Eur Respir J 2006; 27: 714–719
DOI: 10.1183/09031936.06.00034705

Airway inflammation in iron ore miners exposed to dust and diesel exhaust

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ABSTRACT: The aim of the present study was to investigate if underground miners exposed to dust and diesel exhaust in an iron ore mine would show signs of airway inflammation as reflected in induced sputum.

In total, 22 miners were studied, once after a holiday of at least 2 weeks and the second time after 3 months of regular work. Control subjects were 21 ''white-collar'' workers. All subjects completed a questionnaire regarding medical and occupational history, and underwent lung function testing and induced sputum collection. Total and differential cell counts and analyses of the fluid phase of the induced sputum were performed. Sampling of personal exposure to elemental carbon, nitrogen dioxide and inhalable dust was recorded.

The average concentrations of inhalable dust, nitrogen dioxide and elemental carbon were 3.2 mg·m^{-3}, 0.28 mg·m^{-3} and 27 μg·m^{-3}, respectively. Miners had increased numbers of inflammatory cells, mainly alveolar macrophages and neutrophils, and increased concentrations of fibronectin, metalloproteinase-9 and interleukin-10 in induced sputum compared with controls.

In conclusion, miners in an underground iron ore mine demonstrated persistent airway inflammation that was as pronounced after a 4-week holiday as after a 3-month period of work underground in the mine.

KEYWORDS: Airway inflammation, diesel exhaust, dust

Studies have shown increased occurrence of respiratory diseases, such as silicosis and bronchitis, in miners [1, 2]. The air pollution in mines is complex and variable. The emissions come from a variety of sources, including dust from drilling, blasting and handling of the ore/rock and exhaust from vehicles. Silicosis has a well-defined causative agent, silica dust, but the cause of chronic bronchitis and chronic obstructive pulmonary disease in miners is not as clear [3–5]. Even if the air pollution in mines has decreased in recent years due to improved ventilation and new techniques, the levels might still be higher than in other occupational environments since mining occurs in closed spaces. In the past, quartz dust was a serious hazard in Swedish iron mines, but after extensive improvements of the working environment since the beginning of the 1970s, the risk of miners developing silicosis today is low [2]. Studies of Swedish iron mines have indicated an increased risk of chronic bronchitis, although only in underground miners who are smokers [3–5].

The airway effects of high exposures to diesel exhaust have been investigated in controlled experimental studies [6–13]. The investigational methods included lung function measurements [6, 9], bronchoscopy with bronchial biopsies and airway lavages [7, 8, 10] and, more recently, induced sputum [11–13]. Study populations have included healthy control subjects as well as asthmatics with different disease severity [6, 10–13]. The experimental diesel exhaust exposure studies have shown neutrophilic and lymphocytic inflammatory responses in the airway mucosa, bronchial lavage and sputum, as well as markers of activation of various cell types [6–12]. However, the experimental studies have only employed short-term exposure at high concentrations and it is unclear if the results can be generalised to long-term occupational exposure at lower levels.

The aim of the present study was to investigate if airway inflammation, reflected in induced sputum, was present in healthy nonsmoking underground miners working in an iron mine with high levels of dust and diesel exhaust. To the current authors' knowledge, this is the first study to investigate miners in a true occupational situation, using induced sputum to assess airway inflammatory responses.

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Received:
March 23 2005
Accepted after revision:
December 30 2005

SUPPORT STATEMENT
The present study was supported by the Swedish Council for Work Life and Social Research (Stockholm).

European Respiratory Journal
Print ISSN 0903-1936
Online ISSN 1399-3003

METHODS

The mining environment

The present study was carried out in a Swedish iron ore mine, where all mining since the 1920s has been carried out underground. The dominant mode of mining is sublevel caving. Diesel-powered engines were introduced into the mine in the mid 1960s.

The air pollution in the investigated mine was complex. The most important sources include diesel exhaust and rock dust, which are vortexed into the air by the traffic in the mine, and/or dust drilling, loading and crushing of the rock/ore. Blasting routinely happens at 00:00 h. The mine is then ventilated until 05:00 h, at which point the miners can enter the mining areas if the levels of carbon monoxide and nitrogen dioxide are satisfactory. However, these blasting gases are also released, to some extent, during the handling of the blasted rock and ore.

Subjects

Healthy underground miners were invited to take part in the study. Eligible subjects were identified from the company health-service registry according to the following entry criteria: 1) no history of respiratory disorder, including bronchitis or any other respiratory symptoms; 2) never-smokers or ex-smokers for $\leqslant$5 yrs; 3) no history of eye and/or nose allergies; 4) no treatment with anti-inflammatory drugs for any condition; 5) underground work in the mine for $\geqslant$3 yrs; and 6) a work site underground with exposure to diesel exhaust during loading, lorry driving, road maintenance or construction work.

Control subjects

Healthy nonsmoking workers (research workers not affiliated with the study, technical staff and office workers), without a history of respiratory conditions, allergies and other disorders and without any relevant medications were invited to participate as control subjects.

All subjects received both verbal and written information about the study and consented to participation. The Ethics Committee of Umeå University (Umeå, Sweden) approved the study.

Study design

The miners were investigated twice. The first examination took place after $\geqslant$4 weeks of a summer holiday in August, and before returning to the mine. This was to investigate subjects under conditions free of recent occupational exposure to diesel exhaust or dust. The second examination was performed in November after $\geqslant$3 months of regular work in the mine.

The investigation included a thorough occupational history pertaining to exposure to dust and diesel exhaust, as well as previous disorders focusing on respiratory conditions and allergies. No respiratory infection within the last 4 weeks of each examination was allowed. Lung function measurements were performed prior to a sputum induction. The control subjects were studied at a single time point during winter months.

Lung function

Lung function measurements were made using a dry bellows spirometer (Vitalograph Ltd, Buckingham, UK). Three reproducible measurements of forced vital capacity and forced expiratory volume in one second (FEV_1) were performed and the best value recorded. The values were expressed as per cent of predicted normal using the reference values from the Coal and Steel Union [14].

Sputum induction

Sputum induction was performed by a method described by PIN *et al*. [15], which was slightly modified. Hypertonic saline (4.5%) was nebulised using an ultrasonic nebuliser (DeVilbis 2000; DeVilbis Co, Somerset, PA, USA) with an output of $\sim$1.5 mL·min^{-1}.

All subjects were pre-treated with an inhaled β_2-agonist (0.2 mg salbutamol) before the induction. Inhalation of the hypertonic saline was made at three intervals of 5 min.

FEV_1 was monitored before and after each inhalation period. Following each inhalation period, subjects were advised to blow their nose and rinse their mouth with water before coughing sputum into a sterile container. The samples obtained were kept on ice for up to 1 h before processing.

Sputum processing

Sputum was processed according to the method described by PIZZICHINI *et al*. [16]. At least 400 nonsquamous cells were counted and differential cell counts were expressed as percentage of the total nonsquamous cell count. The proportion of squamous cells was obtained by counting 400 additional cells and expressing this as a percentage of the total number of cells. Samples were considered adequate for analysis if the squamous cell contamination was <20% and the viability >50%. The total cell count was calculated by dividing the total number of cells by the volume of processed sputum (1 mg=1 μL).

Fluid-phase measurements

Fluid-phase measurements of matrix metalloproteinase (MMP)-9 and fibronectin reflect the activity of alveolar macrophages. Myeloperoxidase (MPO) is an oxidising enzyme whose levels reflect neutrophil activation. Interleukin (IL)-10 is an inflammatory cytokine with predominantly inhibitory actions and is an important modulator of monocyte/macrophage function [17–20].

Myeloperoxidase

MPO was analysed using a radioimmunoassay (Pharmacia MPO RIA; Pharmacia & Upjohn Diagnostics Sverige AB, Uppsala, Sweden). The detection limit of this assay was <8 μg·L^{-1}.

IL-10, MMP-9 and fibronectin

IL-10, MMP-9 and fibronectin were measured by ELISA technique (IL-10 and MMP-9 kits from R&D systems Europe Ltd, Abingdon, UK, and fibronectin from Pharmacia & Upjohn Diagnostics). The minimum detection limits for IL-10, MMP-9 and fibronectin were <0.5 pg·mL^{-1}, <0.156 ng·mL^{-1} and 10 μg·L^{-1}, respectively.

Air sampling

Elemental carbon (EC), nitrogen dioxide and inhalable dust were measured using sampling equipment attached to the

subjects and measurements obtained in the breathing zone of the workers. Two measurements of EC and nitrogen dioxide, and three measurements of inhalable dust were obtained for each miner. Occupational exposures are often quasi log-normally distributed; that is, the log-transformed concentrations follow the normal distribution [21, 22]. By multiple measurements of each worker, the total variance in a group of workers can be divided by within-worker (day to day) and between-worker (within jobs) variance. A uniformly exposed group characterised by a small between-worker variance is sometimes measured by the ratio (BR95) of the 97.5th to the 2.5th percentiles of the means. A group with a ratio >2 is often considered to be uniformly exposed [21].

Elemental carbon

EC was sampled on a glass-fibre filter (SIMPEDS, Safety In Mines Personal Equipment for Dust Sampling; Casella Ltd, Bedford, UK) and the amount was determined by colorometric analysis. The colorometric analysis was performed according to standard VDI 2465 at a Swiss laboratory (Institute Universitaire Romand de Santeau Travail, Lausanne, Switzerland).

Inhalable dust

The amount of inhalable dust was measured with an IOM personal sampler (SKC Inc., Eighty Four, PA, USA) and sampled according to the standard EN 481 [23]. This samples the fraction of particles that enter the nose and mouth with a 50% cut-off point of particles with a diameter of 100 μm [24]. The sampling flow was 1.7–2.1 $L \cdot min^{-1}$. The amount of dust was determined by weighing the filters.

Nitrogen dioxide

Nitrogen dioxide was measured using personal diffusive samplers and ion chromatographic analysis [25].

Statistics

Empirically, occupational exposures are usually log-normally distributed [21] and the Shapiro–Wilk test was used to test the hypothesis of log-normal distributions.

Paired t-tests were used to compare lung function measurements in miners between investigations. Independent sample t-tests were used for comparisons between subjects and controls. Sputum cell counts and fluid-phase measurements are given as median and interquartile range. For the fluid-phase measurements, the Wilcoxon test was used for comparisons in miners between investigations, and a Mann–Whitney U-test was used for comparisons between miners and controls. A p-value <0.05 was considered statistically significant.

RESULTS

Demographics and lung function

The initial study population comprised of 29 male miners. However, six miners were excluded from all analyses due to the inability to produce sputum of sufficient quality for the cell analyses, and one was unable to complete both investigations. Therefore, data are presented for a total of 22 miners from whom paired sputum samples were available. The mean (range) age was 43 (30–59) yrs and, whilst all were current nonsmokers, 10 were never-smokers and 12 ex-smokers. Of the ex-smokers, six had been regular smokers (five had been smoke free for ⩾10 yrs, and one had been free of smoking for at least 6 yrs) and six were previous occasional smokers. Five of the regular ex-smokers had 10–12 pack-yrs and one had a 6-pack-yr history of smoking. None of the subjects had a history of chronic bronchitis. The mean (range) number of years spent working underground was 18 (3–39) yrs.

The control group comprised of 24 male researchers, technical staff members or office workers without allergies or history of respiratory disease or other disorders. All but one were never-smokers. In the control group, the sputum samples were of insufficient quality to be analysed further in three cases. Thus, data from 21 control subjects are reported. The mean (range) age was 40 (25–63) yrs. All subjects, both miners and controls had normal lung function measurements (table 1).

No significant differences in lung function were seen between miners and controls. Lung function measurements in table 1 are from the first assessment of the miners after the holiday. There was no difference in the lung function of the miners between the two test occasions.

Sputum cell findings

The cell viability in sputum was good, with a mean per cent viability of 79% in miners and 78% in control subjects. There were statistically significant differences in the total number of $cells \cdot mL^{-1}$ of sputum between miners and controls. This was mainly due to increased numbers of macrophages and neutrophils in the miners. As shown in table 2, there were no significant differences in numbers of lymphocytes or eosinophils between groups.

The total cell numbers and the differential cell counts were not statistically different between the first and the second sputum induction in the miners (table 3).

Fluid-phase measurements

Levels of MPO measured in sputum from miners on both occasions and controls did not differ. Fibronectin levels and IL-10 were elevated in sputum from miners from both inductions compared with control subjects, but there was no difference between assessments.

TABLE 1 Demographics and lung function

	Miners	Controls
Subjects n	22	21
Age yrs	43 (30–59)	40 (25–63)
Smoking habits n		
Never-smoker	10	20
Ex-smokers	12	1
Mean working time underground yrs	18 (3–39)	
FEV_1 % pred normal	105±11.6	109±11.4
VC % pred normal	101±9.9	106±10.2
FEV %	102±5.7	101±5.8

Data are presented as mean (range) and mean±SD, unless otherwise stated. FEV_1: forced expiratory volume in one second; VC: vital capacity; FEV: FEV_1/VC. All subjects were male.

TABLE 2 Sputum cells, miners I[#] *versus* control subjects

	Miners I	Controls	p-value
Subjects n	22	21	
Total cells $\times 10^6 \cdot mL^{-1}$	4.4 (3.1–6.5)	1.8 (1.6–2.6)	0.0001
Macrophages $\times 10^6 \cdot mL^{-1}$	2.3 (0.9–3.7)	0.8 (0.5–1.3)	0.002
Neutrophils $\times 10^6 \cdot mL^{-1}$	1.5 (0.6–3.6)	0.5 (0.4–1.3)	0.025
Lymphocytes $\times 10^6 \cdot mL^{-1}$	0.1 (0.05–0.4)	0.06 (0.02–0.13)	0.056
Eosinophils $\times 10^6 \cdot mL^{-1}$	0.01 (0.00–0.02)	0.00 (0.00–0.01)	NS

Data are presented as median (interquartile range), unless otherwise stated. NS: nonsignificant. [#]: investigated during holiday before work period.

MMP-9 levels were greater in miners than controls, but were reduced following a 3-month period at work (table 4).

Exposure

Nitrogen dioxide

In total, 29 samples from 18 individuals were collected. For 11 miners, the measurements were made on two occasions. The mean (range) was 0.28 (0.05–0.68) $mg \cdot m^{-3}$.

TABLE 3 Sputum cells in miners I[#] *versus* miners II[¶]

	Miners I	Miners II	p-value
Subjects n	22	21	
Total cells $\times 10^6 \cdot mL^{-1}$	4.4 (3.1–6.5)	3.0 (2.0–4.4)	NS
Macrophages $\times 10^6 \cdot mL^{-1}$	2.3 (0.9–3.7)	1.4 (0.8–2.5)	NS
Neutrophils $\times 10^6 \cdot mL^{-1}$	1.5 (0.6–3.6)	1.1 (0.4–2.0)	NS
Lymphocytes $\times 10^6 \cdot mL^{-1}$	0.1 (0.05–0.4)	0.07 (0.02–0.15)	NS
Eosinophils $\times 10^6 \cdot mL^{-1}$	0.01 (0.00–0.02)	0.01 (0.00–0.03)	NS

Data are presented as median (interquartile range), unless otherwise stated. NS: nonsignificant. [#]: miners at the end of the holiday; [¶]: miners after ⩾3 months' work period.

TABLE 4 Fluid-phase measurements in miners I[#] *versus* miners II[¶]

	Miners I	Miners II	Controls
Subjects n	22	21	21
MPO $mg \cdot mL^{-1}$	312 (210–491)	244 (140–416)	185 (106–342)
Fibronectin $\mu g \cdot L^{-1}$	108 (56–124)***	120 (64–130)[+]	50 (28–92)
MMP-9 $ng \cdot mL^{-1}$	48 (32–120)	38 (17–64)[§]	28 (13–46)[f]
IL-10 $pg \cdot mL^{-1}$	0.7 (0.0–1.4)[##]	1.2 (0–4)[¶¶]	0.0 (0.0–0.4)

Data are presented as median (interquartile range), unless otherwise stated. MPO: myeloperoxidase; MMP: matrix metalloproteinase; IL: interleukin. [#]: miners at the end of the holiday; [¶]: miners after ⩾3 months' work period; [+]: miners II *versus* control subjects, p=0.02; [§]: miners I *versus* miners II, p=0.048; [f]: miners I *versus* control subjects, p=0.03; [##]: miners I *versus* control subjects, p=0.02; [¶¶]: miners II *versus* control subjects, p=0.004; ***: miners I *versus* control subjects, p<0.001.

Elemental carbon

In total, 27 measurements were made for 18 miners, and in eight individuals the measurements were made on two separate occasions. The mean (range) for all measurements was 27 (5–61) $\mu g \cdot m^{-3}$.

Inhalable dust

From 14 miners, 41 measurements were obtained. For all individuals, two or three measurements were made on separate occasions. A single high value of 35 $mg \cdot m^{-3}$ was included in the analysis. The second highest value was 9.3 $mg \cdot m^{-3}$. The mean (range) dust level was 3.2 (0.1–35) $mg \cdot m^{-3}$.

For all exposures, the hypothesis of log-normal distributions could not be rejected. For nitrogen dioxide and EC, the variations within miners were higher than between miners. The ratios between the 97.5th and the 2.5th percentile of the log-normally distributed mean exposures of the miners (between-worker distribution), equivalent to a factor containing 95% of the individual mean exposures derived from log-normal distribution, were 1.2, 1.6 and 5.0 for nitrogen dioxide, EC and inhalable dust, respectively (table 5).

DISCUSSION

The air pollution in mines is complex. Particulates in the study mine had two major sources, dust from the rock/ore and diesel exhaust. The concentration of inhalable dust was variable both between and within workers, but was much higher than the concentrations of EC measured to reflect diesel particles. The between-worker variability, as measured by BR_{95}, was different for inhalable dust and EC, but similar for nitrogen dioxide and EC. Nitrogen dioxide and EC are mainly measures of exposure to diesel exhaust, while inhalable dust reflects the contribution from rock and ore.

EC concentrations of 27 $\mu g \cdot m^{-3}$ are higher than would be encountered in a busy street or road. ZAEBST *et al*. [26] found average levels of ~5 $\mu g \cdot m^{-3}$ in truck drivers, measured inside the truck. However, the present EC levels were considerably lower than the German maximum allowable concentration (MAC) values of 300 $\mu g \cdot m^{-3}$ during occupational underground work [27]. The average concentration of nitrogen dioxide found in this mine was 0.28 $mg \cdot m^{-3}$ (0.16 ppm). This is well below the Swedish MAC of 2 $mg \cdot m^{-3}$ for nitrogen dioxide from diesel exhaust [28], but considerably higher than concentrations of nitrogen dioxide in some Swedish cities where

TABLE 5 Levels of pollutants in the mine and variability between subjects

	Measurements n	Subjects n	Concentration	BR_{95}
NO_2 $mg \cdot m^{-3}$	29	18	0.28 (0.05–0.68)	1.2
Elemental carbon $\mu g \cdot m^{-3}$	27	18	27 (5–61)	1.6
Inhalable dust $mg \cdot m^{-3}$	41	14	3.2 (0.1–35)	5.0

Data are presented as n or mean (range). BR_{95}: ratio of the 97.5th and 2.5th percentile of the log-normally distributed mean of the workers (between-worker variability).

background levels <0.03 mg·m^{-3} are common [29]. For the general environment, there is a limit of 0.09 mg·m^{-3} [30].

The level of inhalable dust in the mine, average 3.2 mg·m^{-3}, was also considerably higher than dust levels in the general environment. The MAC for inorganic dust, sampled as total dust, in Sweden is 10 mg·m^{-3} [28]. There is no direct conversion between dust sampled as total dust and that of inhalable dust, but it seems reasonable to assume that the level of total dust in the mine would be below the MAC.

The induced sputum measurements indicate an ongoing inflammatory process in the airways of miners, which was present even after 4 weeks of summer vacation. The number of inflammatory cells in induced sputum of miners was more than double that of controls with the increase driven by a three-fold increase in alveolar macrophages. Macrophages have an important role in the clearance of inhaled particles. Substantial increases in macrophage numbers have been discussed following occupational exposures to organic and inorganic dust, and following controlled exposure to diesel exhaust [8, 31]. Increased numbers and lifespan of alveolar macrophages have also been found in cigarette smokers [32]. However, in the present study, most miners had been ex-smokers for many years, had a limited number of pack-yrs of smoking, had normal lung function, and no respiratory symptoms. Therefore, the increase in macrophages is considered to be driven by the dust load from the underground mining and not by their previous smoking.

The macrophage is thought to be the main source of fibronectin, which, in miners, was more than double that of controls. Fibronectin is a proinflammatory glucoprotein that enhances phagocytosis and is involved in cell–cell interaction at sites of inflammation. Furthermore, macrophages can be a source of MMP-9. This metalloproteinase is involved in airway remodelling due to its ability to cleave both structural proteins as well as regulatory proteins in the airways. It can also modify cellular function by interaction with cytokines and other factors. MMP-9 is also produced by neutrophils, which were similarly increased in the induced sputum of miners. Neutrophils might act synergistically with the macrophages in response to inhaled particles and potentially cause damage to the lung. Interestingly, despite the increased numbers of neutrophils, there was no increase in MPO, an oxidative enzyme and marker of neutrophil activation. Increased neutrophil numbers have not been an omnipresent finding after particle exposures, but have been consistently raised following exposure to diesel exhaust. While neutrophilic inflammation may be present in earlier stages of diesel exhaust induced inflammation, the activation of these cells appears to be a later event.

When the study was proposed, it was assumed that miners would have an airway inflammatory response due to exposure in the mine during a work period. A period away from work, such as a holiday, was expected to allow recovery from a potential inflammatory state in the airways. Surprisingly, the (nonsignificant) trend was for a higher level of inflammatory cells after the holiday than after the 3-month period at work. This increase was most noticeable for alveolar macrophages. Interestingly, MMP-9, with its ability to induce airway remodelling as a result of a noxious challenge, was significantly higher in the miners after the holiday as compared with during the work period, and the level was increased significantly compared with the control subjects.

IL-10 is an important regulatory cytokine that mainly has an inhibitory function. It originates from T-lymphocytes, epithelial cells and other cells. While this cytokine was undetectable in most control subjects, the miners had substantially elevated levels in induced sputum. The levels were considerably higher during the work period than after the summer vacation, in contrast to MMP-9 and cell numbers, which tended to be higher after the summer holiday. The acute inflammatory events following air-pollution particle exposure seems to be driven by a unique set of signal transduction pathways and kinases, resulting in enhanced production of chemoattractants from epithelial and other cells and, thus, resulting in an influx of inflammatory cells such as neutrophils, macrophages and lymphocytes. IL-10 is one of the major inhibitory cytokines that acts to normalise acute-phase responses and to prevent uncontrolled inflammation. The present data suggest that airway cells, such as bronchial epithelial cells, may secrete IL-10 to suppress the particle-induced inflammation and prevent an uncontrolled response. The greatest requirement for this regulatory control would be during the work period [33].

In conclusion, the miners in an underground iron ore mine demonstrate an airway inflammatory response in induced sputum, with increased levels of macrophages, neutrophils, fibronectin and matrix metalloprotein-9. Interestingly, the inflammation was as pronounced after a 4-week holiday period as after a 3-month work period underground in the mine. The present authors suggest that interleukin-10, due to its ability to modulate monocyte/macrophage function and inflammatory events, may play a role in controlling airway inflammation caused by the inhalation of rock/ore dust and diesel exhaust. To the current authors' knowledge, this is the first study to address airway inflammation using induced sputum in a true occupational life situation in miners. Additional studies need to be performed to investigate the long-term risk of particle-induced chronic airway inflammation.

REFERENCES

1 Oxman AD, Muir DCF, Shannon HS, Stock SR, Hnizdo E, Lange HJ. Occupational dust exposure and chronic obstructive pulmonary disease. A systemic overview of the evidence. *Am Rev Respir Dis* 1993; 148: 38–48.
2 Jorgenssen HS. Silicosis in the iron-ore mine in Kiruna, Sweden, and the future need for silicosis control. *Int Arch Occup Environ Health* 1986; 58: 251–257.
3 Jörgenssen HS, Svensson Å. Studies on pulmonary function and respiratory tract symptoms of workers in an iron ore mine where diesel trucks are used underground. *J Occup Med* 1970; 12: 348–354.
4 Jörgenssen HS. Medical and hygienic health problems in an iron ore mine with special reference to respiratory illness. Thesis, Umeå University, Umeå, Sweden. *Arbete och Hälsa*, 1986: 22.
5 Jörgenssen HS, Kolmodin-Hedman B, Stjernberg N. Follow-up study on pulmonary function and respiratory

tract symptoms in workers in a Swedish iron ore mine. *J Occup Med* 1988; 30: 953–958.
6 Rudell B, Ledin MC, Hammarström U, Stjernberg N, Lundbäck B, Sandström T. Effects on symptoms and lung function in humans experimentally exposed to diesel exhaust. *Occup Environ Med* 1996; 53: 658–662.
7 Rudell B, Sandström T, Stjernberg N, Kolmodin-Hedman B. Controlled diesel exhaust exposure in an exposure chamber: pulmonary effects investigated with bronchoalveolar lavage. *J Aerosol Sci* 1990; 21: 411–414.
8 Rudell B, Blomberg A, Helleday R, *et al.* Bronchoalveolar inflammation after exposure to diesel exhaust: comparison between unfiltered and particle trap filtered exhaust. *Occup Environ Med* 1999; 56: 527–534.
9 Rudell B, Sandström T, Hammarström U, Ledin MC, Hörstedt P, Stjernberg N. Evaluation of an exposure setup for studying effects of diesel exhaust in humans. *Int Arch Occup Environ Health* 1994; 66: 77–83.
10 Salvi S, Blomberg A, Rudell B, *et al.* Acute inflammatory response in the airways and peripheral blood following short term exposure to diesel exhaust in healthy human volunteers. *Am J Respir Crit Care Med* 1999; 159: 702–709.
11 Nordenhäll C, Pourazar J, Blomberg A, Levin JO, Sandström T, Ädelroth E. Airway inflammation following exposure to diesel exhaust: a study of time kinetics using induced sputum. *Eur Respir J* 2000; 15: 1046–1051.
12 Nordenhäll C, Pourazar J, Ledin MC, Levin JO, Sandström T, Ädelroth E. Diesel exhaust enhances airway responsiveness in asthmatic subjects. *Eur Respir J* 2001; 17: 909–915.
13 Nightingale JA, Maggs R, Cullinan P, *et al.* Airway inflammation after controlled exposure to diesel exhaust particulates. *Am J Respir Crit Care Med* 2000; 162: 161–166.
14 Quanjer PH. Standardization of lung function tests. *Bull Eur Physiopathol Respir* 1983; 19: Suppl. 5, 7–95.
15 Pin I, Gibson PG, Kolendowitz R, *et al.* Use of induced sputum counts to investigate airway inflammation in asthma. *Thorax* 1992; 47: 25–29.
16 Pizzichini E, Pizzichini MM, Efthimiadis A, *et al.* Indices of airway inflammation in induced sputum: reproducibility and validity of cell and fluid-phase measurements. *Am J Respir Crit Care Med* 1996; 154: 308–317.
17 Rennard SI, Hunninghake GW, Bitterman PB, Crystal RG. Production of fibronectin by the human alveolar macrophage mechanism for the recruitment of fibroblasts to sites of tissue injury in interstitial lung diseases. *Proc Natl Acad Sci USA* 1981; 78: 7147–7151.
18 Atkinson JJ, Senior RM. Translational review. Matrix metalloproteinase-9 in lung remodelling. *Am J Respir Cell Mol Biol* 2003; 28: 12–24.
19 Klebanoff S, Clark RA. The neutrophil. Function and clinical disorders. Amsterdam, Elsevier, North Holland Publishing Co., 1978; pp. 409–488.
20 Moncellin S, Panelli MC, Wand E, Nagorsen D, Marincola FM. The dual role of IL-10. *Trends Immunol* 2003; 24: 36–43.
21 Rappaport SM. Interpreting levels of exposure to chemical agents. *In*: Harris RL. Patty's Industrial Hygiene and Toxicology. 5th Edn. New York, John Wiley & Sons Inc, 2000; pp. 679–745.
22 Kromhout H, Symanski E, Rappaport SM. A comprehensive evaluation of within-and between-worker components of occupational exposure to chemical agents. *Ann Occup Hyg* 1993; 37: 253–270.
23 Committee Européenne Normalisation (CEN). Workplace atmospheres - size fraction definitions for measurement of airborne particles. Brussels, Commission of the European Community, 1993.
24 Personal exposure monitoring. *In*: Nieuwenhuijsen MD. Exposure Assessment in Occupational and Environmental Epidemiology. Oxford, Oxford University Press, 2003; pp. 79.
25 Hagenbjörk-Gustafsson A, Lindahl R, Levin JO, Karlsson D. Validation of the Willems badge nitrogen dioxide determinations in occupational environments. *Analyst* 2002; 127: 163–168.
26 Zaebst DD, Clapp DE, Blade LM, *et al.* Quantitative determination of trucking industry workers' exposures to diesel exhaust particles. *Am Ind Hyg Assoc J* 1991; 52: 529–541.
27 Technische Regeln für Gefahrstoffe: Grenzwerte in der Luft am Arbeitsplatz-Luftgrenswerte [Technical regulations for motor fuels: Occupational exposure limits for air (TRGS900)]. *BArbBl* 1997; 4: 57–563.
28 Hygeniska gränsvärden och åtgärder mot luftföroreningar. [Occupational exposure limits and actions against pollution]. Stockholm, Swedish Work Environment Authority (AFS 2000: 3), 2001; 17: 1–74.
29 Le Tertre A, Medina S, Samoli E, *et al.* Short-term effects of particulate air pollution on cardiovascular diseases in eight European cities. *J Epidemiol Community Health* 2002; 56: 773–779.
30 Swedish Environmental Protection Agency. Legislation and Guidelines. Stockholm, 2003; 27: 1–9.
31 Sandström T, Kolmodin-Hedman B, Andersson M-C, Bjermer L, Hörnqvist-Bylund S, Stjernberg N. Peat dust exposure acute effects on lung function and bronchoalveolar lavage fluid content. *Br J Ind Med* 1991; 48: 771–775.
32 Tetley TD. Macrophages and the pathogenesis of COPD. *Chest* 2002; 121: Suppl. 5, 156S–159S.
33 Stenfors N, Nordenhäll C, Salvi SS, *et al.* Different airway inflammatory response in asthmatics and healthy humans exposed to diesel. *Eur Respir J* 2004; 23: 82–86.