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Is potroom asthma due more to sulphur dioxide than fluoride? An inception cohort study in the Australian aluminium industry

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ABSTRACT

Objectives Although an asthma-like syndrome has been recognised in aluminium smelter workers for over 70 years, the causal agent has been difficult to identify.

Methods An inception cohort study was conducted at two Australian aluminium smelters where 446 employees participated over a period of 9 years. Cumulative exposures between interviews were estimated from job histories using a task exposure matrix based on measurements in the smelters. Participants completed an MRC respiratory questionnaire, spirometry and methacholine challenge test. Data were analysed with generalised estimating equations to allow for repeated measurements of each participant.

Results Wheeze and chest tightness, the two symptoms most closely related to asthma, showed associations with occupational exposures. SO₂ exposure was significantly associated with these symptoms, bronchial hyper-responsiveness (BHR) to methacholine (a feature of asthma), airflow limitation (reduced forced expiratory volume in 1 second/forced vital capacity ratio) and longitudinal decline in lung function. Fluoride exposure was associated with the same outcomes, but less strongly. Inhalable dust and the benzene soluble fraction (BSF) were associated with symptoms of asthma and BHR. Although many of the exposures were highly correlated, further modelling suggested that of the known respiratory irritants, SO₂ was more likely than fluoride to be primarily responsible for the symptoms observed. Fluoride, inhalable dust and SO₂ were the most important airborne contaminants associated with effects on lung function.

Conclusions The observed effects were detected at contaminant levels within occupational exposure standards, so further reductions are required, particularly in SO₂ exposures.

INTRODUCTION

Aluminium metal is produced by the electrolytic reduction of alumina (Hall-Heroult process). The production process exposes the smelter workforce to a wide range of airborne respiratory irritants including fluoride and sulphur dioxide. Respiratory irritation was first described in aluminium smelter workers by Frostad in 1936. A systematic review of the peer-reviewed and unpublished literature¹ concluded that potroom exposures were associated with an asthma-like syndrome and chronic airflow limitation. However, the majority of studies

What this paper adds

- Aluminium smelter workers have long been recognised as demonstrating an increased risk of asthma, but the causal agent has not been identified.
- Wheeze, chest tightness, airflow limitation, longitudinal decline in lung function and bronchial hyper-responsiveness were associated with occupational exposures.
- The effects were more closely associated with cumulative exposure to SO₂ than fluoride.
- Further reductions in SO₂ exposure are required in aluminium smelters.

conducted up to that time were cross-sectional and did not adequately characterise occupational exposures. Subsequently Kongerud *et al*² reported a cohort study of potroom workers at Norwegian smelters. Fluoride exposure was associated with the development of asthmatic symptoms in a dose-dependent fashion³ and non-specific bronchial hyper-responsiveness (BHR) in another small substudy.⁴ However, exposure data were incomplete and fluoride may simply have been acting as a marker for other unmeasured contaminants.

'Potroom asthma' continues to occur in aluminium smelters around the world,⁵ despite progressive reductions in all occupational exposures, especially with the introduction of pre-bake smelters which have lower polycyclic aromatic hydrocarbon emission levels than Söderberg smelters.⁶ The identification of the causal agent should permit more targeted interventions to prevent the condition. However, neither epidemiological nor experimental studies have yet identified a specific cause. The best epidemiological evidence is likely to come from an inception cohort study of new workers with detailed longitudinal characterisation of occupational exposures to the wide range of airborne contaminants in aluminium smelters.¹

The Healthwise study of respiratory morbidity, mortality and cancer incidence in an integrated Australian aluminium producer commenced in 1995. The initial cross-sectional studies of smelters,^{7, 8} alumina refineries^{9, 10} and bauxite mines¹¹ have been reported previously. This paper focuses on the inception cohort study of new smelter workers. The aim was to monitor the

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incidence of respiratory symptoms (particularly those related to asthma), changes in lung function and BHR for all new workers throughout their employment. It also aimed to investigate the relationships between occupational exposures and changes in these respiratory outcomes over time.

METHODS (SEE ONLINE DATA SUPPLEMENT FOR FURTHER DETAILS)

This analysis included all eligible new employees starting work after mid 1995 at either of the two smelters excluding anyone previously employed by the company, contractors and vacation students. At initial assessment, participants completed an interviewer-administered questionnaire,¹² lung function and skin prick testing to common aeroallergens. Participants were assessed annually until the end of 2003 or earlier if they terminated employment.

Exposure assessment

All eligible subjects reported a job history at each follow-up assessment comprising jobs and tasks worked, as defined in the site-specific job dictionaries. A task exposure database (TED) was used by the site industrial hygienists to record routine air monitoring for the airborne contaminants: fluorides, sulphur dioxide (SO₂), coal tar pitch volatiles (as benzene soluble fraction, BSF), oil mist and inhalable dust which was added to each site-specific TED each year.¹³ From this a Task Exposure Matrix (TEM) was constructed for each contaminant for each full shift task at each site for each year of follow-up of the study.¹⁴ All individual exposures were assigned using the arithmetic mean for each job/task combination, expressed in mg/m³. By combining the TEM with each subject's job history, the cumulative exposure between interviews (years × mg/m³) was calculated for each contaminant.

Other assessments (see online data supplement for further details)

Demographic and smoking data were recorded at all follow-up assessments. Height was measured at the initial assessment. A rolling seal spirometer was used in accordance with American Thoracic Society (ATS) guidelines.¹⁵ Methacholine was delivered by dosimeter following the ECRHS protocol.¹⁶ *Bronchial hyper-responsiveness* (BHR) was defined as provocative dose causing a 20% fall in forced expiratory volume in 1 second (PD₂₀FEV₁) <4 mg (20 µmol) of methacholine. Skin prick testing¹⁷ was performed with extracts of four common aeroallergens. *Atopy* was defined as a positive reaction to any allergen with an average weal diameter ≥3 mm greater than the negative (saline) control.

Statistical analysis

Statistical analysis was performed using the Generalised Estimating Equations (GEE) method¹⁸ to account for the correlation among repeated measurements from an individual during follow-up. Logistic models were used in the analysis of symptom and BHR data, which adjusted for age, gender, age and gender interaction, smoking, smelter site, atopy, and interaction between gender and smoking. Linear models were used in the analysis of lung function data, which adjusted for age, gender, age and gender interaction, smoking, smelter site, height at entry interview, and interaction between gender and smoking. GEE models with two exposures were fitted by simultaneously including both exposure variables in the mean response equations while adjusting for the other explanatory variables. All statistical analyses were conducted using Stata software¹⁹ V.9. Two-sided p values <0.05 were considered statistically significant.

Ethics

The study was approved by the Standing Committee on Ethics in Research Involving Humans at Monash University. All participants provided written informed consent.

RESULTS

Description of participants

A total of 446 aluminium smelter workers were recruited into the study, being 77% of the 583 eligible workers who commenced during the time period. The study sample consisted of 287 (80%) of the 361 eligible workers at smelter A and 159 (72%) of the 222 at smelter B. Their demographic characteristics at the entry interview and year of entry are described in table 1. There was a higher proportion of male subjects at smelter A than B. Most of the participants were under 35 years old, with a median age for male subjects of 30 (IQR 23–36) years and female subjects 31 (IQR 25–37) years. At baseline interview, symptoms of asthma were reported by some participants (22.6% wheeze, 10.6% chest tightness) and 9.4% had doctor-diagnosed asthma. Baseline lung function was mostly within normal limits, that is, within two standard deviations of predicted values (table 2). A majority of participants (57%) were atopic on skin prick testing. Among male participants, the proportion of current smokers at smelter A (32%) was marginally higher than at smelter B (23%). Among female participants, 39% and 28% were current smokers at smelters A and B, respectively. The overall proportions of former (19%) and never smokers (51%) did not differ significantly between sites.

A total of 1660 interviews were conducted; most (58%) follow-ups were conducted between 300 and 400 days after the previous interview. Employees participated in up to nine interviews with a median of three interviews at smelter A and four at smelter B. Among male participants, the median duration of follow-up was 1064 (IQR 585–1715) days. Among female

Table 1 Demographic characteristics at entry interview by smelter site

	Smelter A (n=287)		Smelter B (n=159)	
	Number	%	Number	%
Year of entry interview				
1995	30	10.5	5	3.1
1996	26	9.1	28	17.6
1997	10	3.5	29	18.2
1998	32	11.1	16	10.1
1999	38	13.2	15	9.4
2000	38	13.2	33	20.8
2001	35	12.2	14	8.8
2002	45	15.7	15	9.4
2003	33	11.5	4	2.5
Gender				
Male	221	77.0	105	66.0
Female	66	23.0	54	34.0
Age (years)				
<25	81	28.2	38	23.9
25–29	66	23.0	31	19.5
30–34	62	21.6	30	18.9
35–57	78	27.2	60	37.7
Broad work group*				
Office	75	27.6	32	21.3
Maintenance	29	10.7	16	10.7
Production	168	61.8	102	68.0

*Twenty-four missing because they did not attend follow-up interviews.

Table 2 Demographic and lung function data at entry interview by gender

	Male (N = 326)		Female (N = 120)	
	Median	Interquartile range	Median	Interquartile range
Age at entry interview (year)	30.0	23.0–36.0	31.0	25.8–37.0
FEV ₁ (litre)*	4.49	4.10–4.89	3.32	3.07–3.68
FEV ₁ (% predicted)*	98.2	91.6–105.8	101.1	94.5–109.2
FVC (litre)*	5.53	4.97–6.05	4.04	3.63–4.34
FVC (% predicted)*	100.4	93.8–107.8	103.2	95.5–110.9
FEV ₁ /FVC* (%)	82.5	78.8–85.4	83.7	80.7–86.4
Bronchial hyper-responsiveness†	n=90	(29.3%)	n=41	(39.1%)
PD ₂₀ (mg methacholine)‡	0.42	0.17–1.57	0.36	0.19–1.05

*Five did not perform lung function tests. See online data supplement for prediction equations.

†Thirty-six employees did not have methacholine challenge tests. Results are numbers and proportions of those tested who demonstrated bronchial hyper-responsiveness (BHR) (PD₂₀<4 mg methacholine).

‡In those participants demonstrating BHR. Six were excluded because of missing skin tests.

FEV₁, forced expiratory volume in 1 second; FVC, forced vital capacity; PD₂₀, provocative dose causing a 20% fall in FEV₁.

participants, the median duration of follow-up was 1190 (IQR 768–2009) days. The duration of follow-up of production workers was similar between the two sites. Change of broad work group from one interview to the next was uncommon, with 98% of production, 96% of office and 95% of maintenance workers remaining in the same group over the follow-up period.

Occupational exposures

Cumulative exposures between interviews to the five contaminants of interest were described by tertiles (table E2). The highest prevalence and range of exposures occurred for inhalable dust. Only the 30 workers in the rolling mill at Smelter A were exposed to oil mist. The 95th percentiles for all contaminants were below the current Australian Exposure Standards for an 8 h shift.²⁰ The only standard ever exceeded was for inhalable dust. Of the 1146 interviews where there was a current exposure to inhalable dust, 13 (1.1%) were above the standard of 10 mg/m³.

Occupational exposures and symptoms

The prevalence of wheeze increased during follow-up among male subjects, but not female subjects (figure 1). The incidence of wheeze ranged from 10/100 to 28/100 person-years in the male subjects and from 9.8/100 to 22/100 person-years in the female subjects (figure 1). Wheeze was associated with cumulative exposures between interviews to BSF, fluoride, inhalable dust and SO₂, but not oil mist (table 3). The coefficients per tertile and trend were most significant for SO₂. Typical effects of covariates and potential confounders are shown in table E3, for example, wheeze was associated with smoking and site in male subjects and atopy in female subjects. The incidence of chest tightness ranged up to 15/100 person-years in the male subjects and up to 27/100 person-years in the female subjects (figure E2). The findings were similar for chest tightness (table 3), although there was no statistically significant effect of fluoride exposure. The association between wheeze and gaseous fluoride (OR 1.19, 95% CI 1.01 to 1.41 per tertile) was very similar to total fluoride (see table E7). When fluoride and SO₂ were fitted simultaneously to the model for wheeze, only the coefficient for SO₂ remained statistically significant (table E4). There was no statistically significant interaction between fluoride and SO₂ for wheeze. When fluoride and inhalable dust were fitted simultaneously, the coefficient for fluoride was no longer statistically significant (see table E4). The incidence of doctor-diagnosed asthma was 1.7/100 person-years, and the numbers were too small to permit further analysis.

Occupational exposures and lung function

None of the contaminants were associated with the levels of FVC or FEV₁ (table E5). However, lower values of the forced expiratory ratio (FEV₁/FVC) were associated with greater

cumulative exposures between interviews to BSF, fluoride and SO₂ (table 4). The findings for gaseous fluoride (−4.48‰, 95% CI −7.24 to −1.73) were very similar to those for total fluoride (table E8). When fluoride and SO₂ were fitted simultaneously to the model, only the coefficient per tertile of SO₂ remained statistically significant (see table E6) and there was no statistically significant interaction between the two contaminants. When inhalable dust and SO₂ were fitted simultaneously, only the coefficient for SO₂ remained statistically significant. When fluoride and inhalable dust were fitted simultaneously, neither coefficient was statistically significant (table E6). When the analysis was stratified by gender, the statistically significant associations were largely confined to male employees. Furthermore consecutive decline in FEV₁ was associated with greater cumulative exposures to fluoride, inhalable dust and SO₂ (table 4). Again the findings for gaseous fluoride (men −8.23, 95% CI −15.6 to −0.90; women −7.97, 95% CI −15.2 to −0.74) were similar to those for total fluoride (table E9). Consecutive decline in FVC was also statistically significantly associated with greater cumulative exposures to the same three contaminants (table 4).

Occupational exposures and BHR

At entry, 131 (32.0%) of 410 participants with acceptable challenge tests demonstrated BHR to methacholine. Male participants were less likely to achieve a PD₂₀ than were female participants, particularly at Smelter B (table 2). Overall, the median PD₂₀ was 0.41 mg (range 0.005–3.67 mg) of methacholine. Of these participants, 93 (22.6%) had only a baseline methacholine challenge test, 98 (23.8%) had two tests and the remaining 221 (53.6%) had three to nine tests. The likelihood of BHR on follow-up tests increased significantly with cumulative exposure to BSF, fluoride, inhalable dust and SO₂ (table 5). The findings for gaseous fluoride were similar to total fluoride (trend per tertile OR 1.27, 95% CI 1.07 to 1.51) (table E10). Conversely BHR was significantly less likely in the tertile with the highest exposure to oil mist. Typical effects of covariates and potential confounders are shown in table E11, for example, BHR was associated with current smoking in female subjects and atopy in both genders. There were no statistically significant relationships between BSF, fluoride, inhalable dust or SO₂ and a continuous measure of bronchial responsiveness — log dose response slope (DRS) (table E5).

DISCUSSION

This is one of the first inception cohort studies to be conducted in aluminium smelter workers. Symptoms of asthma such as wheeze and chest tightness were significantly associated with

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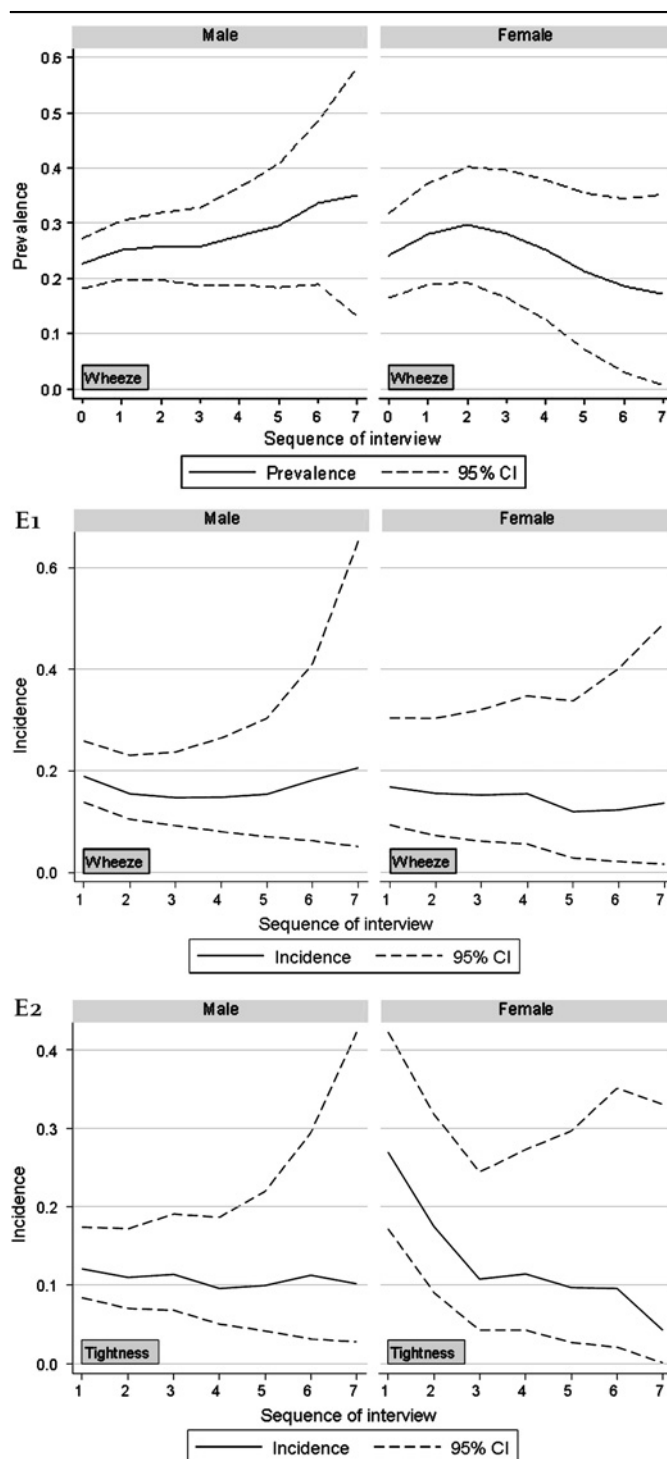


Figure 1 Smoothed prevalence and incidence curves (and 95% CIs) for wheeze and chest tightness reported at successive interviews by gender.

cumulative exposures between interviews to SO_2 , inhalable dust and BSF. Fluoride exposure was weakly associated with wheeze, but not chest tightness. Airflow limitation and longitudinal decline in lung function were associated with exposures to SO_2 and fluoride. Inhalable dust, SO_2 , fluoride and BSF exposures were all associated with BHR, a feature of asthma.

These findings have some consistency with previous largely cross-sectional studies of potroom asthma,^{1 2} although the present design has permitted more detailed investigation of correlated exposures. An increased risk of airflow limitation

Table 3 Associations between wheeze, chest tightness and cumulative exposures between interviews*

Contaminant	Wheeze OR (95% CIs)†	Chest tightness
BSF		
Tertile 1	0.89 (0.60 to 1.33)	0.85 (0.52 to 1.41)
Tertile 2	2.10 (1.41 to 3.12)	1.82 (1.16 to 2.83)
Tertile 3	1.40 (0.90 to 2.16)	1.36 (0.82 to 2.24)
Trend‡	1.21 (1.06 to 1.38)	1.18 (1.01 to 1.38)
	p=0.005	p=0.04
Fluoride		
Tertile 1	0.76 (0.51 to 1.12)	1.03 (0.62 to 1.70)
Tertile 2	0.95 (0.64 to 1.40)	0.83 (0.49 to 1.41)
Tertile 3	1.47 (0.96 to 2.24)	1.40 (0.85 to 2.32)
Trend‡	1.16 (1.00 to 1.34)	1.11 (0.93 to 1.31)
	p=0.04	p=0.25
Inhalable dust		
Tertile 1	0.93 (0.62 to 1.39)	1.02 (0.64 to 1.64)
Tertile 2	1.32 (0.89 to 1.95)	1.31 (0.80 to 2.12)
Tertile 3	1.72 (1.13 to 2.63)	1.66 (1.03 to 2.67)
Trend‡	1.24 (1.08 to 1.42)	1.20 (1.03 to 1.41)
	p=0.002	p=0.02
SO_2		
Tertile 1	0.84 (0.56 to 1.27)	0.63 (0.39 to 1.03)
Tertile 2	1.57 (1.03 to 2.40)	1.05 (0.63 to 1.75)
Tertile 3	1.76 (1.18 to 2.63)	1.72 (1.08 to 2.72)
Trend‡	1.26 (1.10 to 1.44)	1.23 (1.05 to 1.44)
	p=0.001	p=0.01
Oil mist		
Tertile 1	0.76 (0.39 to 1.50)	0.85 (0.34 to 2.14)
Tertile 2	0.61 (0.30 to 1.26)	0.67 (0.24 to 1.87)
Tertile 3	0.75 (0.34 to 1.65)	0.38 (0.15 to 0.98)
Trend‡	0.86 (0.68 to 1.08)	0.76 (0.56 to 1.04)
	p=0.19	p=0.09

*The number of interviews used in the analysis n=1554 for exposures other than oil mist and n=960 for oil mist.

†Adjusted for age, gender, age and gender interaction, smoking status, smelter site, atopy, and interaction between gender and smoking status.

‡The test for trend compared the unexposed (reference) category with the tertiles for each contaminant.

associated with BSF exposure has been demonstrated previously in a prebake smelter.²¹ However, we found fewer associations with fluoride exposure than some studies.² The findings were also consistent with our previous cross-sectional analysis of Healthwise data.⁷ The longitudinal analysis was less affected by movement of workers between broad work groups than was the cross-sectional analysis.

It is generally considered that potroom asthma is likely to represent an irritant effect of pot fumes, although Norwegian studies have raised the possibility of hypersensitivity.² Previous studies have experienced difficulty identifying the causal agent, because of coexposure where most workers are simultaneously exposed to multiple contaminants. While there were significant correlations between the potroom contaminants in our study (table E12), it was still possible to distinguish their effects. Fitting both contaminants simultaneously in models suggested that SO_2 exposure was more likely to be responsible for wheeze and airflow limitation than was fluoride exposure. The site with the least collinearity of exposures also showed the strongest associations with SO_2 (data not shown). However, we were unable to distinguish which contaminant was primarily

Table 4 Associations between forced expiratory volume in 1 second (FEV₁)/forced vital capacity (FVC) (%₀₀), consecutive change in FEV₁ and FVC (ml) and cumulative exposures between interviews*

Contaminant	FEV ₁ /FVC (% ₀₀) Regression coefficient (95% CIs)†	Consecutive change in FEV ₁ (ml)	Consecutive change in FVC (ml)
BSF			
Tertile 1	−9.0 (−15.9 to −2.1)	−0.68 (−25.1 to 23.8)	−39.6 (−76.4 to −2.8)
Tertile 2	−13.8 (−21.5 to −6.1)	−2.1 (−29.8 to 25.7)	−6.5 (−28.7 to 15.7)
Tertile 3	−9.9 (−17.3 to −2.5)	−20.6 (−40.5 to −0.63)	−15.0 (−34.3 to 4.4)
Trend‡	−2.4 (−4.5 to −0.19) p=0.03	−5.8 (−11.8 to 0.19) p=0.06	−4.81 (−10.7 to 1.1) p=0.11
Fluoride			
Tertile 1	−3.2 (−11.1 to 4.7)	−20.5 (−40.6 to −0.42)	−18.4 (−36.5 to −0.30)
Tertile 2	−2.1 (−9.8 to 5.6)	−22.4 (−45.4 to 0.68)	−34 (−57.0 to −10.9)
Tertile 3	−8.3 (−17 to 0.32)	−33.0 (−51.5 to −14.6)	−28.1 (−48.4 to −7.7)
Trend‡	−2.8 (−5.4 to −0.16) p=0.04	−10.5 (−16.3 to −4.6) p<0.001	−10.2 (−16.5 to −3.9) p=0.002
Inhalable dust			
Tertile 1	−7.3 (−14.7 to 0.07)	−15.5 (39.1 to 8.1)	−34.9 (−55.6 to −14.3)
Tertile 2	−7.0 (−14.1 to 0.07)	−8.7 (−36.0 to 18.5)	−32.6 (−54.2 to −11.0)
Tertile 3	−8.0 (−15.8 to −0.14)	−24.0 (−43.9 to −4.1)	−34.1 (−53.1 to −15.1)
Trend‡	−1.3 (−3.3 to 0.75) p=0.22	−6.4 (−11.8 to −1.1) p=0.02	−10.8 (−16.7 to −4.8) p<0.001
SO₂			
Tertile 1	−10.5 (−18.4 to −2.5)	−39.7 (−75.3 to −4.2)	−36.4 (−63.9 to −8.9)
Tertile 2	−10.3 (−17.8 to −2.7)	−32.1 (−53.9 to −10.4)	−24.0 (−51.5 to 3.6)
Tertile 3	−16.8 (−25.1 to −8.4)	−41.7 (−62.2 to −21.1)	−28.0 (−48.6 to −7.3)
Trend‡	−4.0 (−6.1 to −1.9) p<0.001	−13.7 (−20.2 to −7.3) p=0.001	−9.5 (−15.4 to −3.6) p=0.002
Oil mist			
Tertile 1	7.2 (−4.8 to 19.1)	−11.2 (−67.6 to 45.2)	30.9 (−13.2 to 75.1)
Tertile 2	3.4 (−4.7 to 11.4)	−13.1 (−46.9 to 20.8)	2.6 (−42.8 to 48.0)
Tertile 3	10.0 (−1.00 to 21.0)	2.4 (−25.2 to 30.1)	0.62 (−34.5 to 35.8)
Trend‡	2.9 (−0.58 to 6.4) p=0.10	−0.92 (−9.2 to 7.3) p=0.83	1.1 (−9.1 to 11.2) p=0.84

*The number of interviews used in the analysis n=1547 for exposures other than oil mist and n=920 for oil mist.

†Adjusted for age, gender, age and gender interaction, smoking status, smelter site, height at entry interview, and interaction between gender and smoking status.

‡The test for trend compared the unexposed (reference) category with the tertiles for each contaminant.

responsible for BHR or longitudinal decline in lung function. Further investigations would require use of less standard statistical methods, such as Bayesian analysis.²²

Fluoride has long been considered the most likely causal agent for respiratory effects in smelter workers.^{1–2} It has been the only contaminant measured in some previous studies. A North American study suggested that gaseous fluoride exposure and smoking were the only independent risk factors for the development of potroom asthma.⁵ That study analysed health insurance claims, which may have resulted in underascertainment. In addition, exposure was assessed using routinely collected industrial hygiene data, which undersampled jobs and tasks where the exposure was thought to be less than 30% of the exposure standard. This database was designed for regulatory purposes, rather than for an epidemiological study.

The findings for gaseous fluoride in the present study were similar to those presented for total fluoride. Furthermore short-term experimental exposure of healthy volunteers to hydrogen fluoride at concentrations comparable to aluminium smelters primarily demonstrated upper airway and eye irritation rather than effects on FEV₁.²³ In contrast, SO₂ is a more potent respiratory irritant than fluoride and a well-recognised cause of occupational asthma. For example, repeated peak exposures to

SO₂ were associated with a threefold increased risk of physician-diagnosed asthma among sulphite pulp mill workers.²⁴ It has been long recognised that even at levels below 2.6 mg/m³ SO₂ may induce broncho-constriction in adults with mild asthma.²⁵ Such responses have raised concerns about exposure to peak levels of SO₂ around point sources.²⁶ Further characterisation of tasks associated with peak exposures to SO₂ in aluminium smelters is required.

It is possible that the BSF which includes polycyclic aromatic hydrocarbons was responsible for some of the effects observed on symptoms, lung function and BHR. However, most of these substances are not usually considered respiratory irritants and the levels were generally quite low, well below the occupational exposure standards.²⁰ Nonetheless we cannot exclude the possibility that some other constituent of inhalable dust was responsible for at least some of the effects observed. A significant relationship between total dust exposure and longitudinal decline in FEV₁ has recently been reported in a cohort of Norwegian smelter workers.²⁷ It is also possible that any of these measured contaminants are simply acting as a surrogate for some as yet unidentified sensitising agent.

Potroom asthma is unlikely to be classical immunologically mediated occupational asthma.¹ There are no known respiratory

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Table 5 Association between bronchial hyper-responsiveness and cumulative exposures between interviews*

Contaminant	OR (95% CIs)†
BSF	
Tertile 1	1.08 (0.73 to 1.61)
Tertile 2	1.41 (0.94 to 2.12)
Tertile 3	1.48 (0.96 to 2.30)
Trend‡	1.16 (1.01 to 1.32) p=0.03
Fluoride	
Tertile 1	1.09 (0.70 to 1.71)
Tertile 2	1.32 (0.86 to 2.02)
Tertile 3	1.67 (1.05 to 2.66)
Trend‡	1.17 (1.01 to 1.36) p=0.03
Inhalable dust	
Tertile 1	1.07 (0.70 to 1.63)
Tertile 2	1.39 (0.94 to 2.07)
Tertile 3	1.67 (1.10 to 2.54)
Trend‡	1.24 (1.1 to 1.4) p=0.001
SO₂	
Tertile 1	1.21 (0.80 to 1.82)
Tertile 2	1.61 (1.05 to 2.46)
Tertile 3	1.64 (1.06 to 2.54)
Trend‡	1.19 (1.04 to 1.35) p=0.009
Oil mist	
Tertile 1	0.50 (0.20 to 1.27)
Tertile 2	0.59 (0.33 to 1.05)
Tertile 3	0.08 (0.02 to 0.45)
Trend‡	0.55 (0.42 to 0.73) p<0.001

*The number of interviews used in the analysis n=1321 for exposures other than oil mist and n=780 for oil mist.

†Adjusted for age, gender, age and gender interaction, smoking status, smelter site, atopy, and interaction between gender and smoking status.

‡The test for trend compared the unexposed (reference) category with the tertiles for each contaminant.

BSF, benzene soluble fraction.

sensitisers present in aluminium smelters, no evidence of latency and all our analyses of symptoms and BHR were adjusted for atopy. High-level irritant-induced asthma (reactive airways dysfunction syndrome) is possible, but we did not have adequate data on peak exposures to confirm this. It appears most likely that low-level irritant exposures over longer periods may be responsible²⁸ and that airway inflammation may be caused by a combination of different irritants. This requires further controlled human experiments to clarify the contaminants responsible.

The negative association between oil mist and BHR was unexpected. The levels of exposure were very low and well below the occupational exposure standard. However, this result was based on small numbers of subjects and could be a chance finding in the context of multiple comparisons. Previous studies of occupational exposures to oil mist have not found any consistent associations with asthma prevalence or BHR.²⁹ While there is some evidence that exposure to metal working fluids can be associated with the development of BHR,³⁰ there is much less evidence for exposures to mineral or synthetic oils in other industries.²⁹

The strengths of this study are the inception cohort design and comprehensive assessment of occupational exposures. While there would have been some measurement error in exposure, this is likely to have resulted in non-differential misclassification, biasing risk estimates towards the null. Most of the previous studies in the aluminium industry have been cross-sectional and thus prone to survivor bias. While those who left employment during the present study were younger and more likely to be female than those who remained in the cohort for follow-up, there were no differences in baseline symptoms, lung function or smoking (data not shown). Those ever exposed to fluoride or SO₂ were more likely to remain in the study. In any case, a 'healthy worker' effect would be expected to have underestimated the true effects. In fact, a history of asthma diagnosed by a doctor at any time after the age of 10 years was an exclusion criterion for placement in the potrooms (M Donoghue, personal communication, 2008). Another possible source of bias is using the unexposed administration workers as the reference group for comparisons. However, when the analysis for wheeze was repeated using the first tertile as the reference group, there were stronger and more significant associations with fluoride and SO₂ (data not shown). None of the analyses were adjusted for the use of respiratory protective equipment (RPE) and thus may have overestimated the actual exposures, which in turn would underestimate associations.

In conclusion, this study has found clear dose-response relationships between cumulative exposures to several contaminants at levels below the exposure standards and asthma symptoms, airflow limitation, longitudinal decline in lung function and BHR among aluminium smelter workers. The fitting of more than one contaminant in statistical models suggested that SO₂ was likely to play a greater role in respiratory effects than was fluoride. In Australia, the permitted Time Weighted Average occupational Exposure Standard²⁰ for SO₂ over an 8 h shift is 2 ppm (or 5.2 mg/m³) compared to the National Environment Protection Measure for ambient air of 0.2 ppm over 1 h. This study provides some evidence that the Exposure Standard for SO₂ should be revised as effects were found in workers exposed to levels well below 2 ppm. While some fluoride exposure is unavoidable with the Hall-Heroult process, SO₂ is only a byproduct of the combustion of sulphur contaminating the carbon anodes. The use of lower sulphur petroleum coke, improved fume extraction and more effective RPE may potentially prevent potroom asthma in the future.

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Competing interests Malcolm Sim is the principal investigator of the Healthwise programme of studies, which is funded by Alcoa of Australia A\$700 000 per year. This research grant is paid to Monash University and the University of Western Australia and is used to pay for research staff who work on the study and other direct research costs. Malcolm Sim was also an invited keynote speaker at an aluminium industry-sponsored health conference in 2007 and his travel costs were paid for by Alcoa of Australia, but he received no lecturing or other fee for giving this talk. Bill Musk has been paid by Pauline Pfizer Pharmaceuticals to give lectures on the

epidemiology and the management of mesothelioma in Adelaide and Melbourne. Bill Musk, Nick de Klerk and Lin Fritschi are also investigators of the Healthwise programme of studies, which is funded by Alcoa of Australia. Michael Abramson, Geza Benke, Jisheng Cui, Martine Dennekamp and Anthony Del Monaco have no competing interests to declare.

Ethics approval This study was conducted with the approval of the Standing Committee on Ethics in Research Involving Humans, Monash University.

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