Relationship of asthma to irritant gas exposures in pulp and paper mills

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Abstract The potential of chronic or acute irritant gas exposures to cause asthma or a variant condition, reactive airways dysfunction syndrome (RADS), was investigated by observing asthma incidence in a large working population, using person-years at risk (P-YR) to compute relative rates (RR). Health data came from employee examinations at 62 pulp and paper plants. The 39122 workers who denied asthma beginning before the observation period included: 19326 denying irritant exposures, with no gassing exposures; 19349 with self-reported irritant exposures, and no gassing; and 447 with documented gassings. Asthma was defined as self-reported asthma beginning after the start of observation. P-YR accrued from September 29, 1986, for the nonexposed and exposed workers, and from date of first gassing for gassed workers, and ended with disease onset in any who developed asthma. RR of asthma with 95% confidence intervals (CI95) were calculated for the exposed and gassed groups, relative to the nonexposed. Exposed (nongassed) workers had an elevated asthma rate, RR = 1.48, CI95 = 1.17 – 1.86, after adjustment for effects of gender and number of examinations. The rate in gassed workers was not significantly elevated: RR = 1.95, CI95 = 0.75 – 5.08. Of the five asthma cases occurring after gassings, none conformed to diagnostic criteria for RADS. Chronic exposures were associated with increased rate of asthma onset, which must be interpreted with caution because self-reported data defined both exposure category and disease. Documented gassings were not associated with significantly increased rate, and none of 447 gassed persons developed RADS. © 2002 Elsevier Science Ltd. All rights reserved. doi:10.1053/rmed.2002.1475, available online at http://www.sciencedirect.com

Keywords asthma; irritants; chlorine.

INTRODUCTION

The abundant industrial irritants, such as chlorine, ammonia, sulfur dioxide, phosgene, and oxides of nitrogen, have long been recognized as capable of producing permanent, gross structural damage of lungs and airways. Publications on this subject date from the early 1900s and generally document bronchiectasis or obliterative bronchiolitis as potential residuals of acute life-threatening injuries (1–7). Lung function abnormalities, when described, are usually fixed or progressive.

The more recent appreciation of bronchial inflammation in the pathogenesis of asthma has led to interest in so-called irritant-induced asthma and a variant termed “reactive airways dysfunction syndrome” (RADS) (8–17). The latter term is often applied to patients whose acute (or repeated) irritant exposures do not result in permanent structural damage. Airways obstruction may be spontaneous or intermittently provoked by non-specific environmental stimuli, or even (in some cases of RADS) documented only during methacholine or histamine provocation testing. This recent literature, however, consists almost exclusively of either retrospective surveys or case reports. Retrospective surveys are highly sensitive to bias in recall of exposure; persons with symptoms, possibly from other causes, are more likely to remember and report irritant gas exposures. Case reports are open to clinical bias, since they start with identification of symptomatic persons, and, lacking controls, assume that the factor of interest was the cause. Neither approach can prove cause and effect, nor furnish estimates of incidence or risk.

If acute exposures, short of those producing gross structural damage, cause an asthma-like condition, then
persons gassed with potent irritants should experience a higher incidence of asthma. It has also been suggested that an elevated incidence of asthma might be expected in persons experiencing chronic or intermittent but low-level exposures. The present study was undertaken to examine these hypotheses in a large population at risk, using premorbid reports of chronic irritant exposures and prospective ascertainment of gassing incidents.

**MATERIALS AND METHODS**

The target population was all workers examined under a standardized respiratory health surveillance program at 62 participating U.S. pulp and paper plants. Periodic examination is accomplished through the Tulane Pulmonary Surveillance Network, which was established in the mid-1980s to provide remote manufacturing facilities with standardized respiratory health data collection (18). This network utilizes medical work stations (Infodyne Systems Incorporated, Colorado Springs, CO), located at the plant sites, to standardize data collection methods and transmission. In addition, the health screenings are administered on site by nurses and technicians who have successfully completed a training course in spirometric testing (approved by the U.S. National Institute of Occupational Safety and Health), supplemented by instruction in standardized questionnaire administration. The data utilized in this study include: (1) identifying data and age, height, sex, race, weight, plant, test date and time; and (2) the responses to the administered, screen-scrolled respiratory and occupational questionnaire that is a modified version of that recommended by the ATS Epidemiology Standardization Project (19).

Since 1986, medical personnel at the mills have been trained to report the specifics of any accidental gassing. Reporting is required when any individual is examined in the medical department because of a reported chemical exposure. The information recorded on a standardized form includes the specifics of the incident (date, time, location, chemicals or materials handled, exposure time, percent time with respiratory protection and type of respiratory protection); the post-gassing clinical findings (cough, wheeze, vomiting, cyanosis, shock); the medical disposition at the time of initial treatment; the date and time of 1 week and 2 week post-gassing followup spirometric tests (these tests are transmitted through the network); and any respiratory complaints at the follow-up testings.

The target population comprised 47,757 workers who were examined between September 1986 and February 1998. The first documented gassing occurred on September 29, 1986, and this date is the start of the study's observation period. The study population was constituted retrospectively, using information from the latest questionnaire for most subjects and the questionnaire at which asthma was defined for those who developed asthma. We excluded all workers in whom there was a history of asthma developing either before the age of 18 years or before the September 1986, start of the incident reporting and followup program described above. We also excluded any with missing data for age, sex, race, or past exposure history. The population was further limited to subjects between the ages of 18–65 years at first observation. Finally, workers who were not gassed and who denied low-level irritant exposures were also excluded from a reference group if they reported certain past occupational exposures, described below. The exclusions resulted in a final study population of 39,122 workers. Of these workers, 72% were employed at plants with bleaching and/or pulping operations, with most of the remainder working at packaging facilities.

**DATA ANALYSIS**

In the 39,122 workers with neither juvenile onset asthma nor asthma starting before the observation period, rates of asthma acquisition were examined in three groups, the first two defined by their latest questionnaire responses about irritant and other exposures, and the third consisting of those identified through incident reports as having been gassed:

(1) The “nonexposed” group, who denied ever having occupational exposures to irritant chemicals or gasses. They also denied past exposures to other potentially injurious inhalants (“no” to questions about past work in foundries, mines, and quarries; in cotton textile mills; in sandblasting; or with asbestos). This group serves as a reference group for the two following groups.

(2) The “exposed” group, who affirmed occupational irritant chemical or gas exposures. These individuals could have answered either “yes” or “no” to questions about past work in foundries, etc. This group could include persons who had gassing exposures before, but not after, the 1986 initiation of the incident tracking program. Individuals in this group were asked the length of their exposure, which was then used as a continuous variable.

(3) The “gassed” group consists of all workers identified from September 29, 1986, onward, as subjects of the gassing incident reports. Individuals in this group could also have experienced gassing exposures prior to September 1986. Some of these workers spent time in the exposed or nonexposed groups prior to gassing, and others were first examined as a result of gassing.

Asthma was considered present in any subject who answered “yes” to the question “Do you have asthma?” even if he or she subsequently denied having asthma.
Those answering “yes” were also asked their age at asthma onset. Person-years at risk (P-YR) for the nonexposed and exposed groups began to accrue on September 29, 1986, or the date the worker reached 18 years of age, whichever came later. They ended at the individual’s latest examination, or the date of gassing or onset of asthma in those so affected. In the gassed group, P-Y-R commenced at the time of each individual’s first documented gassing and ended at the latest examination or the onset of asthma.

To eliminate transient respiratory responses after a gassing incident, a gassed worker was not considered to have asthma if the only affirmation was within one month of a gassing, with subsequent consistent denials. Note that this does not exclude subjects who might later report that their asthma began at or within one month of gassing. The only negation of the diagnosis would occur when a first report of asthma within 1 month of exposure was given by a subject who later always denied asthma.

Relative rates (RR) and 95% confidence intervals (CI95) for the outcome variable “asthma” were calculated for the exposed (chronic or gassed) relative to the nonexposed workers. RR was computed as the number of new cases divided by P-YR in the exposed or gassed groups, divided by the number of new cases divided by P-YR in the nonexposed group:

$$RR = \frac{\text{Cases}/\text{P-YR}}{\text{exposed or gassed}} \div \frac{\text{Cases}/\text{P-YR}}{\text{nonexposed}}$$

A Poisson regression model (20) was used to compute adjusted relative rates. The logistic procedure in SAS (21) accounting for person-years of followup was used to approximate Poisson regression and provide 95% Wald confidence intervals. Logistic regression provides a good approximation to Poisson regression when the incidence rates are less than 0.05, for large values of P-YR (22). Interactions among age, sex, race, and exposure group were included in the regression model.

### RESULTS

Table 1 shows the composition of the three exposure groups. There are 39,403 records, 31,025 of men and 8,378 of women. The excess of records over subjects (39,122 persons) occurs because 281 gassed subjects had previously contributed person-years in other groups (252 in the [chronically] exposed group and 29 in the nonexposed group). The gassed subjects eventually numbered 447, the 281 entering from the other groups and an additional 166 whose first examination was occasioned by a gassing exposure. Among those not gassed, there were similar numbers of workers in the nonexposed group (19,326) and the exposed group (19,349). Workers in the exposed group and the gassed group were somewhat older than those in the nonexposed group. This is to be expected, as aging increases the opportunities for both chronic irritant exposures and acute gasings.

Table 1 also shows asthma incidence, expressed as cases of new onset asthma per 10,000 person-years. The adverse experience of women is evident and persists in subsequent analyses.

The 447 workers in the gassed group, 425 men and 22 women, included 389 (87.0%) who experienced a single documented gassing, 38 (8.5%) who experienced two, and 20 (4.5%) who experienced three or more. Most of the gassed workers, 291/447 (65.1%), were exposed to chlorine (Cl₂) or chlorine dioxide (ClO₂) as the primary agent: 243 to Cl₂ and 48 to ClO₂. Of 389 experiencing a single gassing incident, 253 were exposed to Cl₂ or ClO₂ or both; one to both sulfur dioxide (SO₂) and Cl₂; 24 to SO₂ alone; and 112 to miscellaneous or unspecified inhaled. Of 38 with two gassings, 26 were exposed to Cl₂ or ClO₂ or both, as were 12 of the 20 workers with three or more gassings. Of the five gassed workers reporting subsequent NOA, each had experienced only one reported gassing: three were with Cl₂, one with ClO₂, and one with unspecified substance.

The complaints, observations and dispositions of the gassed workers were determined from the incident

### Table 1. Study population

<table>
<thead>
<tr>
<th>Exposure group</th>
<th>N</th>
<th>Age Mean ± se</th>
<th>P-YRb Mean ± se</th>
<th>Irr Exp-Yrs Mean ± se</th>
<th>Asthma incidencec</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nonexposed</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Men</td>
<td>13,053</td>
<td>35.9 ± 0.1</td>
<td>6.3 ± 0.0</td>
<td>—</td>
<td>96</td>
</tr>
<tr>
<td>Women</td>
<td>6,302</td>
<td>33.1 ± 0.1</td>
<td>5.8 ± 0.0</td>
<td>—</td>
<td>196</td>
</tr>
<tr>
<td>Exposed</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Men</td>
<td>17,547</td>
<td>41.6 ± 0.1</td>
<td>7.3 ± 0.0</td>
<td>14.2 ± 0.1</td>
<td>13.8</td>
</tr>
<tr>
<td>Women</td>
<td>2,054</td>
<td>35.7 ± 0.2</td>
<td>6.9 ± 0.1</td>
<td>6.2 ± 0.1</td>
<td>34.8</td>
</tr>
<tr>
<td>Gassed</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Men</td>
<td>425</td>
<td>47.3 ± 0.5</td>
<td>6.5 ± 0.2</td>
<td>21.3 ± 0.6</td>
<td>18.1</td>
</tr>
<tr>
<td>Women</td>
<td>22</td>
<td>399 ± 1.7</td>
<td>6.6 ± 0.7</td>
<td>74.1 ± 1.2</td>
<td>0</td>
</tr>
</tbody>
</table>

aExposure group definitions: nonexposed = self-reported absence of occupational exposures to irritant chemicals or gases; exposed = self-reported exposures to irritants; gassed = identified as such in medical department incident reports.
bP-YR: person-years at risk.
cCases of new-onset asthma per 10,000 person-years.
reports. The five who subsequently reported asthma were more likely than the other 442 gassed workers to have complained of cough (60% vs. 48%) and nausea (40% vs. 6%) and to have been found to have conjunctivitis (40% vs. 6%) and wheezing (40% vs. 7%). They were also more likely to have returned to work immediately after receiving first aid (80% vs. 31%). Of the ten workers referred for emergency room care, none developed asthma.

Tables 2 and 3 show, for men and women, respectively, those without and with asthma as they are distributed in the three exposure groups, and their mean age, percentages of whites and current smokers, P-YR, and age at asthma onset. P-YR were lower in the workers developing asthma because they ended at the time of asthma onset.

Table 4 presents the number of examinations by exposure group and asthma status. As expected, nonexposed workers have had fewer health screenings than the chronic exposure or gassed workers, many of whom are enrolled in a respiratory protection program because of opportunity for irritant exposures. The exposed and the gassed groups thus had increased opportunity to report asthma, relative to the reference group. Number of examinations was therefore tested as a potential explanatory variable.

Despite differences in frequency of examinations in each group, individuals who once reported asthma usually continued to do so, with average consistency rates of 77%, 68%, and 86.7% in the nonexposed, exposed, and gassed groups, respectively.

Table 5 presents the unadjusted RRs and CI95 of asthma in the exposed and the gassed groups, relative to the nonexposed reference group. For the exposed group the RR was significantly elevated at 1.26 (CI95 1.02–1.55). For...
the gassed group, the RR was elevated at 1.36 (CI95 0.56–3.31) but was not significant. Among the chronically exposed, women had a higher RR, 1.78, than did men, 1.45.

Multiple logistic regression models were fit to adjust relative rates for the potential effects of age, gender, smoking, race, and historical dust/fiber exposure in the chronic exposure group, and for their possible interactions with each other and exposure. Interactions and race were not significant and are not included in the reported models. Past dust/fiber exposure in the exposed group was not significant and is also not included in the reported models. In comparisons with never-smokers, current smoking had significant effect, and ex-smoking approached significance, in the exposed group. Number of examinations had a significant effect in the exposed group and was included.
Table 7: Effects of years of chronic or recurrent exposures to irritants on relative rate of asthma

<table>
<thead>
<tr>
<th>Variable</th>
<th>Adjusted RR</th>
<th>CI 95</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td>0.94</td>
<td>0.93–0.95</td>
</tr>
<tr>
<td>Gender</td>
<td>2.22</td>
<td>1.76–2.81</td>
</tr>
<tr>
<td>Current smokers*</td>
<td>1.35</td>
<td>1.07–1.72</td>
</tr>
<tr>
<td>Ex-smokers*</td>
<td>1.30</td>
<td>0.99–1.70</td>
</tr>
<tr>
<td>Number of examinations</td>
<td>1.12</td>
<td>1.07–1.16</td>
</tr>
<tr>
<td>Years exposed</td>
<td>1.03</td>
<td>1.02–1.04</td>
</tr>
</tbody>
</table>

Table 6 presents the logistic regression results, with asthma RRls adjusted for age, gender, smoking, and number of examinations. The effect of exposure in the chronic exposure group was significantly elevated: RR = 1.46 (CI95 1.16–1.83). The gassed group’s exposure RR was elevated, 1.68, but did not approach significance (CI95 0.64–4.35). Years worked with reported irritant exposures was included in the logistic regression model to examine for an exposure–response relationship. Table 7 presents the results and indicates that, after adjusting for age, gender, smoking, and number of examinations, the effect of years exposed on the acquisition of asthma was small, but it attained statistical significance.

**DISCUSSION**

Bleach gases, and chlorine in particular, are known to produce chronic effects, in the form of increased bronchial symptom prevalence, and acute injuries with variable persistence of symptoms (23,24). In the present study, the relative risk of developing asthma was significantly elevated in the workers reporting chronic or recurrent exposures to irritants and who were not subjects of gassing incident reports.

There are reasons for caution in assessing the observation. First, longer duration of exposure was associated with only a 3% increase in relative rate of new onset asthma. Second, individuals with nonspecific bronchial hyper-responsiveness (NSBH) from unrelated causes (e.g., preexisting allergy) tend to be more sensitive to and aware of airborne irritants, and could thus be expected to have a greater tendency to self-report into the category of chronically exposed. They also ought to be more likely to acquire the diagnosis of new onset asthma, either from a real effect of a cause unrelated to exposure (in this example, atopy) or from the effect of increased symptoms favoring the chance of an asthma diagnosis. Further followup of this population may provide additional information regarding the association between chronic irritant exposures and asthma.

Conversely, a healthy worker effect, in which sensitive or susceptible individuals declined to work in irritant-exposed jobs, or transferred out of them, would hinder the detection of an association between chronic exposures and disease. If this occurred, the significant association observed here underestimates the true magnitude of the effect.

Strengths of the current study include cohort enumeration based on employment-related risk of chronic or acute exposure; population size and length of observation; determination of claimed or denied chronic exposures, and denials of prior asthma, before development of asthma; and documentation of all gassings that resulted in medical department visits in the period of observation.

An obvious limitation of this study, imposed by the large number and scattered geographic distribution of the subjects, is the reliance on self-reported asthma. The whole question of how to define asthma in epidemiological studies has been considered in a recent review, whose authors conclude that “a single definition of asthma will not be applicable to all studies,” and that “the method of choice for the first phase of prevalence comparisons is a standardized…questionnaire” (25).

The questionnaire ascertainment of irritant exposures could potentially be enhanced by environmental measurements. Most of the subjects, however, are in jobs or plant areas that do not require exposure monitoring, and most of the rest are exposed to multiple irritants. There exists no useful set of environmental measurements for this study, and there is no reasonable hope of acquiring them on a scale that would be helpful. The observation that the gassed subjects drawn from the other two groups were almost nine times more likely (252 vs. 29) to have come from the exposed group lends some confidence to the accuracy of reporting. Another potential problem is the possibility that workers developing asthma would leave the industry. The larger mean numbers of examinations of asthmatics than nonasthmatics, in both the nonexposed and exposed groups, suggests that this was not a large problem. We cannot, however, identify participants who might have left after their latest examination. Enough remained, though, to demonstrate a statistically significant association with chronic exposure. Attrition rates among those reporting asthma in this population can be meaningfully assessed only after longer followup.

A recent study of chlorine-exposed workers in a metals plant provides some indirect support for acute irritant gas exposure as a risk factor for irritant-induced asthma or RADS (26). Serial observations showed increasing methacholine responsiveness and some symptoms (not “asthma” per se) associated with either documented or self-reported “puffs” of chlorine. Longitudinal declines in FEV1 were “related to accidental chlorine
inhalation, mostly among heavy smokers," but this was based on the self-reported puffs, and the lung function declines were computed over only 2 years. An earlier study in pulp mill workers showed significant increases in work-related respiratory symptoms and declines in airway function (over eight years) associated with gas-sings that were reported to first aid (27). But, "Accidental chlorine exposure was not significantly related to chronic bronchitis nor with reported asthma (positive response to the question: 'Have you ever had asthma?')". A recent study of pulp mill workers, exposed now to ozone and formerly to ClO₂, found greater prevalence among the smokers, in comparison to ozone-exposed but nongassed workers (28).

It should be noted that the published retrospective studies of irritant-induced asthma or RADS lack pre-exposure methacholine data. They also often lack documentation of prior asymptomatic status, the latter a crucial assumption when imputing current symptoms to a gassing exposure. And the literature on accidental irritant gassings contains no cohort or population exposures that are adequately quantified. In the present study, serial methacholine testing data would have been helpful to support asthma diagnoses or assess for respiratory injury but could not be accomplished, given the numbers and geographic separation of subjects.

In the present study, the relative rate of new onset asthma was elevated in the gassed workers, but not significantly so. Moreover, the observed nonsignificant elevation could be accounted for in part by self-selection, i.e., workers who have symptoms of preexisting respiratory allergy and NSBH, and are thereby at increased risk of asthma, would presumably also be more likely to report a gassing incident and seek medical attention. The liberal definition of asthma (any affirmation except in the initial evaluation period, irrespective of later denials), coupled with the more frequent examinations of the gassed workers, could also bias toward elevated RR. Finally, a criterion for the diagnosis of RADS is that (chronic) symptoms begin at or shortly after the causative exposure. But of the five gassed workers who subsequently developed asthma in this study, none reported asthma soon after gassing—on average, almost 4 years elapsed (range, 24–80 months) before subject-reported date of onset of asthma, despite the fact that the gassed group had the most frequent interviews.

There were 447 acutely gassed subjects who lacked prior asthma. It must be emphasized that these exposures were minor, in the sense of rarely requiring hospital referral or even convalescence time. But with only five subjects subsequently reporting asthma, none with onset closely related to the exposure, these results suggest that RADS or irritant-induced asthma is rarely an outcome of such gassings.

Acknowledgements
The authors are indebted to Annabelle R.N. Harris, who coordinated many of the activities that made this study possible. In addition, the authors gratefully acknowledge the excellent cooperation of the nursing staffs at the participating facilities, and Mr. Byron Lockhart, the coordinator of the Tulane Pulmonary Network Laboratory. This work was supported in part by the U.S. National Institute of Environmental Health Sciences, Grant #5 P42 ES05946-03.

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