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

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Abstract
Objective—The aim was to determine the prevalence of persistent respiratory symptoms and bronchial hyper-responsiveness due to reactive airways dysfunction syndrome in a population of construction workers at moderate to high risk of developing the syndrome, at an interval of 18 to 24 months after multiple exposures to chlorine gas during renovations to a pulp and paper mill.

Design and participants—71 of 289 exposed workers (25%) were identified on the basis of an exposure and the onset of respiratory symptoms shortly after this event (moderate to high risk). A standardised respiratory questionnaire was first presented, followed by spirometry and a methacholine inhalation test on those whose questionnaire suggested the persistence of respiratory symptoms.

Results—64 of 71 (90%) subjects completed the respiratory questionnaire at the time of the follow up. The questionnaire suggested a persistence of respiratory symptoms in 58 of the 64 workers (91%). Of the 58 subjects, 51 underwent spirometry and assessment of bronchial responsiveness. All of them used bronchodilators as required (not regularly) and four required inhaled anti-inflammatory preparations. Sixteen had bronchial obstruction (forced expiratory volume in one second (FEV1, < 80% predicted) and 29 showed significant bronchial hyper-responsiveness.

Conclusion—Of the subjects (n = 71) who were at moderate to high risk of developing reactive airways dysfunction syndrome after being exposed to chlorine and were seen 18 to 24 months after exposure ended, 58 (82%) still had respiratory symptoms, 16 (22%) had evidence of bronchial obstruction, and 29 (41%) had bronchial hyper-responsiveness.

Occupational and Environmental Medicine 1994;51:225–228

Occupational health hazards at pulp and paper mills include exposure to irritant gases such as chlorine, chlorine dioxide, hydrochloric acid, sulphur dioxide, and hydrogen sulphide. The dangers of chlorine inhalation are well documented. In 1985, Brooks et al described a new condition that they called reactive airways dysfunction syndrome, the symptoms of which are the onset of cough, shortness of breath, and wheezing after a single inhalational exposure to high concentrations of toxic products. This condition, which is also referred to as irritant induced asthma, is characterised by the presence of asthma like symptoms and non-specific bronchial hyper-responsiveness in subjects who have no previous history of asthma. Others had previously described a similar type of syndrome after toxic inhalation and more recent case reports have been published. Several products can cause this syndrome—for example, chlorine, ammonia, acid fumes and sulphur dioxide.

The natural history in terms of the persistence of symptoms and bronchial hyper-responsiveness among subjects who were repeatedly exposed to high concentrations of chlorine is uncertain. Some cross sectional surveys in pulpmills show either no or only slight airway obstruction in workers chronically exposed to chlorine. Follow up studies of workers accidentally exposed to chlorine show the persistence of airflow obstruction and functional respiratory changes only in a few of them although a larger proportion of subjects can be left with persistent bronchial hyper-responsiveness. Kern investigated 56 workers who had been exposed to high concentrations of glacial acetic acid. Only 24 of them (47%) underwent a methacholine inhalation test eight months after the accident, and the author found a dose dependent relation between the magnitude of exposure and the likelihood of persistence of bronchial hyper-responsiveness. The effect of treatment, in particular, anti-inflammatory preparations (oral and inhaled steroids), is also unknown.

The aim of this study was to assess the prevalence of persistent respiratory symptoms and bronchial responsiveness in a group of 71 construction workers at a pulpmill who were at moderate to high risk of developing...
reactive airways dysfunction syndrome 18–24 months after repeated exposure to chlorine, as was ascertained in another study. This study, which included 257 workers (participation rate of 97%) involved in welding and pipefitting procedures in the bleach plant where chlorine gas puffs were released, showed that 78% of them experienced throat irritation, 77% eye irritation, and 67% cough. A flu-like syndrome with a mean duration of 19 days occurred in 63% of subjects. Dyspnoea was significantly more common in subjects who had reported at least once to the first aid station.

Materials and methods

SUBJECTS
From the initial population of 289 exposed workers, we selected 71 subjects (25%) for medical follow-up at 18 to 24 months after the initial investigation (figure). The selection was based on the fact that there seems to be a dose-dependent relation for the risk of developing respiratory airways dysfunction syndrome and on the initial questionnaire, which showed these subjects to be at moderate to high risk of being affected with this syndrome. Those at moderate to high risks had: (1) in the case of moderate risk, either shortness of breath on exertion after the exposure period ended but no longer present at the time of the initial assessment (one month after the event) as well as significant other medical conditions, and/or age > 50; (2) in the case of high risk, persistent shortness of breath one month after the accidental exposure and/or abnormal lung sounds.

QUESTIONNAIRE
A trained interviewer gave a questionnaire derived from the International Union against Tuberculosis and Lung Diseases (IUATLD). Also, information was gathered on acute symptomatology and number of accidental exposures while the workers were employed (three to six month interval).

SPIROMETRY AND ASSESSMENT OF NON-SPECIFIC BRONCHIAL RESPONSIVENESS
Spirometry was assessed according to the criteria of the American Thoracic Society. A methacholine inhalation test was carried out according to a standardized method (output of the nebuliser = 0.14 ml/min). The concentration of methacholine causing a 20% fall in forced expiratory volume in one second (FEV,) (PC20) was interpolated from the individual dose-response curve drawn on a semi-logarithmic scale.

ANALYSIS OF RESULTS
Reference values for spirometry were obtained from Knudson and coworkers. PC20 levels > 16 mg/ml were considered to be normal.

STATISTICAL ANALYSIS
A comparison was made between functional results and various demographic and clinical data using a χ² distribution and unpaired t tests. A p value < 0.05 was considered significant.

RESULTS
As shown in the figure 71 workers at risk were identified and approached for the follow-up assessment. Seven were unavailable. The questionnaire suggested a persistence of respiratory symptoms in 58 workers (82%). Fifty-two of the 58 workers with a questionnaire suggestive of persistent respiratory symptoms agreed to undergo spirometry and methacholine inhalation testing. The other six subjects were unavailable.

The table lists some relevant anthropometric, clinical, and functional characteristics of subjects with significant airways obstruction and bronchial hyper-responsiveness. Only four subjects had taken or were still taking inhaled anti-inflammatory medication (corticosteroids) at the time of the survey. Sixteen subjects (23%) still had bronchial obstruction and 29 (41%), bronchial hyper-responsiveness. Neither age, smoking habits, number of accidental exposures nor initial symptoms differed between those with and without airway obstruction. The same applies to subjects with and without significant bronchial hyper-responsiveness. As expected, a previous history of asthma was found more often among subjects with airway obstruction or hyper-responsiveness. These subjects also tended to require more inhaled anti-inflammatory preparations. As expected, those with a lower PC20 had significantly lower baseline FEV1 and about half the subjects in this category (15 of 29, 52%) had an FEV1 < 80% predicted. Only one subject with normal bronchial responsiveness had an FEV1 value lower than 80% predicted.

The number of visits to a hospital emergency room was a significant predictor of the
likelihood of being left with persistent bronchial hyper-responsiveness. The mean number of visits to the hospital was 0-7 (SD 1-3) among subjects with persistent bronchial hyper-responsiveness as opposed to 0-07 (0-27) in those without bronchial hyper-responsiveness (t = 2-4, p = 0-02). There was also a difference of borderline significance in the number of subjects who had been to an emergency room because of breathing problems after inhaling chlorine at work—namely, 12 subjects in the methacholine positive group as opposed to only three in the methacholine negative group (x^2 = 3-4, p = 0-06).

Discussion
In 1985, Brooks et al. labelled a syndrome which consisted of persistent asthmatic symptoms with airway obstruction or hyper-responsiveness among subjects who had been exposed to high levels of irritant gas and aerosol, reactive airways dysfunction syndrome. This is now included in one definition of occupational asthma. The functional behaviour of subjects exposed to high concentrations of irritant gases such as chlorine has not previously been exhaustively investigated through a combination of spirometry and bronchial responsiveness. From a cohort of 289 workers who had been exposed to chlorine 18 to 24 months before, we identified 71 workers who were judged to be at high or moderate risk based on clinical history and physical signs (chest auscultation). Ideally, we would have been interested in investigating the entire cohort of 289 workers. Workers moved back to their original areas, however, after having worked for three to six months in the plant where repeated exposures to chlorine occurred. This means that they were dispersed over various parts of Quebec. This precluded using all subjects in the follow up survey. We were nevertheless able to question most of the subjects judged to be at moderate to high risk (64 of 71, 90%) 18 to 24 months after exposure ended. Most were still symptomatic. Spirometry and bronchial responsiveness could be assessed in 51 of the 58 subjects (88%), so the participation rate was satisfactory. It is therefore unlikely that results of our study could have been biased by a lack of participation. We found that 16 of 51 (31%) of those who underwent objective testing (23% of the selected group of 71 subjects) had airways obstruction. Few data on the long term functional behaviour of reactive airways dysfunction syndrome have been published. Kaufman et al. found that four of 14 subjects (22%) had persistent airways obstruction 12 to 14 months after inhaling chlorine. Charan and coworkers found that three of 11 (27%) workers exposed to chlorine had airways obstruction about two years later. Schwartz et al. reported that about 40% of subjects accidentally exposed to high concentrations of chlorine had airways obstruction two years after the event. Therefore, the proportion of subjects with persistent airways obstruction in our study (31% or 23% depending on the denominator) is close to that previously found in smaller groups of subjects.

To the best of our knowledge, only two other studies have examined bronchial hyper-responsiveness after acute exposure to irritant gas. Data were obtained in smaller groups of subjects and at different time intervals after the irritant inhalation. Bronchial hyper-responsiveness is a key feature of asthma. In most instances, bronchial hyper-responsiveness to pharmacological agents such as histamine or methacholine is still present in asthmatic subjects when there is no bronchial obstruction. We found that although 16 subjects had bronchial obstruction, a greater proportion (29 subjects or 41% of the 71 subjects) still had bronchial hyper-responsiveness. This figure has to be compared with three of 13 subjects (23%) and nine of 24 subjects (38%) who underwent bronchial response testing 12 years and eight months respectively after being exposed to chlorine and acetic acid. The fact that all but four of our subjects had never taken anti-inflammatory preparations (inhaled corticosteroids) at the time of the follow up might reflect the natural history of reactive airways dysfunction syndrome. Anti-inflammatory preparations may have affected the behaviour of the condition. It is unlikely that smoking affected our results as there were no differences in the distribution of smokers, ex-smokers, and non-smokers among those with and without bronchial

### Table: Anthropometric and clinical data according to results of spirometry and bronchial responsiveness to methacholine

<table>
<thead>
<tr>
<th>FEV1: percentage of predicted value</th>
<th>PC20</th>
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<tr>
<td>≥ 80%</td>
<td></td>
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<tr>
<td>Number</td>
<td></td>
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<tr>
<td>Age (y, mean (range))</td>
<td></td>
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<tr>
<td>Smoking habits:</td>
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<tr>
<td>Smokers/ex-smokers/non-smokers</td>
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<tr>
<td>History of asthma</td>
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<tr>
<td>Accidental habits:</td>
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<tr>
<td>FEV1 value (mean * number of resp. (t), bronchial lesms after number visits)</td>
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<tr>
<td>Medication:</td>
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<tr>
<td>Bronchodilators only</td>
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<tr>
<td>Bronchodilators + anti-inflammatory drugs</td>
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<td>Accidental exposures (mean (range))</td>
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<tr>
<td>Initial symptoms of dyspnoea:</td>
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<tr>
<td>Initial symptoms of cough:</td>
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<tr>
<td>Initial symptoms of dyspnoea and/or cough</td>
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<tr>
<td>FEV1 value (mean (SD))</td>
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<td>FEV1 (n &lt; 80% predicted)</td>
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* x^2 = 6-0, p = 0-01; † x^2 = 11-1; p < 0-001; ‡ x^2 = 3-8, p = 0-05; § x^2 = 3-3, p = 0-07; ¶ r = 4-0, p = 0-001; ** x^2 = 4-2, p < 0-001.
obstruction or hyper-responsiveness. We were unable to detect a difference in the number of acute symptomatic accidental exposures (referred to as puffs by the workers) and the presence or absence of bronchial obstruction or hyper-responsiveness. It is known that repeated exposure to high concentrations of chlorine can occur in paper mills. The number of accidental exposures is not necessarily related, however, to the likelihood of developing more functional sequelae. One large exposure may be as harmful as several smaller but still symptomatic episodes. The fact that all the subjects included in this survey experienced symptoms of cough or dyspnoea at the time of the initial exposure underlines that they had experienced at least one episode of acute accidental exposure. We were able to assess the severity of episodes by distinguishing between those that required a visit to the emergency room and those that did not. Subjects who had been to a hospital emergency room were more likely to be left with permanent bronchial hyper-responsiveness. The severity, therefore, of one or other of several episodes may be a more significant determinant of the likelihood of developing permanent functional sequelae than the number of episodes.

Many questions related to acute exposure to chlorine are still not answered. The physiological pathology of the reaction is still unknown. A recent study suggests that lymphocytic infiltration of the bronchial layers, denudation of the mucosa, and thickening of the basement membrane are key pathological features. Subjects with reactive airways dysfunction syndrome also seem to show less reversibility after inhaling a bronchodilator (β2 adrenergic agent) than subjects with occupational asthma with a latency period—that is, those who become progressively sensitised to a high or low molecular weight product. The effect of anti-inflammatory preparations on reactive airways dysfunction syndrome is unknown. An animal model would be useful in answering these questions. Finally, the time course of functional sequelae has yet to be described. In this respect, changes in airway calibre and bronchial responsiveness that were documented 18 to 24 months after the end of exposure in this study may well not be permanent. A longer follow up is necessary to examine this specific point.

We thank medical student Josée Jetté for collecting the information. We are grateful to Katherine Tallman for reviewing the manuscript. J. L. Maio is a senior researcher with the Université de Montréal School of Medicine and the Fonds de la recherche en santé du Québec.