OBJECTIVES: Summarizing the knowledge status, including the morphology, possible etiological factors, and clinical expression of aluminum potroom asthma and chronic obstructive pulmonary disease related to aluminum potroom exposure. METHODS: A review of the literature from the last two decades as it appears in PubMed. RESULTS: There is substantial evidence for the existence of potroom asthma, although the incidence seems to decline over the last 10 years. Increased mortality from chronic obstructive pulmonary disease and longitudinal decline in forced expiratory volume in the first second of expiration has been shown in aluminum potroom workers. Morphological manifestations in bronchial biopsies and the inflammatory markers NO and eosinophils in airway tissue and blood are consistent with asthma in general. The causative agent(s) is (are) not known. Conclusions: Reduction of exposure and cessation of smoking seem to be the major preventive measures to avoid respiratory disorders in the aluminum industry.

A luminum is used in a broad range of merchandise and in industries like food packing, construction, and transportation, and associated industries. The production of aluminum has increased globally as a consequence of increased industrialization in many developing countries and emerging economies, as well as greater demand for aluminum products. Aluminum has now become the world’s second-most used metal after steel. Aluminum production is accompanied by emissions of dust and gases potentially harmful to the workers and the local environment. Despite enhanced safety measures such as partially shielding of the production cells (pots) and automating of previous manual work, there are probably still reasons to focus on preventive measures to avoid respiratory disorders in aluminum smelter workers. The aims of this review were to summarize the present knowledge of the occurrence of potroom asthma (PA) and other respiratory disorders in the aluminum industry, their pathophysiological manifestations, possible etiological factors, and clinical expression.

METHODS
Our group published, in 1994, a review article on aluminum PA and the Norwegian experience in this field, including an overview of the process of aluminum production involving electrolytic technology as well as types of exposures. The present article reviews and discusses primarily new knowledge achieved in the period 1993 until 2012 with regard to occupational asthma. In addition, we are reviewing the literature on lung function decline and chronic obstructive pulmonary disease (COPD) among the aluminum production workers. It was beyond the scope of this article to prepare a state-of-the-art critical review from this broad thematic area. Therefore, we performed a literature search limited mainly to PubMed, excluding non-English languages except two articles in Norwegian.

The search strategy intended to be broad to maximize the capture of citations of peer-reviewed publications. The following search strategy was conducted, using MeSH (Medical Subject Headings) terms: Asthma (refined with subheadings: etiology, epidemiology) OR Pulmonary Disease, Chronic Obstructive (refined with subheadings: epidemiology, diagnosis, etiology, mortality, physiopathology, pathology, prevention and control, radiography, rehabilitation) AND Occupational Diseases AND Aluminum. On the basis of their experience, two expert authors selected “valid” articles from a pool of 58 citations. In addition, we supplemented the citation pool through the manual assessment of the reference lists including other published reviews or single publications.

Cross-Sectional Studies

Symptoms
Until 1980, most studies of occupational asthma were single-case reports, descriptions of a number of cases, and prevalence studies. Probably because of the methodological insufficiency of prevalence and case studies, conflicting opinions developed as to the existence and number of PA cases. In an overview by Abramson et al, the prevalence of PA ranged from 0% to 14%. In a cross-sectional study among a random sample of a general population in a Norwegian county, Bakke et al found that the odds ratio (OR) of obstructive lung disease (ie, self-reported asthma or COPD) in subjects who had worked with aluminum production and processing was 2.7 (95% confidence interval [CI], 1.2 to 6.1) compared with subjects who had never worked in the aluminum industry (Table 1). The main limitation of this study is that the estimates were based on 40 exposed subjects. Thus, the results were very vulnerable to selection bias. Moreover, the details about the exposure were sparse.

Chan-Yeung et al investigated the prevalence of respiratory symptoms among 1510 employees in an aluminum smelter in British Columbia. The index group consisted of potroom workers (n = 797), of whom 495 workers spend more than 50% of their working time in the potrooms (high exposure), whereas 302 workers spend less than 50% of their working time in the potrooms (medium exposure). The remaining subjects worked in the casting departments or offices (references). The researchers found an increased prevalence of cough (22.6% vs 14.0%) and wheeze (17.1% vs 10.5%) in the high-exposure group compared with references (Table 1). They did not, however, find any subjects with PA. The choice of references could be questioned, because the environment in the casting house is partially shared with the potrooms. In a cross-sectional study among potroom workers in seven Norwegian aluminum plants, the prevalence of work-related asthmatic symptoms, that is, the combination of dyspnea and wheezing reducing during days off work, occurred in 15% of the workers with an exposure period of 10 years or more and in 8% of the workers who had been employed for less than 5 years. The OR for work-related asthmatic symptoms increased with increasing duration of exposure in the potrooms after controlling for sex, age, familial disposition for asthma, allergy, smoking, and use of airway protection (Table 1).

A cross-sectional study among 1529 male employees in two Australian aluminum smelters was conducted by Fritschi et al. In one of the plants, it was found that rhinitis was the only symptom reported more commonly by the potroom employees than by
administration employees. In the other plant, potroom workers had about five times greater odds of reporting each of the work-related symptoms than the administration group (Table 1). The likelihood for reporting work-related symptoms increased with time of employment among the potroom workers. The authors commented that the difference in results seen between the potrooms in the two different smelters may be a reflection of the age of the smelter, the type of respiratory equipment used, or the selection process for employees at the two different plants. In another article from this study, the authors found that subjects with the highest cumulative exposure to fluoride (more than 0.16 mg/m³ years) were two to four times more likely to report work-related wheeze and chest tightness than unexposed subjects.9

Another cross-sectional study conducted in a German aluminum smelter10 investigated the combined influence on the respiratory health of smoking and exposure in an aluminum potroom. No significant effects of potroom work on the prevalence of respiratory symptoms—that is, continuous trouble with breathing (prevalence ratio [PR], 2.5), repeated trouble with breathing (PR, 1.8), wheezing (PR, 1.4), asthma attack (ever) (PR, 2.8), and doctor-diagnosed asthma (PR, 2.6). The cast house is a work environment with quite different exposures than those being seen in the potrooms, although some of the probably important exposures for PA like HF, SO2, and fluoride salts are present in both settings, thereby supporting the evidence of an exposure health effect.

### Pulmonary Function

In a general population in Norway, Bakke et al4 found that the OR for airflow limitation, that is, forced expiratory volume in the first second of expiration (FEV1)/forced vital capacity (FVC) less than 0.7, was 1.5 (95% CI, 0.6 to 4.0), among subjects who had worked with production and processing in the aluminum industry compared with individuals who have never worked in the aluminum industry.4 In an aluminum smelter in British Columbia, Chan-Yeung et al5 found that FEV1 was higher among the references than the cast house (Table 1). Kongerud et al6 found that FEV1 was higher among the references than the administration employees. In the other plant, potroom workers had about five times greater odds of reporting each of the work-related symptoms than the administration group (Table 1). The likelihood for reporting work-related symptoms increased with time of employment among the potroom workers. The authors commented that the difference in results seen between the potrooms in the two different smelters may be a reflection of the age of the smelter, the type of respiratory equipment used, or the selection process for employees at the two different plants. In another article from this study, the authors found that subjects with the highest cumulative exposure to fluoride (more than 0.16 mg/m³ years) were two to four times more likely to report work-related wheeze and chest tightness than unexposed subjects.9

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### Longitudinal Studies

#### Symptoms

To our knowledge, our group conducted the first inception cohort study in the aluminum industry12 on the basis of questionnaires. The probability of developing dyspnea and wheezing was 7% for people who had never smoked and 23% for current smokers during the first 2 years of employment. Adjusting for possible misclassification of disease, these figures are reduced to 3% and 10%, respectively.

In 2006, Taiwo et al13 published the incidence of asthma among aluminum workers on the basis of a register study from Alcoa Inc in North America. This company maintains a number of occupational health programs for its employees. This program includes regular medical examinations, which were used to collect information about asthma incidence. Taiwo et al13 found that the incidence of asthma among aluminum workers was 2.9% (95% CI, 2.0% to 4.0%). The study was conducted in a large aluminum smelter in the United States. The authors found that the incidence of asthma increased with time of employment and that the risk was highest among workers who had worked in the potrooms. The incidence of asthma among workers who had never worked in the aluminum industry was 1.4% (95% CI, 0.7% to 2.3%). The authors also found that the incidence of asthma was highest among workers who had worked in the potrooms for the first 2 years of employment. Adjusting for possible misclassification of disease, these figures are reduced to 1% and 3%, respectively.
of computerized data sets on its US workforce, and the sources of data include human resources, insurance claims (non–work-related), medical surveillance, injury, and industrial hygiene records. This study was designed to assess whether asthma occurs excessively among potroom workers, and if so, to delineate dose–response relationship for possible causal risk factors. 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. Over the 5 years of follow-up, the annual incidence rates among potroom workers and nonpotroom workers were 1.17% and 0.95%, respectively, and the asthma incidence ratio between potroom and nonpotroom workers after adjusting for smoking was 1.40 (95% CI, 1.0 to 1.9).

Although bivariate analyses showed a relationship between asthma incidence and exposure to total fluoride, gaseous fluoride, particulate fluoride, SO2, and smoking, only the effect of gaseous fluoride (relative risk [RR] = 5.1 per mg/m3 gaseous fluoride) and smoking (RR = 7.7) remained significant in a multivariate model. Potroom asthma seemed to occur at doses within regulatory guidelines, and multivariate analyses showed that the asthma hazard ratio increased by 5.09 (95% CI, 2.45 to 10.56) per 1 mg/m3 increase of HF exposure (Table 2). Norwegian physicians are obliged to report occupational diseases to the Labor Inspection Authority, and the registration of this notification was used to study the cases of occupational asthma across all smelters combined at the start of the study was 6869, and at the last registration in 2006, there were a total of 5498 employees. The incidence of occupational asthma across all smelters combined was highest in 1992 at 9.46/1000/year declining to 0.36/1000/year in 2006, which is a 96.2% reduction in incidence. There were statistically significant correlations between the incidence rate of occupational asthma and geometric means of each of the following exposure variables: respirable particulate, total fluoride, gaseous HF, and particulate fluoride. The correlation coefficient (Spearman) was greatest for total fluoride (r = 0.5). There were also statistically significant declines in all exposure variables measured over the study period.

### Pulmonary Function

Longitudinal studies of pulmonary function among employees in the aluminum smelters are, however, sparse. Chan-Yeung et al17 followed up their cross-sectional study from 1980 to 1986. Among 985 employees who participated in both surveys, 560 (57%) did not change their exposure status. The overall annual decline in FEV1 (dFEV1) of 6.41 mL/year (mean initial age, 38.3 years). They

### TABLE 2. Longitudinal Studies: Symptoms

| Symptoms | N | Entity | Scale | Outcome | n | IR (10⁻³ yr) | Effect | Adjustments |
|----------|---|--------|-------|---------|---|-------------|--------|-------------|
| Kongerud and Samuelsen12 | 1301 | TotF | mg/m³ | WASTH | NA | NA | 3.35 (1.51–7.41) | Sex, age, smoking |
| Taiwoe et al13 | 12,022 | Gas HF | mg/m³ | D asthma | NA | NA | 5.09 (2.45–10.6) | Smoking |
| Donoghue et al14 | 5,944 | NA | Year: mg/m³ | PA | 16 | 2.69 |
| | 5,853 | — | 1997: 0.73 | — | 19 | 3.25 |
| | 5,789 | — | 1998: 0.50 | — | 11 | 1.90 |
| | 5,725 | — | 1999: 0.76 | — | 21 | 3.67 |
| | 5,583 | — | 2000: 0.83 | — | 16 | 2.87 |
| | 5,583 | — | 2001: 0.60 | — | 7 | 1.25 |
| | 5,622 | — | 2002: 0.39 | — | 10 | 1.78 |
| | 5,476 | — | 2003: 0.46 | — | 13 | 2.37 |
| | 5,475 | — | 2004: 0.37 | — | 4 | 0.73 |
| | 5,568 | — | 2005: 0.25 | — | 3 | 0.54 |
| | 5,498 | — | 2006: 0.37 | — | 2 | 0.36 |

ρ: Spearman rho; HF, hydrogen fluoride (gas); HR, hazard ratio; N, total number of subjects; n, number of incident cases; NA, not applicable; TotF, total fluorides; WASTH, work-related asthmatic symptoms, that is, the combination of dyspnea and wheezing improving on rest days.
found no association between dFEV₁ and exposure, but the difference in dFEV₁ between current smokers and never smokers was 11.6 mL/year \((P = 0.02)\). Because the longitudinal analyses were restricted to subjects who did not change their exposure status, the lack of exposure effect could be due to selection bias.

A follow-up of spirometry surveys among potroom workers was done at a Norwegian aluminum plant from 1986 to 1992. The workers were investigated annually, and annual estimates of exposure to particulates and fluorides were available. Smoking habits were also updated annually. An autoregressive regression model was applied to estimate the change in FEV₁ between two consecutive examinations. The mean and standard deviation of the time between two consecutive examinations were 12.0 and 0.6 months, respectively (Table 2). After adjustment for relevant confounders, the mean change in FEV₁ per mg/m³ exposure to particulates between two consecutive spirometries was \(-11.9\) mL \((P = 0.004)\) and \(-43.1\) mL \((P = 0.004)\) for smokers and nonsmokers. We have, however, not been able to find any study where the association between exposure measurements and the incidence of airflow limitation or COPD was explored in employees in the aluminum industry has been explored.

### Mortality Studies

Cause-specific mortality among aluminum employees has been investigated in two Norwegian and three Canadian studies (Table 3). The oldest cohort was investigated by Rønneberg. This study encompassed 1209 subjects who had been hired in a Norwegian smelter in 1922 or later. They should have died between 1962 and 1991 or still be alive in 1991. Death certificates were obtained from the Central Bureau of Statistics, where all deaths in Norway were registered during this period. Chronic obstructive pulmonary disease deaths were defined as deaths caused by chronic bronchitis, asthma, or emphysema. Analyses were restricted to subjects who had been employed for at least 3 years. An increased overall standardized mortality from COPD was found (Table 3), but they failed to find any dose–response relationship between mortality and the cumulative exposure to coal tar pitch and pot emissions (qualitative scale). This was, however, a small study encompassing 24,996 person-years and nine deaths from COPD. Data on smoking habits were not available.

In another Norwegian study, Romundstad et al investigated mortality from nonmalignant diseases among subjects who had been employed for 3 years or more in six Norwegian aluminum smelters (Table 3). Exposure data on total fluorides were available, and data on smoking habits were available in three of the plants. The underlying cause of death was defined as that from chronic bronchitis, asthma, or emphysema. Analyses were restricted to subjects who had been employed for at least 3 years. An increased overall standardized mortality from COPD was found (Table 3), but they failed to find any dose–response relationship between mortality and the cumulative exposure to coal tar pitch and pot emissions (qualitative scale). This was, however, a small study encompassing 24,996 person-years and nine deaths from COPD. Data on smoking habits were not available.

In a third Norwegian study, Friesen et al investigated mortality among employees in an aluminum smelter in British Columbia (Table 3). Employees in a power generating station were also included. Information about mortality was obtained from the Canadian National Mortality Database during 1957 to 1999. Chronic obstructive pulmonary disease deaths were defined as deaths caused by chronic bronchitis, asthma, or emphysema. It was not taken into account whether the diagnosis was taken as the underlying diagnosis of death or contributing cause of death. Smoking habits were available in 88% of the employees. Exposure was expressed as cumulative exposure to benz[a]pyrene. Standardized mortality rate was significantly lower in the exposed group than the general population, and in the internal analyses, no dose–response relationship between COPD mortality and benz[a]pyrene was found (Table 3). Nevertheless, the number of cases was small, and the mortality in the first tertile was lower than that in tertiles 2 and 3.

### Symptoms and Cases

In our previous review article, we described the typical symptoms of aluminum PA. Desjardins et al described, in a case report, aluminum PA confirmed by monitoring of FEV₁. A 35-year-old man, lifelong nonsmoker with no history of asthma or atopy, was hired by an aluminum plant that had begun its operation in 1986. Preemployment screening was normal. He worked with changing of anodes in a prepoke plant and experienced episodes of cough and dyspnea, which resolved during withdrawal from work in January and December 1991. He resumed work in the potrooms in March 1992, but his dyspnea recurred at work and at night with a 25% drop in peak expiratory flow rates (PEFs) associated with nonspecific bronchial hyperresponsiveness (NSBHR) (PC₂₀ histamine 1.0 mg/mL). Assessment of the bronchial response to the occupational exposure in potrooms revealed a pattern of dual asthmatic response, accompanied by a drop in PC₂₀ methacholine from 5.1 to 0.7 mg/mL.

Kongerud et al published an investigation of 14 potroom workers suspected of having asthma. They were examined by serial measurements of peak flow at home and work, symptoms diaries, and measurements of methacholine reactivity before and after a 3-week holiday. There was a good correlation between daily symptom scores and peak flow measurements; these showed changes characteristic of occupational asthma in 10 workers, with increased diurnal variation in peak flow and consistent deterioration in relation to work exposure. One further record showed probable occupational asthma, and two showed consistent small changes in peak flow related to work exposure more in keeping with an irritant effect. Only one record was inadequate. Methacholine reactivity on a workday was within the reference range in 9 of 13 subjects. A doubling of PC₂₀ methacholine occurred in five of nine subjects with occupational asthma in whom repeated estimations were possible.

In 2000, the first case of aluminum asthma in a foundry worker was reported. He had a positive specific challenge test to aluminum chloride, and the authors raised the possibility that PA is due to a reaction to aluminum fluoride. A 46-year-old smoker developed cough and chest tightness starting 3 hours after coming to work, and improving on days away from work. He had worked as a caster of molten aluminum for 19 years in the rolling mill. He was nonatopic on skin testing, baseline spirometry showed airflow obstruction, and he had moderate histamine reactivity. Two-hourly PEF measurements showed a significant occupational effect, and specific bronchial provocation testing showed a dual asthmatic reaction after 3-minute exposure to aluminum chloride (10 mg/mL) with a negative reaction to potassium chloride. After replacement, his bronchial...
| Study               | Exposure       | Scale | n   | OR of AFL | Effect          | Adjustments                                      |
|--------------------|----------------|-------|-----|-----------|-----------------|--------------------------------------------------|
| Cross-sectional    |                |       |     |           |                 |                                                  |
| Chan-Yeung et al5  | Potroom        | 495   | 3,913 | 3.913     |                 |                                                  |
|                    | Yes            | ≥50% (H) |     |           |                 |                                                  |
|                    | Yes            | <50% (M) | 3,966 | 3.966     |                 |                                                  |
|                    | No             | Unexposed (U) | 4,003 |           |                 |                                                  |
| Bakke et al4       | Al-production  | 658   | 39  | 1.5 (0.6–4.0) |                |                                                  |
| Kongerud et al7    | Potroom        | 1760  | NA  | 2.2 (1.4–3.5) |                |                                                  |
|                    | Duration of exposure, yr | Yes | 5–9 vs 0–4 | NA |                                                  |
|                    |                | Yes   | 5–10 vs 0–4 | NA | 2.6 (1.7–3.9) |                                                  |
| Longitudinal       |                |       |     |           |                 |                                                  |
| Chan-Yeung et al17 | Potroom        | 269   | 164 | 62.6      | H–U: −0.93; P = 0.60 | Age, smoke, initial FEV1 |
|                    | Yes            | ≥50% (H) |     |           |                 |                                                  |
|                    | 171            | <50% (M) | 114 | 67.5      | M–U: −1.24; P = 0.88 | Age, smoke, previous FEV1 |
|                    | 380            | No    | Unexposed (U) | 308 | 62.2      |                                                  |
| Søyseth et al18    | Tot part       | 630   | 265 | −11.9 mL/mg/m3 | P = 0.004 | Age, smoke, previous FEV1 |

AFL, airflow limitation; al-production, aluminum production or processing; dFEV1, annual decline in FEV1; FEV1, forced expiratory volume in the first second of expiration; ΔFEV1, mean difference of FEV1 between two consecutive measurements; N, the total number of subjects in the cohort; n, the total number of subjects in the analyses; NA, not applicable; OR, odds ratio; Tot part, total particulates.
In a separate cross-sectional study, which included a detailed exposure classification, a significant association between current fluoride exposure and work-related asthmatic symptoms was found. The adjusted OR for work-related asthmatic symptoms was 3.7 (95% CI, 1.4 to 9.6) for subjects exposed to total fluorides more than 0.5 mg/m$, as compared with subjects exposed to less than this level. The longitudinal study of 1301 new workers revealed a similar association between total fluoride exposure and asthmatic symptoms. A dose–effect relationship between current fluoride exposure and asthmatic symptoms was also observed. Subjects exposed to a current fluoride level of 0.41 to 0.80 and more than 0.80 mg/m$ had an RR of 3.4 (95% CI, 1.5 to 7.4) and 5.2 (95% CI, 2.0 to 13.3), respectively, as compared with subjects exposed to fluoride levels of less than 0.41 mg/m$.

In a separate longitudinal study, in which subjects were followed for 1 year, no significant alterations in lung function or lower airway symptoms were observed.34 The second study with a similar study design assessed upper airway inflammation via nasal lavage.35 An inflammatory response in the nasal mucosa was observed after a 1-hour exposure to 3.3 to 3.9 mg/m$ HF. Seven of the 10 tested subjects showed increased reactivity in the nasal mucosa, but he still had asthmatic symptoms in his follow-up.36 Significant increases in the percentage of CD3-positive cells (T-lymphocytes) in the bronchial portion of the lower respiratory tract, as assessed via bronchoalveolar lavage performed 3 weeks before exposure and 24 hours after exposure, was also observed at exposure more than 2.5 mg/m$ but not at 0.6 mg/m$. Nevertheless, no significant alterations in lung function or lower airway symptoms were observed.34 The second study with a similar design study assessed upper airway inflammation via nasal lavage.35 An inflammatory response in the nasal mucosa was observed after a 1-hour exposure to 3.3 to 3.9 mg/m$ HF. Seven of the 10 tested subjects also reported upper airway symptoms (specific symptoms were not presented); most of the subjects scored the severity of the symptoms as very mild to mild.

Mechanisms for possible development of asthma after HF exposure in the aluminum industry have not been clarified, because the vast majority of the HF molecules will be absorbed in the upper airways.37,38,40 It has been suggested that the hygroscopic behavior of inhaled “dry” water soluble particles may be important for the deep lung penetration of HF and SO$_2$. Repeated peak and even low exposures may induce chronic inflammatory changes in the airway mucosa as seen in the experimental studies of HF and lead to “irritant induced” asthma. Accidental high HF exposure may have a direct toxic effect, causing reactive airways dysfunction syndrome.37 As a result of the longitudinal study in Norwegian aluminum smelter workers and also in the conformity with experimental studies of HF exposure, the Norwegian labor directorate lowered threshold limit value for total fluorides from 2.5 to 0.5 mg/m$. Other threshold limit values were not changed, although it was emphasized that fluoride could be a marker for other pollutants that might play a role in occupational asthma occurring among the production workers.

Occupational asthma caused by aluminum welding has been described by several authors. There are, however, despite similarities, quite large differences between the exposure in potrooms and exposure caused by aluminum.38,39 We have, therefore, in this review article, not included or discussed occupational asthma seen in other types of industries where aluminum welding may occur. Welders are exposed to many different agents, depending on which kind of metal they are welding on and what kind of electrodes under various welding processes being used. Therefore, it is not possible to draw reliable associations between such exposure and the exposure in aluminum potrooms.
Morphology and Inflammation Markers

To our knowledge, there has been no characterization of the inflammatory nature of PA on the basis of bronchial biopsies until Sjäheim et al41 published the results from such a study in 2004. Bronchial biopsy specimens from 20 asthmatic workers, 15 healthy workers, and 10 nonexposed controls were analyzed. Median reticular basement membrane thickness was significantly increased in both asthmatic workers and healthy workers compared with nonexposed controls. Nonsmoking asthmatic workers had significantly increased median density of lamina propria CD 45 leucocytes and eosinophils, and significantly increased concentrations of exhaled NO compared with nonsmoking healthy workers and nonexposed controls. Fewer leucocytes were observed in asthmatic smokers than in nonsmokers. Both eosinophilic and noneosinophilic phenotypes of asthma were recognized in the potroom workers, and signs of airway inflammation were also observed in healthy workers.

Eosinophils are principally tissue-dwelling cells, but it is well recognized that asthma and asthma-like symptoms may be reflected by increased levels of blood eosinophils.32 The blood eosinophil count has been shown to increase during asthmatic attacks in potroom workers,49 and case reports of PA with blood eosinophilia have been described.44 Kongerud and Søyseth25 showed a decrease in serum eosinophils among subjects in potroom workers when not exposed for 3 weeks, although atopy is not more common in workers with work-related, asthma-like symptoms than in the general smelter workforce.49

Sorgdrager et al45 conducted a nested case–control study with preemployment data of 364 potroom workers (182 cases and 182 controls). Cases were workers unable to work because of work-related respiratory disease, meeting the criteria for PA. Preemployment eosinophil count was significantly related to the occurrence of PA, although the mean number of eosinophils in cases was within the reference range (less than 275 per mm³). Thirty-nine of the 44 individuals with blood eosinophil counts in the upper range of normal developed PA with time.

In a Norwegian cross-sectional study of 338 workers, Sjäheim et al46 showed that the OR for PA was 4.2 for workers with eosinophils 400 × 10⁶ cells/L or more, compared with workers with eosinophils less than 200 × 10⁶ cells/L. An attenuation of the blood eosinophil increase was actually observed in smoking asthmatic workers, suggesting an immune-modulating effect of smoking.

Two decades ago, there was not any preferred immunological test for asthma in the aluminum industry.2 There is still no valid test for PA; however, Lund et al.47 found that exposure to potroom pollutants was associated with increased concentration of exhaled NO in nonsmoking subjects. A study group comprising 180 male subjects and 40 comparable control subjects recruited from the same aluminum plant was examined by measurements of exhaled and nasal concentration of NO, spirometry, and a questionnaire on respiratory symptoms as a part of an annual health surveillance program. In nonsmokers, the concentrations of exhaled NO were higher in the potroom workers than in the controls. The two groups did not differ in spirometry and asthma-like symptoms. Nonsmoking potroom workers with asthma-like symptoms had higher concentration of exhaled NO than those with no symptoms. The authors suggested that nitric oxide in exhaled air could be an early marker of airway inflammation in aluminum potroom workers.

Genetic Factors and Asthma

To our knowledge, there has been only one article published in the area of genetics and PA.48 The subjects for this study were members of an inception cohort of 161 newly hired potroom workers (Spokane, Washington). Fifty-two subjects agreed to participate, and all had at least one follow-up evaluation after their baseline assessment. Five individuals had new asthma-like symptoms and increased NSBHR, five had only new asthma-like symptoms, and three had only increased NSBHR. Genotyping was performed for the β₂-adreno receptor, high-affinity immunoglobulin E receptor, and tumor necrosis factor. No associations were found between PA case status and genotype. Nevertheless, the number of subjects was small, and the authors suggested that a larger numbers of subjects needed to be tested.

Predisposing Host Factors

Barnard et al49 assessed individual employee risk factors for occupational asthma in primary aluminum smelting in a nested case–control study. Workers were included in the study if they had their first employment medical examination between 1982 and 1995. The cohort was followed until December 31, 2000. In the cohort of 545 workers, there were 45 cases diagnosed with PA, and 4 controls per case were matched for the same year of preemployment and age within ±5 years. There was a significant positive association between hay fever diagnosed either at or during employment and PA with an adjusted OR of 3.58 (95% CI, 1.57 to 8.21). A higher FEV₁/FVC% (FER) at employment reduced the risk of developing PA. The risk of PA was more than three times higher in individuals with an FER of 70% to 75% than in individuals with FER of 80% or more.

Sorgdrager et al50 studied whether preventive measures such as reduction of exposure and the introduction of the histamine provocation test as a selection instrument resulted in a lower incidence of PA or a longer latency time between the commencement of employment and the occurrence of PA. A total of 179 cases of PA diagnosed between 1970 and 1990 were studied. After introduction of the preemployment histamine provocation test, the incidence density of PA decreased substantially but cases still continued to occur (incidence density 11.6 per 1000 person years in 1976 to 1981 vs 2.5 in 1982 to 1990). Even though fluoride exposure was at levels lower than those thought to confer risk for the development of respiratory disorders, a reduction in the mean exposure levels may have contributed to the decrease. The latency time did not differ when subjects with bronchial hyperresponsiveness were screened out, suggesting that agents in the potroom atmosphere act principally as “inducers” and not as simple airway irritants.

Sorgdrager et al51 also evaluated the effectiveness of preemployment screening in the prevention of aluminum PA. He computed the predictive value of a positive test result, the number of medical assessments needed to reduce the number of new cases by one, and the number of rejections for the job needed to reduce the number of new cases by one. The results depended on the incidence rates, but the overall conclusion was that personal risk indicators like low FEV₁ level in preemployment examination, atopic history, and high blood eosinophils at preemployment were far from effective and should not be used as a selection instrument.

Prognosis

In our previous review article, there was substantial evidence from follow-up studies that subjects with PA, even after several years of nonexposure, had persistent symptoms, NSBHR, or both.2 This is not very different from other causes of occupational asthma. Werge et al52 examined 35 men with PA after an average follow-up period of 2.5 years after cessation of exposure, and the group had an increased RR of morning cough (RR = 1.7; 95% CI 0.6 to 5.1), dyspnea on exertion (RR = 2.8; 95% CI 0.9 to 8.4), and wheezing (RR = 6.1; 95% CI 2.3 to 16.3) compared with controls from the same plant, in a 1:2 matched analysis. Ten subjects reported persisting asthma, dyspnea at night, or dyspnea on exertion. In a New Zealand smelter, 47 subjects with PA, diagnosed and transferred to other jobs between 1971 and 1986, were reexamined in 1986.53 Twelve had frequent or persistent symptoms of asthma, and a further 11 were taking some regular medication for intermittent milder symptoms. Persistence of bronchial responsiveness has also been reported several years after cessation of exposure. In one study, 67% retained their NSBHR after...
cessation of exposure.\textsuperscript{35} In a Norwegian study of 12 workers with PA, an improvement of NSBHR with a twofold increase in PC\textsubscript{20} was shown in seven of eight subjects who were hyperreactive at the time of relocation.\textsuperscript{30}

During the last decade, additional knowledge of the benefit of relocation has been produced, which supports earlier findings suggesting that PA may develop into a chronic disease. Among 179 cases of PA identified by Sorgdrager et al, 122 workers were still present at the factory 5 years after their relocation to an exposure-free department. A follow-up study was carried out among the 122 workers. A long exposure time (the time interval between start of exposure and diagnosis) seemed as a significant factor affecting FEV\textsubscript{1} % predicted at follow-up. The authors concluded that the results of this study gave support for additional prevention measures to be taken, such as early recognition of work-related respiratory complaints and repeated education.

In his doctoral thesis, Sorgdrager\textsuperscript{34} looked at determinants of medical outcome in 39 workers with PA 5 years after transfer to exposure-free departments. Increased bronchial responsiveness was still present in 47% of the workers. All PA cases with an atopic history had increased bronchial responsiveness at follow-up. Cases that were detected by means of consulting hours had statistically significant higher mean FEV\textsubscript{1} % predicted as compared with cases detected by periodic medical examination. Sickness absence in workers with PA was slightly higher as compared with the whole plant population. The authors conclude that once diagnosed, patients with PA need to be carefully followed up and educated to prevent further development of health impairments. Generally it seems wise to introduce regularly surveillance of potroom workers with spirometry and respiratory questionnaires, so workers with PA can be detected at an early stage and removed from exposure as soon as possible to improve their prognosis. Similarly, Wergeland et al\textsuperscript{52} found that a considerable proportion of workers with PA had respiratory symptoms 1 to 43 months after relocation to nonexposed jobs compared with never-exposed workers. Nevertheless, improvement of bronchial responsiveness is to be expected after relocation to less-exposed or nonexposed jobs.\textsuperscript{29,30}

Prevention

As already described, Donoghue et al\textsuperscript{14} could show a 96% reduction of the incidence of PA from 1991 to 2006 accompanied by a significant decline over the years for total fluoride, particulate and gaseous fluoride, $P$ values 0.010, 0.031, and 0.007, respectively. Respirable particles did not decrease significantly. From 2004 to 2006, total fluorides was measured less than 0.40 mg/m\textsuperscript{3} and gaseous fluoride 0.13 to 0.17 (geometric means).

Reduction of exposure by the use of airway protection is common in all type of work with inhalable pollution. There is, however, scarce documentation of such equipment reducing symptoms or improving prognosis. Kongerud and Rambjør\textsuperscript{56} studied the efficiency of the Racial Airstream helmet respirator in improving PEFs and reducing symptoms (dyspnea, wheezing, and cough) in 19 aluminum potroom workers with respiratory complaints. Peak expiratory flow readings and symptom recording from a 2-week working period with use of the respirator were compared with a period when the 3M 9906 disposable mask was used. The study was designed as a randomized, parallel, cross-over study with five or six daily measurements of PEF and daily symptom recording. A significant number of workers\textsuperscript{56} had a higher mean peak flow in the helmet period than in the nonhelmet period ($P < 0.01$), while symptoms did not improve significantly in the helmet period. Objective evidence of respiratory protection was observed for the group of workers as a whole, but the effect on symptoms as well as individual effect on peak flow was minor in most workers. There are, however, circumstances and types of jobs with peaks of exposure that such types of personal equipment are recommended. Prevention by selection has been discussed in another section of this article and has not been shown to successfully prevent development of PA. Also, such selection rather than reduction of exposure may also be looked upon as unethical.

### The Evidence of PA and Work-Related COPD

#### PA: Occupational Asthma or Work-Aggravated Asthma?

Occupational asthma is a disease characterized by airflow limitation, NSBHR, or both associated with inflammation due to causes and conditions attributable to a particular occupational environment and not to stimuli encountered outside the workplace.\textsuperscript{28} It can be divided into three subgroups: (1) immunoglobulin E–mediated occupational asthma, (2) occupational asthma due to specific occupational agents with unknown pathological mechanisms, and (3) irritant occupational asthma. In addition, work-aggravated asthma, that is, worsening of preexisting asthma due to causes and conditions attributable to particular exposures encountered at work.

Potroom asthma was first described in three Norwegian reports.\textsuperscript{27,43,55} The cause(s) and mechanism(s) of this condition are, however, still unknown. First, immunoglobulin E–mediated asthma is unlikely, because these cases are usually caused by sensitizing to high-weight molecular agents that usually have a biological origin. Low-weight molecular agents acting as sensitizers by unknown mechanism are also less likely though it cannot be excluded. Gylraa et al\textsuperscript{57} found, in one study, an inhalable fiber (aluminum sodium tetrafluoride—diameter 0.1 μm and length 5 μm) that could be a candidate.

It is probably most likely that PA is mediated by irritants. Such agents may induce asthma by accidental high exposures or repeated exposures at moderate to low levels of exposure. Irritant asthma caused by accidental high exposure (ie, “reactive airways dysfunction syndrome”)\textsuperscript{37} is very unlikely, as such episodes have not been described in the aluminum industry. Thus, PA is probably mediated by repeated low to moderate levels of exposure to irritants. Such agents may, however, also act as provokers of asthma in subjects with preexisting or latent asthma. Hence, differentiating between occupational irritant asthma and work-aggravated asthma is difficult.

The following arguments favor that PA represents an occupational irritant asthma:

- Serial peak flow measurements have identified an occupational pattern in 10 of 14 workers who reported the combination of chest tightness and wheezing, improving on rest days.\textsuperscript{45}
- Repeated measurements of bronchial responsiveness have shown that the level of bronchial responsiveness is associated with the level of exposure to irritants as well as blood fluorides.\textsuperscript{31,32}
- In many aluminum plants, subjects with a history of asthma are precluded from employment in the potrooms.
- The prevalence of NSBHR among potroom workers seems to be low.

Thus, it is most likely that PA is irritant-induced occupational asthma.

#### COPD in the Aluminum Industry

The most widely used definition of COPD was introduced by the Global Initiative on Obstructive Pulmonary Disease in 2001.\textsuperscript{58} This definition has later been revised several times, the latest in 2011. In all these definitions, “enanced chronic inflammatory response in the airways and the lung to noxious particles or gases” has been retained (www.goldcopd.org/). Although tobacco smoking is the dominating cause of the disease, this definition opens the possibility of other causative agents of COPD such as pollutants encountered at work.
The association between COPD and occupational exposure can be investigated using several approaches. Ideally, the relationship between the incidence of COPD, for example, expressed as airflow limitation, and occupational exposure should be investigated using prospective studies in occupational cohorts. Until now, results from no such studies in the aluminum industry have been published. Alternatively, an indirect approach can be applied by investigating the association between annual decline in lung function and occupational exposure can be used. Actually, Chan-Yeung et al. found no difference in FEV₁ decline between unexposed employees and potroom workers in a follow-up of 820 employees at a plant in British Colombia. Nevertheless, only 54% of those were included at the initial survey were available at the follow-up. Thus, selective dropout rate could have distorted the estimates toward a zero effect, which has been described in similar settings. The difference between two consecutive measurements of FEV₁ was, however, negatively associated with exposure to particulates during 6-year follow-up of 630 potroom workers. In this study, an autoregression model was used that did not allow for estimation of annual decline in lung function.

Because of the risk of selection bias, cross-sectional studies using the prevalence of COPD or airflow limitation are less valid than follow-up studies. Nonetheless, Kongerud et al. found that the OR of airflow limitation increased with increasing duration of occupational exposure can be used. Actually, Chan-Yeung et al. found no difference in FEV₁ decline between unexposed employees and potroom workers. In this study, an autoregression model was used that did not allow for estimation of annual decline in lung function.

Most of both cross-sectional and longitudinal studies have shown an increased occurrence of respiratory symptoms in general as well as work-related asthmatic symptoms in aluminum potroom workers compared with controls. Fortunately, the number of workers with PA seems to have decreased during the last decade, concurrent with a decrease in dust and gas exposure in the plants. Mortality studies have shown an increased mortality from COPD, and in cross-sectional studies, an increased number of subjects with airflow limitation have been observed in potroom exposed groups.

**SUMMARY**

Most of both cross-sectional and longitudinal studies have shown an increased occurrence of respiratory symptoms in general as well as work-related asthmatic symptoms in aluminum potroom workers compared with controls. Fortunately, the number of workers with PA seems to have decreased during the last decade, concurrent with a decrease in dust and gas exposure in the plants. Mortality studies have shown an increased mortality from COPD, and in cross-sectional studies, an increased number of subjects with airflow limitation have been observed in potroom exposed groups.

### TABLE 4. Mortality Studies: Chronic Obstructive Pulmonary Disease

| Study                        | Obs Years | Exposure | Outcome |
|------------------------------|-----------|----------|---------|
| **Exposure**                 | **Entity** | **Scale** | **Deaths** | **Outcome** |
| Ronneberg                    | 24,996    | Potroom  | Yes vs no | Total = 20* | SMR — 197 (P < 0.05) |
| Romundstad et al             | 239,246   | Cum F-exp | mg/m³ × yr |      |   |
| Gibbs et al                  | 214,023   | BSM      | mg/m³ × yr | Total = 321 | SMR P trend < 0.001 151 (135–168) |
| Desjardins et al             | 172,799   | Cum B(a)P | μg/m³ × yr | Total = 44 | SMR P trend > 0.2 146 (106–196) |
| Friesen et al                | 150,750   | Cum B(a)P | μg/m³ × yr | Total = 28 | HR P trend = 0.78 64 (42–94) |

*Underlying cause of death.

BSM, benzene-soluble matter; Cum B(a)P, cumulative Benzo[a]pyrene; Cum F-exp, cumulative exposure to fluorides; HR, hazard ratio; MRR, mortality rate ratio; Obs years, observation years; SMR, standardized mortality rate (per 100,000 years); T1, 0 to 9.77 μg/m³ × year; T2, 9.78 to 36.8 μg/m³ × year; T3, more than 36.8 μg/m³ × year.
associated with duration of employment. Nevertheless, increased occurrence of COPD has not been examined in longitudinal studies yet. It is possible that employees with PA have an increased risk of COPD.

Lung function is also undoubtedly affected by potroom exposure, causing an increased longitudinal decline in FEV$_1$ as well as cross-shift changes. Typical cases of occupational asthma have been described, and typical peak flow patterns have been documented. Potroom asthma represents probably an irritant-induced occupational asthma. Morphological manifestations in bronchial biopsies and the inflammatory markers NO and eicosanoids in airway tissue and blood are consistent with asthma in general. The causative agent(s) is (are) not known and may be a mixture of two or more irritants that are present in the workplace atmosphere. Unknown sensitizers are less likely although not precluded. Reductions in respiratory symptoms as well as improvements in bronchial responsiveness are to be expected after relocation, but a considerable proportion of relocated subjects still have some symptoms. Genetic factors and preemployment selection have so far not been shown to influence the occurrence of PA. The most important preventive measures are to decrease exposure through decreased pollution in the work atmosphere, use of airway protection during the most-exposed work tasks, and cessation of smoking.

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