Incidence of Asthma Among Aluminum Workers

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Exposures to respiratory irritants encountered in aluminum smelters in Europe, Australia, and New Zealand have been suggested as the cause of "potroom asthma." However, there remains disagreement in North America regarding the existence of this entity. This study was designed to assess whether asthma occurs excessively among potroom workers and if so, delineate dose–response relationships for possible causal risk factors. The asthma incidence ratio between potroom and nonpotroom workers after adjusting for smoking was 1.40. Although bivariate analyses showed a relationship between asthma incidence and exposure to total fluoride, gaseous fluoride, particulate fluoride, sulfur dioxide, and smoking, only the effects of gaseous fluoride (relative risk [RR] = 5.1) and smoking (RR = 7.7) remained significant in a multivariate model. Potroom asthma appears to occur at the studied U.S. aluminum smelters at doses within regulatory guidelines. (J Occup Environ Med. 2006;48:275–282)

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Exposure to fluorides and other respiratory irritants (airborne particulate and gaseous fluorides as hydrogen fluoride, sulfur dioxide, coal tar pitch volatiles, and dusts) encountered in aluminum smelters have been suggested as the cause of an asthma-like syndrome called "potroom asthma." Studies from Europe, Australia, and New Zealand have estimated the annual incidence of asthma in the potroom to be approximately 2% with prevalence as high as 10% in long-term workers.[1–6] Clinical observation and case reports of potroom workers have described asthma characterized by both immediate and late responses.[3,7] Furthermore, both irritant[3,8,9] and allergic[7,10,11] mechanisms have been reported as plausible disease pathways.

Work-related asthmatic symptoms and airflow limitation have been reported to be closely associated with duration of potroom employment.[2] Studies of aluminum potroom workers, which included detailed exposure assessment, have also demonstrated dose–effect relationships between current fluoride exposure and work-related asthmatic symptoms.[12,13] As with other causes of occupational asthma, follow-up studies of symptomatic potroom workers have shown that early removal from the potroom environment results in improvement in symptoms and decrease in bronchial hyperactivity. Workers who continue to be exposed for prolonged periods more often remain symptomatic after removal.[4,13–15]

Despite international evidence linking asthmatic symptoms with currently acceptable levels of fluoride exposure, there remains disagreement in North America regarding the existence of this entity, its cause, and the dose–

response relationship with potroom environments. In a health survey conducted in two aluminum smelters in New York, Kaltreider et al reported that the diagnosis of respiratory disorders, including asthma, made by history and objective measures of airway resistance was not different between potroom workers and controls.[16] In a cross-sectional study of North American aluminum workers, Discher and Breitenstein reported no difference in the prevalence of chronic respiratory diseases, determined by respiratory symptom questionnaires and spirometric measurements, between a group of current and former aluminum workers and matched controls of manual workers from a university and telephone company.[17] Chan-Yeung et al completed a health survey of aluminum smelter workers in British Columbia and reported that potroom workers had a significantly greater prevalence of respiratory symptoms and lower lung function than workers in the control group. However, they were unable to demonstrate potroom asthma.[18]

The U.S. Occupational Health and Safety Administration (OSHA) and National Institute for Occupational Safety and Health (NIOSH) have continued to support an occupational exposure limit (OEL) of 2.5 mg/m^3 for fluorides.[19,20] This OEL was designed to prevent fluorosis, an alteration of bone and teeth from chronic high-level fluoride exposure, and to protect against irritation of the eyes and respiratory tract. In contrast, based on the observed respiratory effects of fluoride exposure in aluminum production workers, the Norwegian government lowered its hygienic standard for total fluorides in 1996. Their current OEL is 0.6 mg/m^3, down from a previous OEL of 2.5 mg/m^3.[21] Most recently, the American Conference of Governmental and Industrial Hygienists (ACGIH) have adopted a threshold limit value (TLV-TWA) of 0.4 mg/m^3 for hydrogen fluoride to pre-

vent its irritant effects on the respiratory tract.[22]

Using administrative data from personnel, industrial hygiene and health claims records of 13 aluminum production facilities from a major aluminum manufacturer, the main objectives of this study are to answer the following questions: 1) is there more asthma in U.S. aluminum potroom workers than in other populations of aluminum production workers? 2) if so, what is the cause; and 3) if so, what is the dose–response relationship?

Materials and Methods

Alcoa Inc. (formerly the Aluminum Company of America), with a core business of mining, refining, and smelting aluminum, has almost 60,000 employees in the United States at several geographically dispersed sites. To support its operations, this company maintains a number of computerized data sets on its U.S. workforce. These sources of data include human resources, insurance claims (nonwork-related), medical surveillance, injury, and industrial hygiene records. Although they were originally collected separately and serve discrete purposes within the company, a system of encrypted unique identifiers has enabled the company, in collaboration with a research team from Yale University School of Medicine, to link the datasets into a unified database. This study used 7 years (1996–2002) of these health and workplace exposure data from 13 production locations including six smelters. The other seven locations include chemical production facilities, rolling mills, extrusion plants, a can reclamation facility, and a refinery.

The exposure data were obtained from the company's industrial hygiene exposure assessment software system "HYGenius." Random routine personal industrial hygiene samples of each chemical hazard of concern are obtained for each similar exposure group (SEG) to establish an exposure level for that SEG. A SEG

is defined as a group of employees who have similar job functions with similar exposure profiles and is described by the department, job, task, and exposure material at each location. Samples are not obtained if, after a qualitative exposure assessment, the plant industrial hygienist believes a SEG has only "insignificant exposure" defined as having no possibility under foreseeable circumstances of ever exceeding 30% of the company's occupational exposure limit. For all contaminants present, the sampling strategy requires a sufficient number of random short-term and/or time-weighted average samples to create a database that reflects the magnitude and variation in exposure for the SEG.

Although sampling occurred earlier, the industrial hygiene database contains all sampling measurements for exposure to total dusts beginning in 1977 and all sampling measurements for exposure to fluorides, CTPV, and SO$_2$, beginning in 1982, 1982, and 1984, respectively. In addition to the results of all personal samples, information contained in the HYGenius database for each sample result includes location name, department name, job title, task name, employee name and identification number, sample sampling date, sampling strategy exposure type, personal protective equipment used, agent identification, agent name, duration of sampling, and shift length. All air samples are acquired through personal monitoring in the breathing zone of employees outside of any personal protective equipment, thereby evaluating exposures without regard to the use of personal protective equipment. These personal samples are collected over the work shift and represent at least 70% of shift length. Short-term exposures with focus on specific tasks were also measured for SO$_2$ and HF. This is measured as a 15-minute short-term exposure rather than a true (instantaneous) peak.

The information obtained through sampling was entered into "HYGenius," which provided descriptive statistics

for each similar exposure group. Standard descriptive statistics include: number of samples, geometric mean, geometric standard deviation, range of sampling deviation, range of sampling results, and percent of samples exceeding permissible limits. In addition to routine measurements of each chemical of concern, several campaigns have been undertaken over the years to augment the database as part of efforts to better characterize exposures to fluorides and coal tar pitch volatiles.

The health insurance claims database allowed investigators to review physician diagnoses for each hospital and outpatient visit made by active male hourly employees at the 13 plants during the period under study (1996–2002). Only those employees who appeared at least once in the medical claims database during the 7-year period were eligible for inclusion in the study population. Medical diagnosis of asthma was determined by International Classification of Diseases, 9th Revision code of 493 in the insurance claims database as primary, secondary, or tertiary diagnosis on any single occasion. The individuals with a diagnosis of asthma at baseline were identified to establish the prevalence of asthma in the population. The "at-risk cohort" was defined as those individuals who were asthma-free for the first 2 years of study (January 1, 1996 through December 31, 1997) or, for employees hired after 1996, those who were asthma- free for the first 2 years after hire. These individuals were then followed until December 31, 2002, or the date of leaving employment to determine the annual incidence of asthma.

Medical surveillance records were maintained by plant medical departments, which typically serviced over 99% of all hourly employees at each site. As part of other ongoing research activities, a medical record abstraction project was undertaken to enter information contained in on-site plant medical records into a computerized database. Trained research assistants were sent to each study location from 1999–2002 to complete the abstraction process, which resulted in successful abstraction of medical records from 12 of the 13 locations included in this study population. Data obtained included date of examination, height, weight, education level, blood pressure, lipid profile, and smoking status. No clinical end points from plant medical records were recorded or used for this analysis.

Statistical Analysis

A linear regression of measured exposure levels by agent showed that there was no significant change in exposure for any of the agents over time except for CTPV, which showed a decline. Therefore, the assigned exposure for each SEG was the mean value of all the time-weighted average measurements taken for that SEG. However, for CTPV, the assigned exposure was the expected value based on the linear regression at the midpoint of the study (June 30, 2000). Values below the level of detection were set to zero. The incidence rate of asthma (per 1000 person-years) within a similar exposed group (SEG) was initially plotted against the 8-hour time-weighted average of total fluoride exposure for the SEG. Using the SAS version 8.02 generalized linear model procedure and incorporating a Poisson distribution, a log link function, and an offset equal to the natural log of person-years, the maximum likelihood estimate of the slope of the regression line was calculated. The same analysis was repeated for particulate fluoride, gaseous fluoride (HF), coal tar pitch volatiles, sulfur dioxide, and total dust. In addition, the incidence rate of asthma within a SEG was separately plotted against the short-term exposures of SO_2 and HF.

The association among the contaminants, personal risk factors, and asthma incidence rate was further evaluated with a multivariate generalized linear model incorporating a Poisson distribution and a forward selection criterion. All of the exposures listed here, as well as four covariates—age (as a continuous variable), ethnicity (white, non-white), smoking status (current smoker or not), and obesity (yes/no)—were included in the multivariate model. A 95% level of significance was required for a parameter to be incorporated in the model. Interaction among significant parameters was also evaluated to determine if there were any nonadditive effects.

Results

Figure 1 shows the derivation of study population through a schematic diagram. There were a total of 14,002 male hourly workers employed for at least 1 year at the 13 study locations between 1996 and 2002. Whites made up 86.12% of the population studied, 8.80% were black, 4.35% were Hispanic, 0.55% were American Indian, 0.16% were Asian/Pacific Islander, and 0.02% were of unknown ethnicity.

Of this group, 13,272 employees were enrolled in a noncapitated medical insurance plan, whereas 745 individuals were enrolled in an HMO for which no insurance claims data were available. Among the former group, 97% (12,918 employees) submitted at least one health insurance claim between January 1, 1996, and December 31, 2002, which indicated at least one physician encounter during this time; only these individuals were included in the study. Of the 12,918 individuals comprising the study population, there were 896 with a diagnosis of asthma at baseline (prevalence 6.9%). Therefore, the "at-risk cohort" was defined as the remaining 12,002 male hourly employees at the 13 locations for whom there were 46,672 person years of follow up during the 7-year study period. Potroom employees made up 10% of the study population with an average age of 43.7 years (standard deviation [SD], 10.1 years) and an average tenure of 16.1 years (SD, 10.8 years). The remaining 90% of the study population were employed in other aspects of alumi-
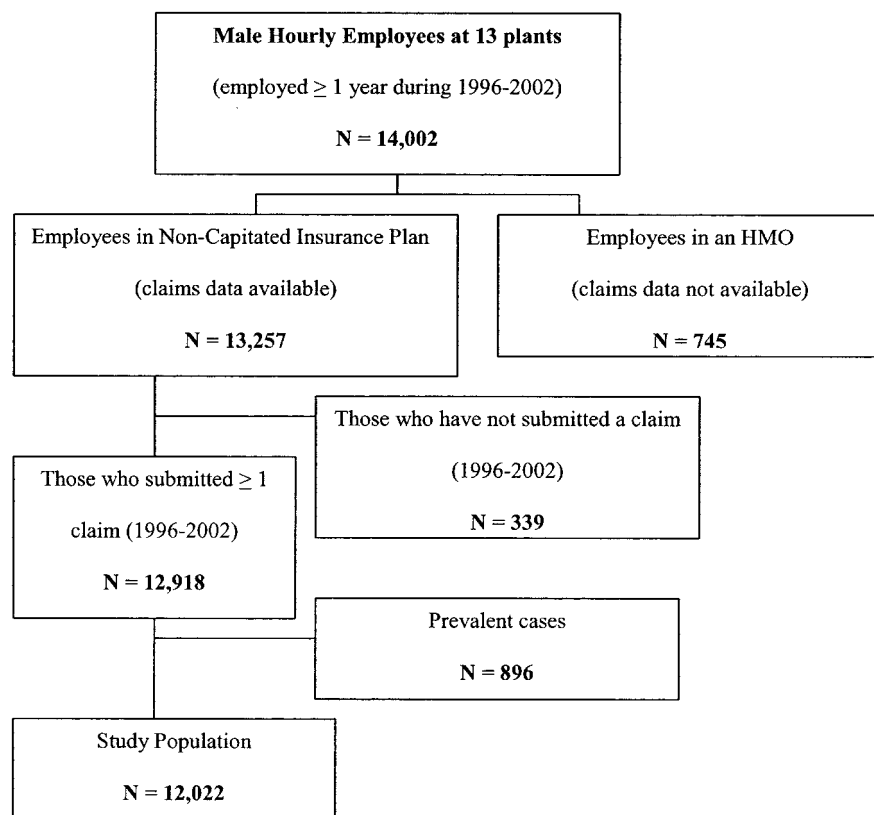
Fig. 1. Derivation of study population.

num manufacturing with an average age of 46.7 years (SD, 9.2 years) and an average tenure of 19.0 years (SD, 11.4 years).

We were able to obtain the current smoking status (a known risk factor for airway disease) for 5839 individuals representing 48.5% of the study population. Among these individuals, there were 4076 current nonsmokers and 1763 current smokers. In this study population, a smaller percentage of potroom workers were current smokers compared with nonpotroom workers.

Over the 5 years of follow up, there were 455 new cases of asthma diagnosed in the study population. The annual incidence rate of asthma among potroom and nonpotroom workers was 1.17% and 0.95%, respectively, with an incidence ratio (IR) of 1.24 (95% confidence interval [CI] = 0.93–1.63). However, after adjusting for smoking, the asthma incidence ratio between potroom

workers and nonpotroom workers increased to 1.40 (95% CI = 1.0–1.9), because a smaller percentage of potroom workers smoked compared with nonpotroom workers.

Table 1 shows the distribution of the various air contaminant measurements contained in the industrial hygiene database. The mean total fluoride level for exposed workers was 1.25 mg/m³. Particulate fluorides had a mean exposure level of 1.024 mg/m³, whereas gaseous fluoride (HF) had a mean level of 0.22 mg/m³. Based on this data, 82% of the total fluoride was in the particulate form, whereas 18% was in the gaseous form. Total dust, CTPV, and SO_2 had mean levels of 7.0 mg/m³, 0.09 mg/m³, and 0.45 mg/m³, respectively. The short-term HF exposure had a mean of 1.89 mg/m³, whereas short term SO_2 had a mean of 1.6 mg/m³. The average exposure to each of the contaminants was highest in the potrooms.

Figure 2 shows the raw data as well as the linear relationship between the incidence rate of asthma within each SEG and mean exposure level of each contaminant. Mean 8-hour averages for total fluoride, particulate fluoride, HF, and SO_2 each showed an apparent positive correlation with asthma incidence rate. Short-term HF and SO_2 exposures also showed a positive correlation with asthma incidence rate. The mean 8-hour averages for CTPV and total dust, however, did not show any relationship.

Table 2 shows effect estimates from Poisson generalized linear models. In

TABLE 1
Description of Specific Agents in the Industrial Hygiene Database (mg/m³)

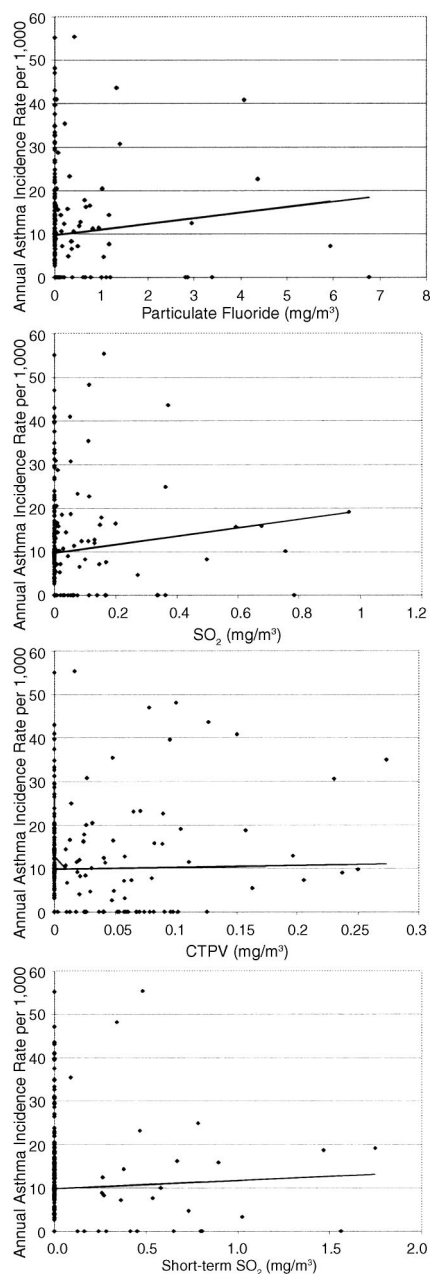| Agent	No. of Samples	Minimum	Maximum	Arithmetic Mean	Arithmetic Standard Deviation
Total fluorides	1903	0.0005	134.08	1.25	5.40
Particulate fluorides	2003	0.00016	134.00	1.02	5.26
HF	2014	0.00004	7.81	0.22	0.43
SO_2	1825	0.000026	36.81	0.45	0.40
CTPV	3676	0.00019	15.35	0.10	0.55
Total dust	8577	0	6576	7.03	85.10
Short term HF	1425	0.001	37.00	1.89	3.39
Short term SO_2	1259	0.0026	35.13	1.60	0.92

Fig. 2. Relationship between the incidence rate of asthma and exposure by agent (best fit line based on Poisson distribution).

the initial bivariate analyses, a strong relationship is observed between the incidence of asthma and the mean weighted average concentrations of gaseous fluoride (risk ratio, RR = 4.20; 95% CI = 2.1–8.5), sulfur dioxide (RR = 2.3; 95% CI = 1.1–4.6), and smoking (RR = 8.0; 95% CI = 3.3–19.4). The mean weighted average concentrations for total fluoride (RR = 1.15; 95% CI = 1.0–1.3) and particu-

late fluoride (RR = 1.11; 95% CI = 1.0–1.2) show weaker, although still significant relationships, whereas the mean weighted average concentrations of CTPV and total dust, mean short-term HF and SO_2 concentrations, obesity, ethnicity, and age show nonsignificant relationships.

Results of the multivariate generalized linear model are defined in the following equation:

$$Ln\ (predicted\ Asthma\ rate)$$
$$= -5.2558 + 1.6525\ (mean\ HF)$$
$$+ 1.7067\ (current\ smoker\ \%)$$
$$+ error$$

where error is random error, normally distributed with mean of zero and constant variance. In the multivariate model, only the effects of gaseous fluoride (RR = 5.1; 95% CI = 2.5–10.6) and current smoking (RR = 7.7; 95% CI = 3.2–18.9) remain significant. The RR of 5.1 for a 1 mg/m^3 change in HF is equal to an RR of 1.18 (95% CI = 1.09–1.3) per 0.1-mg/m^3 HF change. There was no interaction between hydrogen fluoride and smoking, indicating that both are independent risk factors for physician-diagnosed asthma in this dataset.

Discussion

The prevalence of asthma in our study population at baseline was 6.9%. The current prevalence of physician diagnosed asthma in adults in the United States has been estimated as 6.5% (6.1–6.9%)[23]; therefore, the asthma prevalence of our study population is approximately that of the national average, although we would have expected a lower prevalence of asthma in the study population as a result of the healthy worker effort.

The annual incidence of asthma observed in potroom workers in this study population was 1.17%. Studies in Europe, Australia, and New Zealand have reported a higher annual incidence of asthma in the potroom,[1,3–5,12] whereas other studies, mainly in North America, have either

been unable to demonstrate asthma or shown a lower incidence of asthma in potroom workers.[16–18] This observed difference could be related to the study design, employment selection criteria (eg, eliminating individuals with respiratory symptoms, history of atopy and asthma), healthy worker effects, exposure misclassification, different criteria used for definitions of asthma, and over- or underreporting of asthma symptoms in certain industrial populations.

Many studies of aluminum potroom workers have reported that irritants encountered in the potroom increase the risk of respiratory symptoms and asthma; however, most have not identified a specific etiologic agent.[1,3,11,18] Soyseth and Kongerud[13] reported a positive association between respiratory symptoms and particulate fluorides as well as gaseous fluorides. The effects of particulate and total fluorides were roughly of the same magnitude and showed borderline significance, whereas the effect of gaseous fluorides was weaker. These investigators also reported that exposure to particulates in the potroom increased the rate of decline in forced expiratory volume in one second (FEV_1), thereby increasing the risk for development of chronic obstructive lung disease in pot operators.[24] In a more recent study, Fritschi et al[25] reported that the agents associated with respiratory symptoms in aluminum smelters were total fluorides and inspirable dusts, whereas sulfur dioxide and coal tar pitch volatiles were less closely linked. In this study, we have demonstrated a significant relationship between mean gaseous fluoride exposure and the incidence rate of asthma. The effects of mean total fluoride, particulate fluoride, sulfur dioxide, total dust, and CTPV exposure were not statistically significant in our final multivariate model.

Acute exposures to high concentrations of respiratory irritants can cause reactive airways dysfunction syndrome (RADS) defined as the sudden onset of asthma after a high

TABLE 2
Relationship Between the Incidence of Asthma and Each Exposure/Variable (Poisson Regression Model)

Agent	Bivariate Analysis				Multivariate Analysis			
	Risk Ratio	Standard Error	Confidence Interval	P Value	Risk Ratio	Standard Error	Confidence Interval	P Value
Total fluoride	1.15	0.07	(1.02–1.30)	0.0209				
Particulate fluoride	1.11	0.06	(1.01–1.23)	0.0320				
HF	4.20	1.51	(2.07–8.50)	<0.0001	5.09	1.89	(2.45–10.56)	<0.0001
SO_2	2.25	0.88	(1.05–4.85)	0.0381				
CTPV	1.31	0.25	(0.91–1.90)	0.1444				
Total dust	1.00	0.01	(0.99–1.01)	0.9323				
Short term HF	1.17	0.10	(0.99–1.38)	0.0660				
Short term SO_2	1.13	0.25	(0.73–1.73)	0.5861				
Obese	1.82	0.89	(0.70–4.74)	0.2193				
Smoke	8.03	3.62	(3.32–19.44)	<0.0001	7.74	3.53	(3.17–18.90)	<0.0001
Age	0.99	0.01	(0.97–1.01)	0.2784				
White	0.99	0.01	(0.98–1.00)	0.0128				

level exposure to a corrosive gas, vapor, or fume.[26] Lund et al[27] demonstrated a transient but significant increase in respiratory symptoms as well as changes in lung function in volunteers after acute exposure to HF at concentrations known to occur in potrooms; however, they reported no additive effects when HF was combined with SO_2.[27] We were unable to show any significant association between short-term HF or short-term SO_2 and asthma incidence in our study population. However, the hypothesis that frequent short-term exposures to lower levels of airway irritants like HF resulting in higher time-weighted averages can result in low-level RADS remains a plausible mechanistic explanation for our findings and requires further investigation.[28,29]

Although some of the information on previous exposures accumulated for each individual before follow up began was available, we chose to use the current exposure at the time of diagnosis based on all available knowledge of the job being done at the time. The possibility exists that past exposures may be highly relevant and the cause of disease may be cumulative, but it is highly unlikely that omission of such a measure in the model would falsely increase the association between exposure and effect; quite the contrary, if cumulative

exposure was causal, estimating it by current exposure (and hence inducing misclassification) would drive the association toward the null.

One of the major limitations of this study, as in other epidemiologic studies of asthma, is the case definition of asthma. Three epidemiologic definitions of occupational asthma that have been found to be useful for research purposes include: 1) clinically recognized occupational asthma identified through physician reports or workers' compensation records, 2) asthma meeting a working definition of occupational asthma based on combination of exposure, symptoms, and physiological or clinical data; and 3) excess asthma occurrence among workers exposed to noxious agents as compared with referents.[30] Although most studies of asthma in aluminum workers have relied on a combination of symptom questionnaires, measurement of pulmonary function tests or measurements of nonspecific bronchial reactivity,[11,31,32] we relied on physician diagnosis for asthma. Although use of this case definition could underestimate the true incidence of asthma, especially in individuals with subclinical and mild asthmatic symptoms, most workers with symptoms of asthma severe enough to seek medical treatment would be identified. In these cases, physicians in the office or emergency room setting rely on symptoms

suggestive of asthma: shortness of breath, cough, chest tightness, and wheezing, presence of wheezing on examination, results of obstruction on office spirometry, and response to treatment (bronchodilators, inhaled steroids and systemic steroids). Likewise, the effect of discounting the first 2 years of exposure in new employees is very conservative and may have resulted in the exclusion of some cases of newly diagnosed asthma. On the other hand, the choice to identify disease by virtue of only one asthma diagnosis by the treating physician could lead to some overdiagnosis of asthma, especially in smokers and others with nonspecific respiratory complaints. However, when we examined the effects of a different algorithm for asthma diagnosis, using two diagnoses of asthma coded on at least at two separate visits during the study period, we had fewer cases of asthma but results remained unchanged.

Although diagnoses contained in the company medical surveillance database were available to investigators, these were not used to establish the diagnosis of asthma for several reasons. First, most of the employees in the study population were not included in the medical surveillance program because the trigger for medical surveillance is exposure to half of the occupational exposure limit (OEL) for at least 12 days a year.

Given that the current OEL for fluoride is 2.5 mg/m^3, few workers have exposures of sufficient magnitude to require inclusion in medical surveillance. Second, asthma symptoms may be underreported by workers concerned about work restrictions or reassignment to a less desirable job, or overreported because of heightened work concerns.

There are several known risk factors for asthma. These include atopy, history of childhood asthma, family history of asthma, ethnicity, smoking history, and obesity.[6,33,34] We examined the effects of smoking, ethnicity, and obesity in our study population. Information on smoking status was available for only 48.5% of the study population. Analysis of this subgroup showed a significant and independent risk of asthma in current smokers compared with nonsmokers. This observation is consistent with other studies in smelter workers that have reported a strong association between smoking and work-related asthmatic symptoms[12,13] and a decline in FEV_1.[24] Although this subset represents only half of the population, we believe that the availability of data, recorded routinely at required surveillance examinations, is random and the smoking pattern depicted is likely representative of the total population.

One of the study limitations resulted from our inability to examine host factors like history of atopy, family history of asthma, and childhood asthma because of the study design. However, there is no a priori reason to believe that these characteristics would be distributed in such a way as to cause the observed association. More likely, atopics and sensitive workers are underrepresented in the potrooms as a healthy worker effort, falsely lowering our estimates of relative risk.

In conclusion, potroom asthma appears to occur in the United States at the studied aluminum smelters. There was a significant statistical relationship between the incidence of asthma and the mean gaseous fluoride exposure in the study population, whereas the relationship between asthma incidence and the other contaminants was less significant. Previously shown in aluminum workers, smoking was also a significant and independent risk factor for asthma. Control measures to reduce fluoride exposure, focusing on gaseous fluoride, and strategies to reduce smoking, like prohibiting smoking in the workplace could, in theory, reduce the incidence of asthma in this population. The causal roles of frequent short-term exposures to HF and SO_2 in the potroom during certain activities require further investigation. Finally, this study also documents the use of health claims data linked with administrative exposure and personnel databases for the conduct of etiologic research in the workplace setting.

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