1.9	1.0	

IRR: incidence rate ratios; CI: confidence interval; HR: hazard ratios. #: employment time from mill personnel files; ¶: number of new cases per 1,000 person-yrs; +: stratified for sex, adjusted for atopy (proxy yes to hay fever and/or childhood allergy), time-dependent smoking status (not/quit/current), time-dependent age ⩾50 yrs.

TABLE 4 Incidence and risk of adult-onset asthma in different strata of atopy and ever-smoking for sulphite mill workers exposed to gassings to sulphur dioxide (SO_2) compared with unexposed during the employment period of 1980–2000 plus 1 yr

Atopy	Ever-smoking	Unexposed#	Gassings to SO_2#	IRR
No	No	1.4 (4)	5.3 (10)	3.7 (1.3–11)
No	Yes	1.8 (7)	3.4 (9)	1.9 (0.7–5.1)
Yes	No	4.3 (3)	28.5 (11)	6.6 (2.2–20)
Yes	Yes	2.2 (1)	9.8 (3)	4.4 (0.6–35)

Data are presented as incidence (cases) or incidence rate ratios (IRR; 95% confidence interval). #: number of new cases per 1,000 person-yrs.

Furthermore, 63% of all cases of new-onset asthma were caused by exposure to SO_2. These results underscore the importance of preventive actions in this work environment.

The current results are based on a retrospective analysis on information gathered from a postal questionnaire. Retrospective analysis of asthma incidence is associated with less accurate recall the further back in time the analysis is applied [13]. In order to limit the magnitude of a possible recall bias, the study was restricted to the period of 1980–2000. There is a possibility that recall of asthma may differ between exposed and unexposed subjects. However, the incidence rate of adult-onset asthma found among unexposed workers in the current study (1.9 per 1,000 person-yrs) was similar to that reported for the general population in other Swedish studies [1, 3].

The reported year of onset for asthma may be sensitive to misclassification, meaning that a subject may report an incorrect year. The current authors are aware of two studies that validated the self-reported year of diagnosis or disease onset among subjects with asthma [3, 14]. In the first study, 85% of subjects who reported the onset year deviated <4 yrs. In the second study, 90% of the subjects reported the correct year of asthma onset ± 1 yr. In addition, there is one study in which the reliability of the temporal aspect of reported onset of asthma has been analysed. It reports a finding that 80% of the subjects correctly reported the year of asthma onset ± 1 yr [15].

Self-reported occupational exposure data could be differentially misclassified by disease status. In a Norwegian study, the sensitivity of the question on exposure to dust and gas was biased by respiratory symptoms, but hardly at all by physician-diagnosed asthma [16], the outcome used in the present study. Bias is more important in sensitivity than it is in specificity for the effect of misclassification of exposure for a common exposure, such as the gassings in the present study [17]. Self-reporting of gassings may be sensitive to recall bias, as workers with pre-existing respiratory symptoms may be more prone to recall gassings. In the present study, among workers exposed to irritant gases, 63% of nonasthmatics reported gassings compared with 86% of subjects with childhood asthma (which were excluded in this study) and 69% of subjects with atopy but no asthma. Although the differences are slight, these figures do not indicate an obvious recall bias by disease status. Prompted questions on exposure, as in the present study, are less likely to be subject to recall bias than open-ended questions, according to a Canadian study on reliability of recall of occupational exposure [18]. In this study, work in the digester area, regardless of reported irritant exposure, was also associated with an increased risk for asthma. This further supports the present findings of a relationship between irritant gas exposure and asthma. In sulphite mills, workers are mainly exposed to SO_2 but exposure to Cl_2 also exists. The current authors' underlying assumption, based on interviews with process workers, is that exposed workers can distinguish between gassings to SO_2 and Cl_2/ClO_2.

Possible confounding factors, such as atopy and smoking, were controlled for in the Cox regression models. Among adults <50 yrs of age, the incidence of asthma seems to be similar over age [1], and controlling for age >50 yrs in the models did not change the results. The current authors also observed that workers with atopy and reported gassings had a very high risk of asthma (table 4). This may reflect a biological interaction, *i.e.* subjects with atopy are more sensitive to exposure to irritating gases. However, an alternative explanation is reporting bias, *i.e.* workers with atopy, are more prone to report gassings due to an increased sensitivity.

Subjects reporting asthma before the start of employment were excluded, but there could still be subjects with nonidentified previous asthma. There are studies showing that subjects with asthma in remission have asymptomatic airway hyperreactivity and persistent inflammation in the airways [19, 20]. Such subjects may be at an increased risk of relapsed asthma due to exposures to gassings, which, to some extent, may explain the increased risk among subjects with atopy.

The response rate in the present study was not high; however, adding results from the late respondents (*i.e.* the short questionnaire) and the interviews with nonrespondents did not change the results. It has been shown that, when initial respondents are compared with all respondents, hardly any changes in prevalence and odds ratios are noted [21]. Even assuming there is no risk increase among those not responding and the same exposure frequency as among respondents, a significant risk of asthma will still be obtained (IRR (95% CI) 2.2 (1.4–3.2) for gassings to SO_2).

There are other studies from pulp mills showing similar results, with irritant gassings increasing the risk of asthma. In a Canadian pulp mill, the incidence of asthma among workers in the production area was 4.2 compared with 0.8 per 1,000 person-yrs among railyard workers. However, this difference was not statistically significant [22]. The main exposure in that study was Cl_2ClO_2. Gassings were not studied. In a study of bleachery workers mainly exposed to Cl_2ClO_2, the present authors found an increased incidence of asthma, 5.4 per 1,000 person-yrs compared with 1.0 among paper workers, especially among subjects reporting gassings [8]. In a large recent prospective study, including 62 USA pulp and paper mills, there was an increased incidence of asthma among

irritant-exposed workers, of 1.4 and 3.5 per 1,000 person-yrs for males and females, respectively, compared with 1.0 and 2.0 per 1,000 person-yrs, respectively, for unexposed subjects [9]. The adjusted risk was 1.48 (1.17–1.86). Compared with the present study, gassings were more strictly defined in that study; however, the asthma outcome was less strict. Asthma was defined as ''yes'' answered once (there were several examinations during the study period of 1986–1998) to the question ''Do you have asthma?''. This outcome is less specific than physician-diagnosed asthma [11].

Occupational exposure to SO_2 is common in some industries, in addition to pulp mills. Accidental occupational exposure to SO_2 in a pyrite mine resulted in obstructive impairment of ventilatory function and persistent bronchial hyperresponsiveness at follow-up [23]. Repeated peak exposures to SO_2 have also been reported in seasonal farming workers involved in apricot sulphurisation [24], and several cases of new-onset asthma were described in that group.

The risk of developing respiratory symptoms due to gassings may increase among those already exposed to gassings, as the inflammatory response due to repeated peaks may not completely disappear [25]. There is a longitudinal study from Quebec, Canada, showing that Cl_2 gassings increase airway responsiveness [26, 27]. OLIN and coworkers [28–30] found increased nitric oxide in exhaled air among bleachery workers reporting ozone gassings, which may indicate chronic airway inflammation. Irritants are known to trigger inflammation through epithelial injury, but it has also been proposed that neuronal activity through neuropeptides gives rise to, and maintains, inflammation (*i.e.* neurogenic inflammation) in response to irritant exposure [31].

Irritant-induced asthma not occurring within 24 h of massive irritant exposure has rarely been recognised as being related to occupation, but the current study and other recent studies show that persons exposed to repeat peak exposures to irritant gases, such as SO_2, Cl_2 and ozone, have a considerably higher risk of new-onset asthma.

The associations observed in the present retrospective study should ideally be studied in a prospective study, with recurring health examinations and exposure assessments. However, there are great problems with catching the ''gassings'' with continuous personal monitoring; hence, additional methods with diaries and area samplings must be considered.

In conclusion, repeated peak exposure to sulfur dioxide giving rise to respiratory symptoms increased the incidence of asthma during work in sulphite pulp mills supporting the hypothesis of irritant-induced asthma.

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