

Occupational asthma caused by automated salmon processing

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Summary

Within 3 months of the opening of a salmon-processing plant in the UK, some workers complained of symptoms suggestive of occupational asthma.

A survey of all 291 employees identified 24 (8.2%) with occupational asthma. The employees worked near machines which generated respirable aerosols containing salmon-serum proteins. The IgE response to these proteins was associated with occupational asthma ($p<0.001$), with increasing severity of symptoms ($p<0.001$), and with working distance from the aerosol source ($p=0.037$). The main factor which predisposed to IgE-antibody production and asthma was cigarette smoking ($p<0.001$), whereas atopy and a previous allergic history did not. The affected employees were reallocated to a low-exposure worksite and factory ventilation was improved. Eleven showed significant clinical and pulmonary function improvement, and continued in employment. Thirteen who still had symptoms were advised to leave, thereafter becoming symptom-free, and regaining normal respiratory function.

Early recognition of symptoms and prompt action to reduce aerosol exposure avoided the long-term reduction in pulmonary functions often associated with occupational asthma.

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Introduction

Occupational asthma has been reported in response to many agents¹ and confidential reporting to the Survey of Work Related Occupational Respiratory Disease (SWORD) project suggests it is under-diagnosed.² In seafood processing, asthma has been described in workers handling prawn, crab, sea squirts, and trout.^{3–6} The salmon farming industry is of increasing economic importance and recent developments include automatic processing. Within three months of the opening of a salmon-processing plant in the UK, several of the workers complained of symptoms suggestive of occupational asthma. We investigated the nature and cause of these symptoms.

Materials and methods

Study design

Cross-sectional survey of the prevalence of occupational asthma and serology among employees of a factory processing Atlantic salmon (*Salmo salar*), 18 months before and 24 months after environmental hygiene improvement, and a nested case-control study of identified cases to examine the host characteristics, exposure, and their interaction.

Subjects

All 291 employees were interviewed to determine occupational, smoking, and medical history, and respiratory symptoms.^{7,8} Subjects had been employed for at least 3 months before environmental improvements. 37 people who joined and remained for more than 3 months after improvements were the post-modification group. A diagnosis of occupational asthma was made on the basis of a new history of asthma with a work-related pattern of symptoms and pulmonary function changes. A group of index cases with severe symptoms were compared in a case-control study with symptom-free workers, matched on smoking habit. Since all the cases were smokers, and there were only 36 symptom-free smokers, these were all included as controls.

Pulmonary function

Pulmonary function was measured with a Vitalograph model S spirometer (Vitalograph Ltd, Buckingham, UK). Predicted normal values were calculated from Knudson's tables.⁹ Subjects recorded daily peak-flow over several weeks; diurnal patterns required 15% variation at work for diagnosis.¹⁰

Serology

IgE levels were measured by radio-immunoassay (Pharmacia Ltd, Milton Keynes, UK); serological atopy was defined as a level greater than 100 IU/mL. IgE and IgG antibody against salmon

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Exposure grade	Job classification	Respirable aerosol concentration, (mg/m ³ , mean [CI])
1	Office work, yard duties, loading and unloading lorries (n=37)	<0.01
2	Dry processing: fish butchery and packing in the cold store and box store (n=122)	0.05 (0.04–0.05)
3	Wet processing: grading, gutting and packing fish, automatic gutting machine (n=131)	3.14 (2.71–3.57)

Table 1: Grades of antigen exposure according to job classification and aerosol concentration

	Cross-sectional survey		Case-control study	
	All employees	Post-modification	Case	Control
Number	291	37	13	36
Age (yr)*	34.8 (33.4–36.1)	35.0 (28.1–41.8)	38.5 (31.8–45.1)	37.3 (33.4–41.2)
Gender (m:f)	214:77	28:9	8:5	24:12
Employment (month)*	18.5 (16.0–21.0)	4.7 (3.7–5.7)	5.0 (0.8–9.2)	19.7 (10.1–29.3)
Exposure (grade)*	2.37 (2.15–2.32)	2.42 (2.18–2.66)	2.9 (2.8–3.1)	2.4 (2.2–2.6)
Smokers†	56% (164)	49% (18)	100% (13)	100% (36)
FEV ₁ (% predicted)*	98.1 (95.3–100.9)	97.6 (92.8–102.5)	52.8 (40.6–65.0)	99.4 (93.7–105.1)
FVC (% predicted)*	102.1 (99.4–104.8)	103.6 (98.3–108.9)	64.4 (50.1–78.7)	103.1 (97.4–108.8)
IgE antibody†	8.6% (25)	0% (0)	84.6% (11)	5% (2)
IgG antibody†	33% (96)	8.1% (3)	61.5% (8)	8% (3)
Total IgE (IU/mL)*	100.1 (74.4, 125.7)	NA	178.7 (–1.6, 359.0)	153.0 (33.5, 272.5)

*mean (95% CI); †% (number); NA=not available.

Table 2: Demographic, pulmonary function and serological data of the study groups

serum was measured by radio-immunoassay¹¹ and enzyme-immunoassays.¹²

Environmental hygiene

Salmon were gutted and washed by automated machines which generated aerosols. This air was recirculated through dry-processing areas but not offices. Concentrations of respirable aerosol (0.01–10 mg/m³) were measured by near-infra-red light scatter (Miniram analyser, model PDM/3, M.I.E. Inc, Bedford, Mass, USA). Two calibrated analysers were used in parallel each passively sampled the atmosphere 10 times in 100 s giving instantaneous readings; each measurement was the mean level of 20 readings.

Analysis

Continuous variables were described by their mean and 95% CI. Significance of differences were assessed by two-sample *t*-test, and associations by Pearson product moment. Associations between categorical variables were assessed by Fisher’s exact test.

Results

Aerosol exposure and study groups

Measurement of respirable aerosol levels in different departments of the factory allowed the grading of exposure to salmon antigen (table 1). There were high concentrations throughout the wet-processing area, and areas distant from the machinery, which shared the recirculated air, had moderate amounts of respirable aerosol. The gutting machines were identified as the source of the aerosols and, after fitting an exhaust ventilation system, the aerosol concentrations were reduced to less than 0.01 mg/m³. The demographic, pulmonary function, and serological details of the study groups are shown in table 2.

Cross-sectional study

Approximately half (144) of the workforce had no symptoms (table 3); 26 had asthma before employment; 121 described symptoms specifically related to their

Symptom category	Symptoms	Proportion
Unrelated to work	Pre-existing asthma or chronic obstructive airways disease, no worsening on employment	9% (26)
Work-related		
0	No symptoms	50% (144)
1	Sneezing, blocked nose, dry cough, sweating, temperature	17% (51)
2	Wheeze, chest tightness, dyspnoea, but no treatment	16% (46)
3	Variations of wheeze and cough with work pattern. Helped by shift to low exposure area. Bronchodilator used	4% (11)
4	As category 3, severe symptoms not helped by shift of work site. Advised to leave work	(13)

Table 3: Symptom severity

working environment; 97 had minor intermittent symptoms suggestive of occupational allergy, which did not need treatment; and 24 had symptoms which required treatment and reversible airways obstruction. In these 24 subjects, there were changes from base-line peak-flow recordings during the working day, and marked changes in daily mean peak-flow levels (figure), confirming the association with work exposure. All were transferred to low exposure areas where 11 had no further symptoms; 13 others remained symptomatic and were advised to leave employment.

There were significant associations between categories of increasing symptom severity and with increasing exposure grade (*p*<0.001), IgE (*p*<0.001), and IgG (*p*=0.037) antibody (table 4). The prevalence of occupational asthma was higher in smokers than in non-smokers (*p*<0.001); in those with IgE antibody (*p*<0.001); atopy (*p*=0.06); and a history of pre-existing asthma (*p*=0.81).

None of the new workers (post-modification group, table 2) developed occupational asthma, but 3 (8%) developed symptoms. There were no remarkable

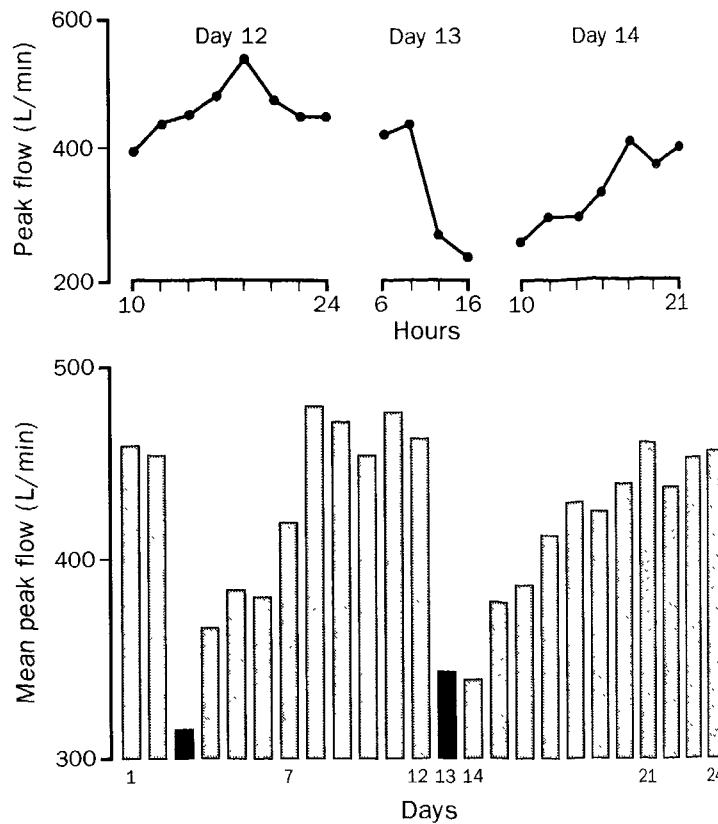


Figure: Top: Diurnal peak-flow measurement in equal hourly intervals during one working day (day 13) with one day at home on either side. Bottom: Mean daily peak-flow measurements for 24 days. Solid bar days at work, grey bar days at home.

	Number	IgE antibody	IgG antibody
Symptom category			
0	144	2.8% (4)	27.8% (40)
1	51	3.9% (2)	27.5% (14)
2	46	2.2% (1)	47.8% (22)
3	11	36.4 (4)	54.6% (6)
4	13	84.6% (11)	61.5% (8)
Exposure grade			
1	37	0% (0)	32.4% (12)
2	122	5.7% (7)	23.0% (28)
3	131	11.5% (15)	42.7% (56)

Table 4: IgE and IgG antibodies

	Current smokers n=164	Never-smokers n=91
Total IgE (IU/mL)	106.5 (69.4–143.4)	85.8 (46.1–125.5)
Salmon-specific IgE (U/mL)	3.8 (2.3–5.4)	0.9 (0.9–1.0)
Salmon-specific IgG (U/mL)	13.5 (5.9–21.0)	53.3 (21.4–85.1)

Table 5: Immunoglobulin and antibody isotype levels (mean CI) according to smoking history

differences in age, gender-distribution, or smoking habit between the two groups. The IgE and IgG seropositivity in the post-modification group was 0% and 8.1% (3) respectively whereas in the exposed group it was 8.6% (25) and 33% (96).

Case-control study

Index cases were matched with asymptomatic controls (table 2). Because smoking itself may contribute to pulmonary function abnormalities and smoking was associated with disease in the cross-sectional study, controls were matched for smoking status (mean pack years 19.5 [CI 12.8–25.5] and 17.7 [12.3–23.1] respectively), as well as for age and gender. Index cases had significantly less exposure in terms of months in employment (p=0.006), and had significantly reduced pulmonary function measurements (p<0.001).

After 3 months follow-up, the pulmonary function of the index cases improved. The FEV₁ (% predicted mean [CI]) increased to 87.7% (83.0–92.4), and the mean FVC increased to 94.5%, within the normal range (80–120%).

Interactions between variables

There was no significant effect of age, gender, or months of exposure on either the serology or the symptom category. There was a significant association between exposure grade and IgE antibody (p=0.037), and IgG antibody (p=0.004) production. There was a significant association between symptoms and serology, and between symptoms and smoking, therefore the association between antibody and smoking was investigated (table 5). Smokers had significantly greater IgE and IgE responses, and non-smokers had significantly greater IgG responses (p<0.001 for both).

Discussion

We have shown an 8.2% prevalence of occupational asthma caused by exposure to respirable aerosols containing salmon-serum antigens generated by processing machinery which persisted in the factory atmosphere because the ventilation system was enclosed, as required by food hygiene standards. Static aerosol levels of up to 3.14 mg/m³ were recorded, which meant that peaks around 5 mg/m³ were likely. There was sufficient antigen in the aerosol to be detectable by immunoprecipitation, about 0.1–1 ug/mL.

There is no agreed safe level for toxic or biologically active respirable dusts, and levels of antigen at tens of

ng/m³ are sufficient to cause respiratory disease.^{11,12} Noxious aerosols were eliminated by isolating and ventilating the source, thereafter normal background levels were maintained.

Long-term lung damage can occur when occupational asthma is not recognised and treated,^{14–16} and exposures of 10 years are common.¹⁷ Dealing with our episode took 18 months; there were no subsequent cases of asthma, no further seroconversion to IgE antibody production and only a few new cases with minor allergic symptoms. All subjects with occupational asthma became symptom-free and almost half were able to continue work.

The allergen was salmon serum distributed by aerosol. IgE antibody production and disease were associated with working close to the aerosol source, but not to length of exposure. The onset of symptoms was rapid; between 2 weeks and 3 months of commencing employment, as in other reports,^{18,19} suggesting that a constitutional factor predisposed to asthma. We found that atopy was not a predictor for this occupational asthma, the most important factor was IgE antibody production, associated with cigarette smoking.^{13,20,21} 56% of the workers were smokers compared with 35% in the local population. The recognition that smoking was a major cause of asthma increased interest among factory personnel in a stop-smoking educational campaign and the introduction of a no-smoking canteen.

The workforce continue to be screened regularly with a health surveillance system required by Health and Safety Executive regulations²³ but no new cases of occupational asthma have been detected. Improvements to the United Kingdom's Industrial Injuries Disablement Benefit Scheme have recently widened the categories for occupational asthma to include fish processing.²⁴

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References

1 Chan-Yeung M, Malo JL. Aetiological agents in occupational asthma. *Eur Respir J* 1994; 7: 346–71.

2 Meredith S. Reported incidence of occupational asthmas in the United Kingdom 1989–1990. *J Epidemiol Community Health* 1993; 47: 459–63.

3 Gaddie J, Legge JS, Friend JAR, Reid TMS. Pulmonary hypersensitivity in prawn workers. *Lancet* 1980; ii: 1350–53.

4 Hudson P, Cartier A, Pineau L, Lafrance M. Follow up of occupational asthma caused by crab and various agents. *J Allergy Clin Immunol* 1985; 76: 682–88.

5 Meguro T, Ogata M. Analysis of maximal expiratory flow volume patterns in sea squirt asthma patients. *Indust Health* 1990; 28: 133–38.

6 Sherson D, Hansen I, Sigsgaard T. Occupationally related respiratory symptoms in trout processing workers. *Allergy* 1989; 44: 336–41.

7 Cartier A. Definition and diagnosis of occupational asthma. *Eur Respir J* 1994; 7: 153–60.

8 Sherwood Burge P. Problems in the diagnosis of occupational asthma. *Chest* 1987; 81: 105–15.

9 Knudson RJ, Lebowitz MD, Holberg CJ, Burrows B. Changes in the normal maximal expiratory flow curve with growth and ageing. *Am Rev Dis* 1983; 127: 725–34.

10 Burge PS. Use of serial measurement of peak flow in the diagnosis of occupational asthma. *Occup Med* 1993; 8: 279–94.

11 Edwards RG, Spackman DA, Dewdney JM. The development and use of three new radioallergosorbent tests in the diagnosis of penicillin allergy. *Int Archs Allergy Appl Immunol* 1980; 68: 352–57.

12 McSharry C, Anderson K, McKay IC, et al. The IgE and IgG antibody responses to aerosols of *Nephrops norvegicus* (prawn) antigens: the association with clinical hypersensitivity and with cigarette smoking. *Clin Exp Immunol* 1994; 97: 499–504.

13 Venables KM, Topping MD, Howe W, Luczynska CM, Hawkins R,

- Newman-Taylor AJ. Interactions of smoking and atopy in producing specific IgE antibody against a hapten protein conjugate. *BMJ* 1985; **290**: 201-04.
- 14 Malo JL, Cartier A, Ghezzi H, et al. Patterns of improvement in spirometry, bronchial hyperresponsiveness, and specific IgE antibody levels after cessation of exposure in occupational asthma caused by snow-crab processing. *Am Rev Respir Dis* 1988; **128**: 807-12.
- 15 Gannon PF, Weir DC, Robertson AS, Burge PS. Health, employment and financial outcome in workers with occupational asthma. *J Allergy Clin Immunol* 1993; **91**: 1121-27.
- 16 Paggiaro PL, Vagagnini B, Bacci E, et al. Prognosis of occupational asthma. *Eur Respir J* 1994; **7**: 761-67.
- 17 Stenton SC, Sandhu PS, Hendrick DJ. Industrial injury benefit for occupational asthma in north east of England. *BMJ* 1995; **310**: 1299-300.
- 18 Gross NJ. Allergy to laboratory animals: epidemiologic, clinical and physiological aspects, and a trial of cromolyn in its management. *J Allergy Clin Immunol* 1980; **66**: 158-65.
- 19 Davies GE, Thompson AV, Niewola Z, et al. Allergy to laboratory animals: a retrospective and prospective study. *Br J Indust Med* 1983; **40**: 442-49.
- 20 Venables KM, Upton JL, Hawkins ER, Tee RD, Longbottom JL, Newman-Taylor AJ. Smoking, atopy, and laboratory animal allergy. *Br J Indust Med* 1988; **45**: 667-71.
- 21 Burrows B, Halonen M, Barbee RA, Lebowitz M. The relationship of serum immunoglobulin E to cigarette smoking. *Am Rev Respir Dis* 1981; **124**: 523-25.
- 22 Newman-Taylor A, Tee RD. Environmental and occupational asthma. Exposure assessment. *Chest* 1990; **98**: 209-11.
- 23 Surveillance of People Exposed to Health Risks at Work. Principles and practice for the surveillance of people exposed to physical, chemical and biological health risks at work. HSE HS(G) 61. HMSO, London 1990.
- 24 Industrial Injuries Disablement for Occupational Asthma. Benefits Agency. UK. Department of Social Security, form BI 100 (OA). London 1991.

Use of glycosaminoglycans to increase efficiency of long-term continuous peritoneal dialysis

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Long-term continuous ambulatory peritoneal dialysis (CAPD) frequently induces progressive structural changes in the peritoneal membrane, leading to dialysis failure. Because heparin and glycosaminoglycans favourably remodel anatomical barriers exposed to injury, we studied the effect of intraperitoneal administration of glycosaminoglycans on peritoneal dialysis efficiency. 16 CAPD patients received glycosaminoglycans for 30 days followed by a 30-day wash-out. Glycosaminoglycans in urea and creatinine dialysate-to-plasma ratios significantly increased (means 0.86 and 0.78 at baseline, 0.92 and 0.82 at 30 days, respectively). Peritoneal protein loss was reduced, and serum albumin concentration increased. We now need to assess whether glycosaminoglycans can postpone dialysis failure in the long term.

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One of the major limiting factors in long-term continuous ambulatory peritoneal dialysis (CAPD) is the anatomical and functional derangement that frequently occurs in the peritoneal membrane, due to the synthetic nature of available dialysis solutions.¹ We recently demonstrated that the administration of heparin or other glycosaminoglycans prevented nephropathy in diabetic rats by maintaining a normal glomerular basement-membrane thickness and anionic charge-density with parallel prevention of the onset of albuminuria.^{2,3} Heparin prevents glomerulosclerosis in uraemic rats with subtotal renal ablation, and in nephropathy induced by chronic administration of puromycin, habu snake venom, or Thy 1-1 antibodies.²⁻⁴ In the experimental model of endothelial stripping of the carotid arteries, heparin administration prevents intimal thickening.⁵ Breborowicz et al⁶ reported that chondroitin sulphate, another glycosaminoglycan, prevented ultrafiltration loss in rats during peritoneal dialysis. We have also observed that the administration of a glycosaminoglycans mixture has a protective effect on peritoneal structure and function in

the peritoneal fibrosis induced by the toxicity plasticiser (diethylexylphthalate) in the subtotally nephrectomised rat.⁷ These observations led us to verify the effect of glycosaminoglycans on the efficiency of peritoneal dialysis in patients on long-term CAPD.

We studied 16 patients (mean age 62 years, range 38-72; four women) who were selected consecutively from those on long-term CAPD (more than 2 years) and who had not had more than one peritonitis episode in the 6 months before study. All patients gave informed consent to participate. Mean duration of CAPD was 38 months (range 32-49). CAPD was administered for end-stage renal failure due to glomerulonephritis in 12 cases, interstitial nephropathy in two, and diabetic nephropathy and lupus nephritis in one each.

Throughout study, the scheduled dialysis programme during the day consisted of three 2000 mL bags containing (mmol/L): sodium 136.0, potassium 2.0, chloride 104.7, calcium 1.75, magnesium 0.38, lactate 37.5, and glucose 83.3, and one 2000 mL bag with the same composition except for glucose at 220.2 mmol/L. During the night, we used one 500 mL bag of the same solution except glucose was at 111.1 mmol/L. During the initial 30-day intervention period, 50 mg sulodexide, a heparinoid formulation, was administered intraperitoneally in the night bag, which was supposed to stay in the peritoneal space for 8-10 h. Sulodexide (Vessel Due F, Alfa Wassermann SpA, Bologna) is 80% low-molecular-weight heparin and 20% low-molecular-weight dermatan sulphate, as is approved for human use in chronic vascular diseases by the Italian Ministry of Health. The intervention period was followed by a 30-day wash-out. During the 60 days of study, oral fluid and protein intake (1.2 g/kg) were kept constant.

Blood was drawn after an overnight fast. Peritoneal fluid samples were collected from all five daily dialysis exchanges on 2 consecutive days immediately before intervention, on days 29-30, and at the end of wash-out. Coagulation status was monitored by evaluation of platelet count, blood fibrinogen, prothrombin, and activated prothrombin times. Urea was measured by the urease enzymatic method. Creatinine was assayed by Jaffe's colorimetry and total proteins by the biuret method. The urea and creatinine dialysate-to-plasma (D/P) ratios were calculated. Net ultrafiltration was calculated by weighing as the difference between drained volume plus samples and infused fluid. Data are expressed as mean and SD of five dialysis changes per day, for the 2 consecutive days.

In both the interventional and wash-out periods, the patients' hydration status, blood pressure, residual renal function (creatinine clearance), and coagulation indices remained constant at their usual levels. The patients' ordinary drug therapy (diuretics, antihypertensive drugs, &c) did not require changes, and no patient had peritonitis or coagulation disorders.

Sulodexide induced a significant increase in urea and creatinine D/P ratios but significantly decreased peritoneal protein losses, an effect that was paralleled by