

Adult-Onset Asthma and Wheeze Among Irritant-Exposed Bleachery Workers

Eva Andersson, MD,^{1*} Anna-Carin Olin, MD,¹ Stig Hagberg, MSc,¹
Ralph Nilsson, MD, PhD,¹ Tohr Nilsson, MD, PhD,² and Kjell Torén, MD, PhD^{1,3}

Background Whether new-onset asthma is associated with irritant exposure is unclear. The aim was to investigate if occupational exposure to irritant gases, especially repeated peak exposure (gassings), increased the risk of obstructive airways disease.

Methods Data on airway symptoms and exposure among bleachery ($n = 101$) and paper department workers ($n = 314$) were collected by a questionnaire. Incidence rates and hazard ratios (HR) (Cox regression) were calculated. Non-responders were interviewed by telephone.

Results The incidence rate for adult-onset physician-diagnosed asthma among bleachery workers reporting gassings giving rise to respiratory symptoms was $7.6/10^3$ person-years and for those without gassings $2.2/10^3$ person-years, compared to $1.0/10^3$ person-years for paper workers. In a Cox regression model for asthma ($n = 12$), stratified for sex, HR for gassings were 5.6 (95% confidence intervals (CI) 1.6–20), for hay fever 3.0 (95% CI 0.8–11), and for ever smoking 0.7 (95% CI 0.2–2.4). The same model for adult-onset wheeze gave HR of 5.2 (95% CI 2.2–12), 1.7 (95% CI 0.6–5.4), and 1.1 (95% CI 0.5–2.7), respectively.

Conclusions Repeated peak exposure to irritant gases, here studied as gassings in the pulp industry, increased the risk for both adult-onset asthma and wheeze. *Am. J. Ind. Med.* 43:532–538, 2003. © 2003 Wiley-Liss, Inc.

KEY WORDS: occupational asthma; gassings; irritant-induced asthma; pulp and paper industry; wheeze; chlorine; sulfur dioxide

INTRODUCTION

Pulp mill workers have been exposed to irritant gases, mainly chlorine/chlorine dioxide (Cl_2/ClO_2) but also sulfur dioxide (SO_2). Compared to SO_2 , Cl_2 is less water-soluble and, therefore, affects the whole of the respiratory tract [Winder, 2001]. Acute exposure to Cl_2 causes a response to irritants in the airways characterized by bronchoconstriction, cough, and dyspnea. Epidemiological studies have shown that pulp mill workers have an increased prevalence of wheeze and a decreased lung function [Kennedy et al., 1991; Salisbury et al., 1991; Henneberger et al., 1996]. A history of gassing events seems to be a major risk factor and most of the gassings occurred in the bleachery departments [Salisbury et al., 1991]. Also in other occupations, peak exposures to irritants are of importance for respiratory symptoms [Das and Blanc, 1993]. In a longitudinal study of 211 metalworkers,

¹Department of Occupational and Environmental Medicine, Sahlgrenska University Hospital, Göteborg, Sweden

²Department of Occupational and Environmental Medicine, Sundsvall Hospital, Sundsvall, Sweden

³Department of Respiratory Medicine and Allergy, Sahlgrenska University Hospital, Göteborg, Sweden

Contract grant sponsor: Swedish Council for Worklife Research; Contract grant sponsor: Torsten and Ragnar Söderberghs Foundation; Contract grant sponsor: Göteborg Medical Society.

*Correspondence to: Dr. Eva Andersson, Department of Occupational and Environmental Medicine, Sahlgrenska University Hospital, St. Sigfridsgatan 85B, SE 412 66 Göteborg, Sweden. E-mail: Eva.Andersson@ymk.gu.se

Accepted 5 December 2002

DOI 10.1002/ajim.10203. Published online in Wiley InterScience (www.interscience.wiley.com)

self-reported and first aid unit reported peak exposure to Cl_2 were associated with increased bronchial hyperresponsiveness and impaired lung function [Gautrin et al., 1999]. It is, however, not confirmed that repeated peak exposures to low/medium levels of Cl/ClO_2 contributes to the development of new-onset asthma among adults [Torén and Blanc, 1997].

We have earlier reported an increased mortality from asthma among sulfite mill workers, probably due to exposure to SO_2 [Andersson et al., 1998]. The aim of this study was to investigate the association between repeated peak exposure to irritant gases (gassings) and adult-onset asthma and wheeze among bleachery workers in a sulfate mill.

MATERIALS AND METHODS

Study Design and Subjects

All bleachery, maintenance, and laboratory workers ($n = 101$) in the bleaching department of a large sulfate-based pulp mill were selected as subjects potentially exposed to irritant gases. In the pulp mill, Cl_2/ClO_2 has been used as a bleaching agent since the 1940s and there was a chlorine-alkali plant from 1945 to 1983. All process workers ($n = 314$) from three paper departments, producing printing paper, were selected as referent subjects.

Information on disease and exposure was collected by a postal questionnaire in 1995. The questions have been used in previous studies [Torén et al., 1993; Torén and Hermansson, 1999] and are based on questionnaires from the American Thoracic Society and the Division of Lung Diseases, National Heart, Lung and Blood Institute (ATS-DLD-78), and the European Coal and Steel Community questionnaire (ECSC-87) [Ferris, 1978; Minette, 1989]. The key questions regarding respiratory symptoms and exposure are listed in Table I. The response rate was 90% ($n = 91$) among the bleachery workers and 71% ($n = 223$) among the paper department workers. In order to evaluate possible selection bias, the non-responders were interviewed by telephone and asked the key questions (Table I). Almost all of the non-responders (88%) answered the telephone interview, but 12 referent workers did not participate. In the subsequent analyses, the workers with a history of childhood asthma (16 paper and two bleachery workers) were excluded. The study population thus consisted of 99 bleachery workers and 286 paper mill workers (Table II) with a total response rate of 97% on the most important questions. Of the subjects, 91% were males.

The analyses were performed by a historical cohort approach. Data on which year different respiratory symptoms started and year of diagnosis, employment, and episodes of gassings allowed calculation of incidence rates and chronological relation to bleachery work and gassings. Person-years were calculated from the first year of employment at

TABLE I. Key Questions Used in the Non-Responders Interview (in this order) Taken from the Questionnaire (order there as numbers)

Question number	Key question
5a	Have you ever had bronchial asthma?
5b	Have you ever had hay fever?
6	Have you been diagnosed as having bronchial asthma by a physician? If "Yes," what year?
13	Have you had wheezing or whistling in your chest after 15 years of age? If "Yes," what year did you first notice it?
3.1	Have you been exposed to chlorine/chlorine dioxide (Cl_2/ClO_2) in your work? (Only in questionnaires: if "Yes," during which years)
3.5	Have you been exposed to sulfur dioxide (SO_2) in your work? (Only in questionnaires: if "Yes," during which years)
3.4/3.8	Have you been exposed to ClO_2/SO_2 with respiratory symptoms as a result? (Only in questionnaires: separated in two—one for each exposure, and if "Yes" when did this occur?)
23	Have you ever smoked daily for more than 1 month? (Only in questionnaires: more detailed questions on smoking)

the sulfate mill or paper mill, respectively, until 1995 or until the year of reported diagnosis for cases. Each person-year was also classified as to whether the subject was exposed to irritant gases and gassings (with Cl_2/ClO_2 and/or SO_2). Person-years were defined as exposed up to 1 year after cessation of exposure. The year of onset of adult-onset asthma and adult-onset wheeze was reported in the questionnaires and each case was classified as exposed or not when appearing. All asthma cases ($n = 12$) started during mill working years. Of the wheeze cases ($n = 44$), 20% were

TABLE II. Characteristics of the Study Subjects; Bleachery Workers

	Bleachery department (n = 99)	Paper department (n = 286)
Questionnaire	89	210
Age, mean $\pm$ SD	41.3 $\pm$ 7.8	39.1 $\pm$ 11.6
Employment time, mean $\pm$ SD	18.2 $\pm$ 8.0	14.0 $\pm$ 10.3
Ever hay fever	11 (12%)	27 (13%)
Smoking habits		
Current smokers	22 (25%)	43 (20%)
Ex-smokers	26 (30%)	60 (29%)
Never smoked	40 (45%)	107 (51%)
Non-responders interview	10	76
Age, mean $\pm$ SD	45.2 $\pm$ 8.6	40.4 $\pm$ 13.5
Ever hay fever	2 (20%)	3 (4%)
Smoking habits		
Ever smoked	5 (50%)	39 (52%)
Never smoked	5 (50%)	36 (48%)

undated and 27% started before mill working years, leaving 23 for incidence analysis.

Definitions

Asthma in this study was defined as adult-onset physician-diagnosed asthma, that is an affirmative answer to question 6 (Table I), physician-diagnosed asthma, if the onset was after the age of 15. Wheeze and hay fever were defined as “Yes” to question 13 and 5b, respectively. Only adult-onset wheeze is included in the study. The definition of “gassing” was an affirmative answer to question 3.4 or 3.8, i.e., respiratory symptoms due to exposure to high levels of irritant gases. The questionnaire also encompassed questions regarding exposure to different irritant gases and the frequency of exposure.

Statistical Methods

The analyses of incidence rates of asthma were restricted to the persons ($n = 299$) answering the questionnaire. Incidence rate ratios have been calculated.

To control for confounding, Cox regression analyses were performed for those answering the questionnaire with millwork person-years as the dependent variable and asthma and wheeze, respectively, as events, stratified for sex. Hazard ratios (HR) for explanatory variables, work in bleachery or paper departments (model 1) and gassings (models 2 and 3), are given, controlling for hay fever and ever smoking. Univariate results for each variable are also presented.

To assess the impact of selection bias, additional analyses were performed with information about non-responders included. In that analysis, we lack information about person-years; hence, only cumulative incidence rate ratios were calculated. These ratios included the period after the age of 15 until 1995 for 385 subjects. Bleachery workers were compared with paper department workers and workers with gassings were compared with paper department workers not reporting any exposure to irritant gases. Ratios for different subpopulations (ever smoked, never smoked, hay fever, and not hay fever) are presented when there were more than three cases in each group.

The 95% confidence intervals (CI) for incidence rate ratios and risk ratios were calculated by the test-based method [Miettinen, 1976]. The statistical analyses were performed with the statistical software package SAS versions 6.12 and 8 (SAS Institute, Cary, NC).

RESULTS

Exposure

Of the bleachery workers, 90% reported exposure to Cl_2/ClO_2 and 73% to SO_2 (Table III). Of all Cl_2/ClO_2 -

TABLE III. Reported Exposure Among the Study Subjects

	Bleachery department ($n = 99$)	Paper department ($n = 286$)
Questionnaire	89	210
Exposure to irritant gases		
Cl_2/ClO_2	80 (90%)	44 (21%)
SO_2	65 (73%)	22 (10%)
Gassings giving respiratory symptoms	40 (45%)	21 (10%)
Cl_2/ClO_2	39 (44%)	21 (10%)
SO_2	22 (25%)	2 (1%)
Both Cl_2 and SO_2	21 (24%)	2 (1%)
Non-responders interview	10	76
Exposure to irritant gases	6 (60%)	12 (16%)
Gassings giving respiratory symptoms	1 (10%)	6 (8%)

exposed subjects, 65% reported exposure to SO_2 also. Among the bleachery workers, one third reported exposure to Cl_2/ClO_2 more than once a week. The exposure to SO_2 was less frequent, only 20% reporting exposure more than once a week. About 50% of the irritant gas-exposed workers had experienced gassings giving respiratory symptoms (Table III).

Respiratory Health Effects

There was an increased incidence rate of asthma among the bleachery workers compared with paper workers (Table IV). The incidence rate was higher for years with reported irritant gas exposure with gassings. In the Cox regression analyses, a history of gassings was a strong risk factor for asthma almost unrelated to a history of hay fever (Table V). Univariate HR for asthma among those reporting gassings were 6.3 (95% CI 1.8–22), among subjects with hay fever 3.8 (95% CI 1.1–13), and for ever smoking 1.0 (95% CI 0.3–3.4). Adjusting for age did not change HR substantially. Limiting the study population to those only reporting gassings with Cl_2/ClO_2 did not change the findings, although HR for smoking increased insignificantly (Table V). The HR for wheeze and bleachery work were not as high as that for asthma but for gassings it had the same magnitude (Table V).

Of the 12 subjects with asthma identified in the questionnaires (onset age 20–50 years, mean 35.5, SD 7.6), nine were exposed to Cl_2/ClO_2 and/or SO_2 before the asthma onset. Furthermore, eight of them had also experienced respiratory symptoms due to gassings before onset.

The risk ratio of cumulative incidence was analyzed with non-responders included but that did not change the findings (Table VI).

TABLE IV. Incidence Rates and Incidence Rate Ratios With 95% Confidence Intervals (CI) of Adult-Onset Physician-Diagnosed Asthma and Adult-Onset Wheeze During Years in Different Exposure Categories*

	Asthma		Wheeze	
	Incidence rate ^a	Incidence rate ratio (95% CI)	Incidence rate ^a	Incidence rate ratio (95% CI)
Paper departments	1.0 (3)		4.0 (11)	
Bleachery department	5.4 (9 ^b)	5.3 (1.7–17)	8.1 (12)	2.0 (0.9–4.5)
Without gassings giving respiratory symptoms	2.2 (2)	2.2 (0.4–12)	3.6 (3)	0.9 (0.3–3.2)
With gassings giving respiratory symptoms	7.6 (6)	7.5 (2.3–24)	13.4 (9)	3.3 (1.5–7.7)

*Other rates are compared with paper department rates.

^aNumber of new cases per 1,000 person-years (number of incident cases).

^bOne case is omitted from the analyses below, he was exposed to gassings, got wheeze then but asthma onset 10 years later.

DISCUSSION

The incidence of asthma was significantly increased among bleachery workers during mill working years compared to paper workers, especially among workers who reported gassings with respiratory symptoms, controlling for hay fever and ever smoking. The incidence of wheeze was increased among workers who reported gassings.

There are few studies of new-onset asthma among irritant-exposed workers. In a Canadian pulp mill study [Enarson et al., 1984], analyzing the incidence rate of new-onset asthma in a similar way as we did, the investigators found a higher rate of asthma among workers in the production area when compared to rail yard workers (4.2 compared to 0.8 per 1,000 person-years) but the difference was not statistically significant. A higher proportion of pulp mill

workers complained about wheeze and the young non-smokers in the bleach plant had a higher frequency of airway obstruction. Gassings were not studied.

In a study showing wheeze but not asthma among “gassed” pulp mill workers in Canada, the authors defined asthma as an affirmative answer to the question “Have you ever had asthma” [Salisbury et al., 1991], including childhood asthma and asthma that is not physician-diagnosed. For first aid unit report of Cl₂ gassing, they found an OR for asthma of 1.7 (95% CI 0.6–4.7) controlling for age and smoking status. Analysis of our data with the same asthma definition (multiple logistic regression on all included along with the previously excluded subjects with childhood asthma), controlled for ever smoking, showed OR 1.7 (95% CI 0.8–3.6) for bleachery work and 2.5 (95% CI 1.1–5.4) for gassings giving respiratory symptoms. With our definition of asthma, physician-diagnosed adult-onset (childhood asthmatics excluded), the same analyses gave OR 3.9 (95% CI 1.4–11) for bleachery work and 4.9 (95% CI 1.8–14) for gassings. This shows the importance of a highly specific disease definition, which physician-diagnosed asthma is, when studying a disease with low prevalence [Torén et al., 1993].

The influence of smoking on airway symptoms after irritant gas exposure is not clear. Respiratory symptoms following different irritant exposures have been reported to be associated with smoking [Blanc et al., 1993]. For Cl₂ exposure, there are conflicting results. In some studies, reduced lung function was seen mostly among smokers [Henneberger et al., 1996; Gautrin et al., 1999] but Kennedy et al. [1991] found more respiratory symptoms and obstruction among non-smokers and former smokers. When Salisbury et al. [1991] compared change in lung function between 1981 and 1988 among non-smokers and current smokers with first aid unit report of gassings in these years, they found a reduction for both compared with workers with no gassings. Our study did not give any answer to this. The prevalence of wheeze among bleachery workers was 27%

TABLE V. Cox Regression Hazard Ratios (HR) With 95% CI of Adult-Onset Physician-Diagnosed Asthma and Adult-Onset Wheeze During Years Worked in a Bleachery Department and Paper Departments

Models stratified for sex	Asthma HR (95% CI)	Wheeze HR (95% CI)
Model 1	N = 12	N = 23
Bleachery department	4.5 (1.2–16)	1.8 (0.8–4.2)
Hay fever	4.2 (1.2–14)	2.1 (0.7–6.3)
Ever smoked	1.0 (0.3–3.3)	1.3 (0.5–3.0)
Model 2	N = 12	N = 23
Gassings giving respiratory symptoms	5.6 (1.6–20)	5.2 (2.2–12)
Hay fever	3.0 (0.8–11)	1.7 (0.6–5.4)
Ever smoked	0.7 (0.2–2.4)	1.1 (0.5–2.7)
Model 3 ^a	N = 7	N = 17
Gassings with Cl ₂ /ClO ₂	3.1 (0.7–14)	4.2 (1.6–11)
Hay fever	3.4 (0.7–18)	2.4 (0.7–8.6)
Ever smoked	1.7 (0.3–9.0)	2.1 (0.7–6.5)

^aThose with gassings with SO₂ giving respiratory symptoms are excluded.

TABLE VI. Risk Ratios of Cumulative Incidence With 95% CI of Asthma and Wheeze Among all Included Workers (Both Those From Questionnaires and Non-Responders Interview) in the Bleachery Department of a Sulfate Mill and Referent Workers at Paper Departments

	All	Ever smoked	Never smoked	Hay fever	No hay fever
Asthma					
Bleachery department	9/99	5/54	4/45	4/13	5/86
Paper departments	7/286	5/141	2/144	1/30	5/250
Risk ratio (95% CI)	3.7	2.6	—	—	2.9
	1.5–9.2	0.8–8.4			0.9–9.3
Gassings	8/68	4/42	4/26	4/10	4/59
Unexposed referents	4/220	3/102	1/117	0/22	3/191
Risk ratio (95% CI)	6.5	3.2	—	—	4.3
	2.3–18	0.8–13			1.1–17
Wheeze					
Bleachery department	19/99	12/54	7/45	5/13	14/86
Paper departments	34/286	23/141	11/144	6/30	28/250
Risk ratio (95% CI)	1.6	1.4	2.0	1.9	1.5
	0.96–2.7	0.7–2.6	0.8–4.9	0.7–5.3	0.8–2.6
Gassings	21/68	14/42	7/26	6/10	15/59
Unexposed referents	21/220	12/102	9/117	3/22	18/191
Risk ratio (95% CI)	3.2	2.8	3.5	4.4	2.7
	1.9–5.5	1.5–5.5	1.5–8.4	1.5–13	1.5–5.0

Risk ratios also for those reporting gassings giving respiratory symptoms, compared to unexposed paper workers.

among current smokers, 15% among ex-smokers, and 17% among those who had never smoked, and among paper workers it was 16, 15, and 10%, respectively. But subjects that had ever smoked were not more prone to report asthma in our study.

The proportion of workers exposed to irritant gases and gassings in this study seems to be similar to that reported from other pulp mills. Henneberger et al. [1996] reported that 51% and Kennedy et al. [1991] that 60% of the pulp mill workers reported gassings either with or without symptoms. The same frequencies of gassings were reported in 1963 as we found in 1995. Of pulp mill workers in departments with potential exposure to irritant gases, 23% reported gassings with SO₂ and 42% with Cl₂ [Ferris et al., 1967]. In this study, the corresponding figures for the bleachery workers were 25 and 44%.

Aspects of Validity

The retrospective design of the study could be a limitation but the incidence rate of adult-onset asthma found among paper mill workers in our study, 1.0 per 1,000 person-years, is similar to that found in the general population according to other studies [Torén and Hermansson, 1999]. The time of onset of asthma is crucial when incidence rates are calculated. The reliability of the question when a person's

asthma started has been shown to be good [Brisman and Järholm, 1995].

As in most populations of industrial workers, selection bias could be of importance. Bleachery workers with respiratory problems may leave the pulp mill, for example, obtaining a new job in an adjacent paper mill, which we have examples of in this study. A few paper mill workers reported "gassings," but exclusion of them did not change the findings. About 50 of the workers had worked both as pulp and paper workers. As this is a retrospective study, only those still at work are included in the study population. Half of the asthma cases found in this study had their onset during the last 2–3 years, indicating a healthy worker effect and the true risk is then probably underestimated [Punnett, 1996].

Self-reported occupational exposure data could be differentially misclassified by disease status, according to Bakke et al. [2001]. In that 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. Bias in sensitivity is more important than in specificity for the effect of misclassification of exposure for a common exposure, like gassings here [Flegal et al., 1986]. Self-reporting of gassings has been used by others [Kennedy et al., 1991; Henneberger et al., 1996]. It may be sensitive to recall bias, as workers with preexisting respiratory symptoms may be more prone to

recall gassings. But using first aid unit reports of gassings instead of questionnaire data to eliminate recall bias in the Canadian study strengthens the associations with respiratory symptoms [Salisbury et al., 1991]. Prompted questions on exposure, as in this study, are less likely to be subject to recall bias than open-ended questions, according to a Canadian study [Teschke et al., 2000]. The exposure categories bleachery worker and paper worker were defined prior to the questionnaire data.

Bleachery workers may be more disposed to reporting their respiratory symptoms than the referent workers. Such bias is not possible to estimate in this study, and it may to some extent explain the increased prevalence of respiratory symptoms among bleachery workers. Questions about respiratory symptoms are probably more influenced by recall bias than questions about specific conditions such as physician-diagnosed asthma.

Possible confounding factors like hay fever (as a marker for atopy) and smoking are controlled for in the Cox regression models. Among adults before the age of 50, the incidence of asthma seems to be similar over age [Torén and Hermansson, 1999] and controlling for age in the models did not change the results. Asthma incidence may be different among males and females [Torén and Hermansson, 1999]; in this study 91% are men and in the Cox regression we have stratified for sex.

Non-response to the questionnaire was more common among paper mill workers than among bleachery workers, but through telephone interview we got a response rate of 97% on the most important questions. The prevalence of adult-onset physician-diagnosed asthma was 4.0% among responders and 4.7% among non-responders; for adult-onset wheeze it was 14.7 and 10.5%, respectively.

It was not really possible to study the effect of Cl_2/ClO_2 alone since there were few asthma cases and many SO_2 -gassings among the bleachery workers.

Irritant-Induced Asthma

RADS—reactive airway dysfunction syndrome—has been recognized as giving persistent obstructive airways disease [Brooks et al., 1985], but new-onset asthma due to repeated moderate or low-level irritant exposure is still an area of controversy [Tarlo, 2000]. The risk of developing respiratory symptoms due to gassings may increase among those already exposed to gassings, as the inflammatory response due to repeated Cl/ClO_2 peaks may not completely disappear [Kennedy et al., 1991]. There are also data showing that accidental occupational chlorine exposure can lead to long-lasting impairment of airway caliber [Bhérier et al., 1994; Gautrin et al., 1999]. Olin et al. [1999] have found increased nitric oxide in exhaled air among bleachery workers reporting ozone gassings, which may indicate chronic airway inflammation.

CONCLUSIONS

Workers in a bleachery department had an increased incidence rate for asthma compared to paper department workers. Workers reporting gassings (repeated peak exposure) with irritant gases giving respiratory symptoms had an increased incidence rate of both asthma and wheeze. As far as we know, this is the first study to show an increased risk for asthma among workers exposed to repeated peak exposure to irritant gases, here mostly Cl_2/ClO_2 . The results underscore that peak exposure to irritants in pulp mills must be prevented.

REFERENCES

- Andersson E, Nilsson T, Persson B, Wingren G, Torén K. 1998. Mortality from asthma and cancer among sulfite mill workers. *Scand J Work Environ Health* 24:12–17.
- Bakke PS, Hanoa R, Gulsvik A. 2001. Relation of occupational exposure to respiratory symptoms and asthma in a general population sample: Self-reported versus interview-based exposure data. *Am J Epidemiol* 154:477–483.
- Bhérier L, Cushman R, Courteau J-P, Quévillon M, Côté G, Bourbeau J, L'Archevêque J, Cartier A, Malo J-L. 1994. Survey of construction workers repeatedly exposed to chlorine over a three to six month period in a pulpmill: II. Follow up of affected workers by questionnaire, spirometry, and assessment of bronchial responsiveness 18 to 24 months after exposure ended. *Occup Environ Med* 51:225–228.
- Blanc PD, Galbo M, Hiatt P, Olson KR, Balmes JR. 1993. Symptoms, lung function, and airway responsiveness following irritant inhalation. *Chest* 103:1699–1705.
- Brisman SJ, Järholm BG. 1995. Occurrence of self-reported asthma among Swedish bakers. *Scand J Work Environ Health* 21:487–493.
- Brooks SM, Weiss MA, Bernstein IL. 1985. Reactive airways dysfunction syndrome (RADS). Persistent asthma syndrome after high level irritant exposures. *Chest* 88:376–384.
- Das R, Blanc PD. 1993. Chlorine gas and the lung: A review. *Toxicol Ind Health* 9:439–455.
- Enarson DA, Maclean L, Dybuncio A, Chan-Yeung M, Grzybowski S, Johnson A, Block G, Schragg K. 1984. Respiratory health at a pulpmill in British Columbia. *Arch Environ Health* 39:325–330.
- Ferris BG. 1978. Epidemiology standardization project (American Thoracic Society). *Am Rev Respir Dis* 118:1–120.
- Ferris BG, Jr., Burgess WA, Worcester J. 1967. Prevalence of chronic respiratory disease in a pulp mill and a paper mill in the United States. *Br J Ind Med* 24:26–37.
- Flegal KM, Brownie C, Haas JD. 1986. The effects of exposure misclassification on estimates of relative risk. *Am J Epidemiol* 123:736–751.
- Gautrin D, Leroyer C, Infante-Rivard C, Ghezzi H, Dufour JG, Girard D, Malo J-L. 1999. Longitudinal assessment of airway caliber and responsiveness in workers exposed to chlorine. *Am J Respir Crit Care Med* 160:1232–1237.
- Henneberger PK, Lax MB, Ferris BG, Jr. 1996. Decrements in spirometry values associated with chlorine gassing events and pulp mill work. *Am J Respir Crit Care Med* 153:225–231.
- Kennedy SM, Enarson DA, Janssen RG, Chan-Yeung M. 1991. Lung health consequences of reported accidental chlorine gas exposures among pulpmill workers. *Am Rev Respir Dis* 143:74–79.

- Miettinen O. 1976. Estimability and estimation in case-referent studies. *Am J Epidemiol* 103:226–235.
- Minette A. 1989. Questionnaire of the European Community for Coal and Steel (ECSC) on respiratory symptoms. 1987—updating of the 1962 and 1967 questionnaires for studying chronic bronchitis and emphysema. *Eur Respir J* 2:165–177.
- Olin A-C, Ljungkvist G, Bake B, Hagberg S, Henriksson L, Torén K. 1999. Exhaled nitric oxide among pulpmill workers reporting gassing incidents involving ozone and chlorine dioxide. *Eur Respir J* 14:828–831.
- Punnett L. 1996. Adjusting for the healthy worker selection effect in cross-sectional studies. *Int J Epidemiol* 25:1068–1076.
- Salisbury DA, Enarson DA, Chan-Yeung M, Kennedy SM. 1991. First-aid reports of acute chlorine gassing among pulpmill workers as predictors of lung health consequences. *Am J Ind Med* 20:71–81.
- Tarlo S. 2000. Workplace respiratory irritants and asthma. *Occup Med* 15:471–483.
- Teschke K, Smith JC, Olshan AF. 2000. Evidence of recall bias in volunteered vs. prompted responses about occupational exposures. *Am J Ind Med* 38:385–388.
- Torén K, Blanc PD. 1997. The history of pulp and paper bleaching: Respiratory health effects. *Lancet* 349:1316–1318.
- Torén K, Hermansson B-A. 1999. Incidence rate of adult-onset asthma in relation to age, sex, atopy, and smoking. A Swedish population-based study of 15,813 adults. *Int J Tuberc Lung Dis* 3:192–197.
- Torén K, Brisman J, Järvholm B. 1993. Asthma and asthma-like symptoms in adults assessed by questionnaires: A literature review. *Chest* 104:600–608.
- Winder C. 2001. The toxicology of chlorine. *Environ Res* 85:105–114.