

Occupational asthma in aluminium potroom workers related to pre-employment eosinophil count

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ABSTRACT: Occupational asthma still occurs in aluminium potroom workers despite pre-employment medical selection. The purpose of our study was to identify workers with an increased risk of developing "potroom asthma".

A nested, case-control study was carried out in two Dutch aluminium producing plants. Pre-employment data of 364 potroom workers (182 cases and 182 controls) were analyzed. Cases were workers unable to work because of work-related respiratory disease, meeting the criteria for potroom asthma. The selected controls were matched for age, year of starting employment and working conditions.

Pre-employment eosinophil count was significantly related to the occurrence of potroom asthma, even though the mean number of the eosinophils in cases was within the normal range ($<275 \text{ cells}\cdot\text{mm}^{-3}$; $0.28 \text{ cells} \times 10^9\cdot\text{L}^{-1}$). Hence, 39 of the 45 individuals with blood eosinophil counts in the upper range of normal ($>220 \text{ cells}\cdot\text{mm}^{-3}$; $0.22 \text{ cells} \times 10^9\cdot\text{L}^{-1}$) developed potroom asthma with time.

We conclude that workers without respiratory symptoms, with normal lung function and normal bronchial responsiveness before employment developed potroom asthma. Fluoride exposure, combined with an elevated eosinophil count, might induce an immunological or cytotoxic process.

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In aluminium workers, exposure to fluorides is an important cause of work-related obstructive respiratory disease [1, 2]. Major features of this occupational disease, known as "potroom asthma", are: an initial period of symptom-free exposure (a few weeks to several years) followed by nocturnal wheezing; dyspnoea; cough; reversible bronchoconstriction; and increased bronchial reactivity without evidence of allergy (normal Immunoglobulin E (IgE), and negative skin-prick tests). The current incidence of potroom asthma ranges from 0.0006 to 0.04 per 100 workers per year [1, 2].

The occurrence of the disease has been described in Dutch aluminium producing plants [3, 4]. In these plants, the incidence was reduced from 5 to 15 per year per 100 workers in the 1970s, to 1 case per year per 100 workers in recent years.

This was achieved by a variety of preventive measures, such as reduction of exposure, medical selection at pre-employment, and education. The cases described by DE VRIES *et al.* [3] had hyperreactive airways and many of them showed eosinophilia.

During aluminium production by electrolysis of alumina (Al_2O_3), various fluorides, particulate fluorides and hydrogen fluoride, escape into the potroom atmosphere, which also contains SO_2 , CO and dust, composed mainly of alumina, aluminium trifluoride and cryolite, as well as minor amounts of metals, such as nickel, chromium

and vanadium. Although many of these emissions are potentially harmful to the airways, KONGERUD and co-workers [5, 6] recently found a dose-response relationship between symptoms of asthma (a combination of dyspnoea and wheezing) and occupational exposure to fluorides. Previous exposures and smoking were also associated with these symptoms. The authors found no relationship between patients giving a history of hay fever and/or atopic eczema and the occurrence of work-related dyspnoea and wheezing.

We present the results of an investigation in two aluminium producing plants in The Netherlands, using data derived from pre-employment medical examinations. The purpose of the study was to identify workers with an increased risk of developing potroom asthma.

Material and methods

Environmental exposure in the aluminium smelters

This study was carried out in two plants (table 1). Plant A was located in the northern, and Plant B in the southwestern part of The Netherlands. Exposure to fluorides has been measured systematically since 1976 in these plants. There was no difference in exposure levels between the two plants (table 1). Time-weighted

Table 1. – Characteristics of the two aluminium producing plants in The Netherlands

	Plant A	Plant B
Started up	1965	1972
Hooded pots	Since 1978	Since 1973
Fluoride levels*		
Fluoride dust	0.29–0.42	0.25–0.63
Hydrogen fluoride	0.10–0.34	0.14–0.27
Histamine provocation test as selection tool	Since 1965	Since 1982

*: 8 h time-weighted averages in $\text{mg}\cdot\text{m}^{-3}$.

averages during 8 h were around or less than $0.5 \text{ mg}\cdot\text{m}^{-3}$. Exposure shows peaks when pots are unhooded. Incidental measurements of peak exposures were $7.5 \text{ mg}\cdot\text{m}^{-3}$ for gaseous fluorides, $7.7 \text{ mg}\cdot\text{m}^{-3}$ for particulate fluorides, and $13.0 \text{ mg}\cdot\text{m}^{-3}$ for respirable dust.

Study population

A retrospective analysis was carried out using a nested case-control design. Both cases and controls were male potroom workers from two dynamic cohorts. One cohort contains workers employed in Plant A between 1978 and 1988. This period was chosen because in Plant A the registration of cases was systematically carried out from the beginning of 1978 onwards. Data were collected in early 1988. The second cohort (from Plant B) consisted of workers employed at any time after the establishment of the plant in 1971 to 1991, when we collected the data.

Cases were found and administered by the Departments of Occupational Health. Cases were potroom workers unable to work because of work-related respiratory disease and meeting the clinical criteria for potroom asthma [1]: 1) asymptomatic periods of 2 weeks or more; 2) symptoms of airflow obstruction (usually several hours after exposure, or during sleep), such as cough, wheezing and dyspnoea; 3) significant and reversible airflow obstruction; and 4) improvement of symptoms after absence from work for several days or longer.

The majority of cases (70%) were identified following consultation with the occupational health officer for respiratory complaints. The remaining cases were identified in the course of periodic medical examinations. The decision to stop work and remove the patient from the potroom was based on symptoms of airflow obstruction confirmed by spirometry and improvement of symptoms in absence of work.

Controls were individually matched with cases for age and year of starting employment. Figure 1 shows the subjects selected. In Plant A, 300 potroom workers were employed in the study period. Potroom asthma was diagnosed in 57 of them. Controls were selected from the current employees ($n=170$). For 49 subjects, it was possible to find suitable controls for analysis. In the dynamic cohort of Plant B ($n=1,208$), 174 workers were registered as having potroom asthma. After matching, we were able to compare 133 case-control pairs. Cases, for whom no control subject could be found, were older than current nondiseased exposed workers and employed earlier.

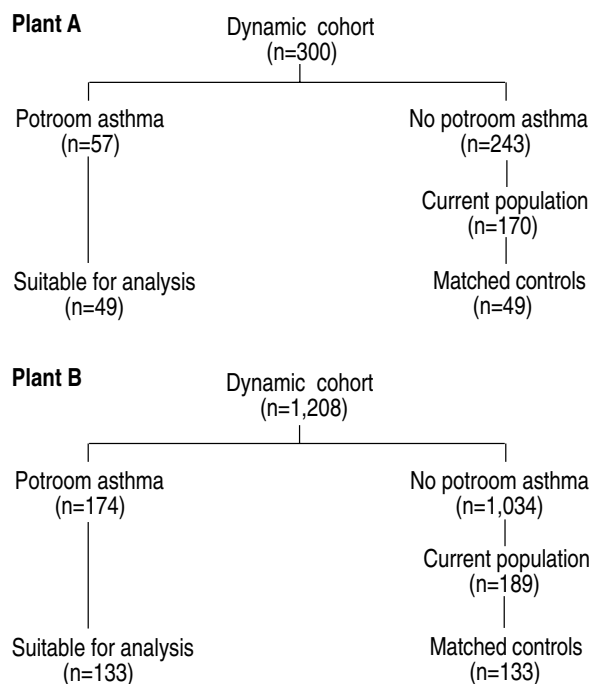


Fig. 1. – Population selection (for explanation see Methods)

Table 2 shows the variables for which matching was undertaken in the cases and selected controls. In plant A a significant decrease in the incidence of potroom asthma was observed after hooding of the pots. In 1982, the histamine provocation test was introduced in Plant B as a selection instrument for employment. This was also followed by a reduction in new cases [7].

Since the presence of a history of chronic obstructive pulmonary disease (COPD) and/or current asthma at pre-employment precluded working in the department with fluoride exposure, the role of these variables could not be studied as risk factors for potroom asthma. In Plant A, this selection method has not been changed. In Plant B, history and spirometric data were used as selection criteria, and from 1982 onwards the histamine provocation test has been added in pre-employment examination.

Table 2. – Pre-employment characteristics of cases and controls in two aluminium producing plants (matched factors: age at starting employment and year of starting employment)

	Cases	Controls
Age at starting employment yrs		
Plant A	29±6	30±5
Plant B	28±6	29±6
Plant A employed		
Before 1979 n (%)	38 (78)	38 (78)
After 1979* n (%)	11 (22)	11 (22)
Plant B employed		
Before 1982 n (%)	118 (89)	118 (89)
After 1982** n (%)	15 (11)	15 (11)

Plant A (49 cases, 49 controls); Plant B (133 cases, 133 controls). Age and data are presented as mean±SD. *: in 1978, significant exposure reduction was achieved by the introduction of hooded pots; **: in 1982, pre-employment histamine provocation tests were introduced to select workers.

Clinical and laboratory data

The following data were collected at pre-employment examination: medical history obtained by self-administered questionnaire; spirometry; bronchial responsiveness measured with histamine provocation; and blood eosinophil count. In Plant B, a leucocyte count was also obtained.

The questionnaire included standard questions concerning current respiratory symptoms, respiratory problems in childhood, and family history of chronic nonspecific respiratory disease.

In Plant A and Plant B, different types of spirometers have been used in the course of time. In the early years, lung function tests were performed on water-sealed spirometers (Lode). Subsequently, dry spirometers have been used. By using guidelines for standardization, forced expiratory volume in the first second (FEV₁), expressed as percentage predicted (FEV₁% pred), inspiratory vital capacity (VC) in Plant A and Forced Vital Capacity (FVC) in Plant B, and FEV₁/FVC, were measured by trained analysts [8]. Calibration of the equipment was performed weekly by means of a 3 L syringe. VC and FVC were analysed separately [8]. Bronchial responsiveness was measured by means of the De Vries method since 1965 in Plant A, and since 1982 in Plant B [9]. Subjects were considered to be hyperresponsive if inhalation of ≤ 32 mg·mL⁻¹ histamine during 30 s resulted in a $\geq 10\%$ decrease in FEV₁.

Statistical analysis

Statistical analyses were performed on a personal computer with the Statistical Package for Social Sciences (SPSS-PC version 2.0). Results of univariate analyses were presented as mean \pm SD and proportions. The eosinophils were log transformed to obtain normality. Chi-squared test, student's t-test and multiple regression analysis were used to compute the contribution of each potential risk factor. Odds ratios were used for estimated relative risk in unmatched analyses [10]. A 95% confidence interval (two-sided) was used as the limit of significance.

Results

Analysis of pre-employment characteristics of cases and controls is shown in table 3.

In Plant A, neither respiratory disease in childhood nor positive family history differed significantly between cases and controls. Smoking habits of the workers employed the longest in Plant A were unknown at pre-employment examination, because questions about smoking habits were not included in questionnaires until 1970. Subsequent questionnaires indicated a prevalence of smoking of 80–90% in this plant. Lung function was not different between cases and controls in plant A. Pre-employment eosinophil count was statistically significantly higher in cases than in controls from Plant A.

In Plant B, respiratory problems in childhood and a positive family history were observed significantly more frequently in cases than in controls. Of the spirometric measurements, only FEV₁/FVC was significantly lower in cases than in controls at pre-employment examination. In addition, in Plant B eosinophil counts were significantly higher in cases than controls. The total number of leucocytes was comparable in cases and controls in Plant B. The proportion of eosinophils in the total leucocyte count was significantly higher in cases at pre-employment examination than in controls.

Combining the results of Plant A and Plant B also showed that the mean pre-employment total eosinophil count was statistically significantly higher in cases than in controls (table 3). The crude odds ratios for different eosinophil count at pre-employment are shown in table 4. Eosinophil counts at pre-employment of 220 or more seem to indicate a strongly increased risk for the occurrence of potroom asthma (fig. 2). Of the 45 subjects above this count, 39 developed potroom asthma.

The mean lung function (FEV₁% pred) was normal at pre-employment examination in both plants, and no significant difference was seen between cases and controls. Significantly more cases than controls had respiratory problems in childhood. A trend towards a positive family history was detected in cases as compared to controls.

Multiple regression analysis showed that only pre-employment eosinophil count was related to the presence

Table 3. – Pre-employment characteristics of cases and controls in two aluminium producing plants

	Respiratory disease in childhood		Positive family history		Cigarette smoking [#]		FEV ₁ [†]	FEV ₁ /(F)VC [†]	Total leucocytes [†]	Eosinophil count [†]	$\geq 4\%$ eosinophils per total leucocytes	
	n	%	n	%	n	%	% pred	%	$\times 100 \cdot \text{mm}^{-3}$ blood	cells·mm ⁻³	n	%
Cases												
Plant A	7	14	3	6	19	39	102 (13)	80 (6)		173 (87)		
Plant B	19	14	11	8	107	80	99 (11)	79 (7)	76.0 (21.2)	148 (112)	14	11
Plant A+B	26	14	14	8	126	69	99 (12)			154 (106)		
Controls												
Plant A	2	4	4	8	17	35	107 (16)	79 (5)		110 (66)*		
Plant B	1	1*	1	1*	120	90	99 (10)	81 (6)*	75.4 (21.4)	98 (62)*	2	2*
Plant A+B	3	2*	5	3 [§]	137	75	101 (12)			102 (62)*		

Plant A (49 cases, 49 controls); Plant B (133 cases, 133 controls). [†]: values are presented as mean and SD in parenthesis. [#]: in Plant A smoking habits were unknown in 56% (28 cases, 27 controls). Leucocytes were only measured in Plant B. FEV₁: forced expiratory volume in one second; (F)VC: (forced) vital capacity. NB Plant A - FVC, Plant B -VC measured. IVC: inspiratory vital capacity. *: p<0.05; [§]: p=0.05 cases vs. controls.

Table 4. – Crude odds ratios (ORs) for pre-employment eosinophil count (according to figure 2)

Eosinophils·mm ⁻³	OR	95% CI
0–54	0.39	0.20–0.75
55–109	0.79	0.63–0.99
110–164	0.82	0.65–1.05
165–219	1.23	0.63–2.3
220–274	6.0	3.2–10.7
≥275	8.6	4.4–14.6

95% CI: 95% confidence interval.

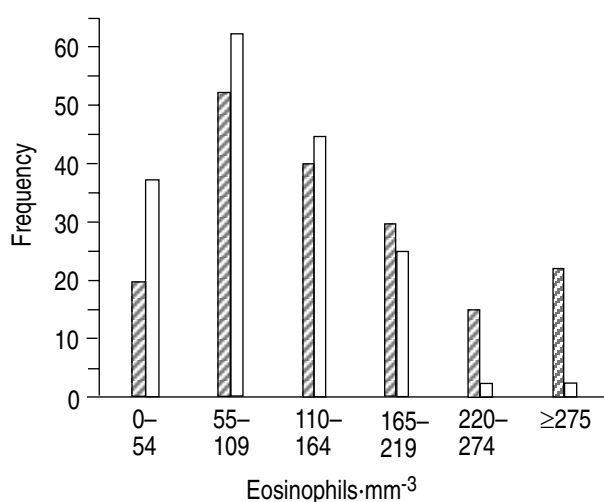


Fig. 2. – Distribution of eosinophils·mm⁻³ blood at pre-employment examination (n=364). ▨: cases; □: controls.

of potroom asthma (odds ratio=1.28; $p=0.0002$), controlled for respiratory childhood problems, positive family history, smoking and lung function. The mean pre-employment blood eosinophil count, in cases and also in controls, of Plant A was higher, but not statistically significant, as compared to the mean eosinophil count in cases and controls of Plant B.

There were slightly more smokers within the controls as compared to cases at pre-employment examination. The percentage smokers shows a decreasing trend from previous to recent years. Nonsmokers at pre-employment examination more frequently reported a positive childhood history. Smoking at pre-employment examination was associated with a higher leucocyte count, but not with a higher eosinophil count (not shown in the table).

Discussion

Determinants of potroom asthma

Potroom asthma is a work-related respiratory disorder and meets the criteria for occupational asthma [1]. Symptoms usually occur several hours after exposure in the potroom. Exposure to fluorides may be the most important cause of potroom asthma [1, 2, 5, 6]. SOYSETH and KONGERUD [6] established 0.5 mg·m⁻³ time-weighted average as a cut-off value between low and high exposure to fluorides. In our plants, the exposure level is 0.10–7.5 mg·m⁻³ (incidental peaks). We assume that cases and controls were similarly exposed because they had the same job

and were matched for age and year of starting employment.

One of the most characteristic features of asthma is increased bronchial responsiveness, as determined by challenge tests with inhalation of histamine or methacholine [11]. Pre-existing bronchial hyperresponsiveness in subjects who start working in the potrooms has been cited as a risk factor for potroom asthma, and may also cause direct bronchoconstriction on first exposure. These latter "asthmatic" reactions are not considered to be true potroom asthma, which, like all forms of occupational asthma, develops after an initial symptom-free period of exposure varying from weeks to years [1, 2]. All employees in the potroom of Plant A were tested for bronchial hyperresponsiveness at pre-employment examination. Those with increased bronchial responsiveness were excluded from work in the potroom. Nevertheless, a considerable number of employees developed symptoms with time.

Our study shows that blood eosinophil numbers may be a risk factor for potroom asthma in workers without clinical signs of respiratory disease at pre-employment examination. A selection effect is not likely to account for these results because prospective employees with a current history of obstructive lung disease and/or bronchial hyperreactivity were excluded from work in the potroom. Such individuals generally have higher eosinophil counts [12, 13], and their inclusion would, thus, have resulted in even higher eosinophil counts amongst cases. It should be noted that the mean number of eosinophils in cases at pre-employment was within the normal range (<275 eosinophils·mm⁻³ blood) [12].

Cigarette smoking is the most important risk factor for COPD [14], and is also recognized to be a risk factor for occupational asthma [15]. The results of our study do not confirm this in the case of potroom asthma. Smoking was not reported more frequently by cases than by controls.

Respiratory disease in childhood and a positive family history of COPD were more frequent in cases than in controls. These findings confirm earlier suggestions on risk factors for potroom asthma [1, 2]. If exclusion of subjects with obstructive lung disease at pre-employment examination had not taken place, childhood and family history might have been even more frequent among cases.

The association between the number of eosinophils measured in pre-employment examination and the occurrence of potroom asthma is interesting in the light of its possible pathogenesis. The role of the eosinophil in the case of potroom asthma has not been well-studied. In studies carried out more than 20 yrs ago in this country and in a more recent Swedish study published in 1985, cases of potroom asthma with blood eosinophilia were published [3, 16]. It is known that the eosinophil is an important effector cell in the pathogenesis of allergic inflammation [17]. The late onset of the asthmatic reaction in patients with potroom asthma also suggests an immunological (allergic) mechanism. However, an antigen recognized by the immune system has not been described in fluoride-induced lung disease [1, 18–20].

Analysis of bronchoalveolar lavages (BAL) fluid and bronchial histology in potroom asthma patients might be helpful in understanding the influence of fluorides on the airways. In the only clinical study on potroom workers

published to date, healthy nonsmoking potroom workers were compared with healthy nonsmoking volunteers. A discrete alveolitis and a significantly lower FEV₁ was found in potroom workers [21]. No eosinophils were detected in the BAL fluid. The authors suggest that a low level of exposure and/or frequent use of respiratory protection equipment may have accounted for these relatively normal findings.

Eosinophilic inflammation without allergic sensitization has been shown in asthma due to exposure to toluene di-isocyanate (TDI) [22], and to a hardener containing reactive diamines [23]. Recent studies on the pathogenesis of isocyanate-induced asthmatic reactions show increased numbers of eosinophils and an increase in numbers of cytotoxic (CD8+) lymphocytes [24, 25]. Exposure to fluorides could lead to the development of potroom asthma by a similar process as an immunological mechanism cannot be excluded [5, 20]. Alternatively, it may be possible that in subjects with slightly elevated peripheral eosinophil counts, a higher number of these cells are also present in the airways prior to fluoride exposure. This would assume that an early triggering of eosinophils takes place at fluoride-exposure, particularly during peak exposures. Fluoride is known to have a stimulating effect *in vitro* on enzymes from the eosinophil, for instance peroxidase [26]. The toxic characteristic of the cell may, thus, be enhanced during natural exposure to fluorides.

Our results are consistent in the two plants studied, thus supporting the overall conclusion, that relatively elevated eosinophil numbers is a risk factor for the subsequent development of potroom asthma in workers without respiratory symptoms, normal lung function and normal bronchial responsiveness. Further research is necessary to confirm the hypothesis that fluorides can induce an immunologic process or trigger eosinophils directly.

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