Acute exposure of symptomatic steelworkers to sulphur dioxide and carbon dust: effects on mucociliary transport, pulmonary function, and bronchial reactivity

R K WOLFF,* G OBMINSKI, AND M T NEWHOUSE

From McMaster University and St Joseph's Hospital, Hamilton, Ontario, Canada

ABSTRACT Nine steel workers participated in controlled exposures to sulphur dioxide alone and sulphur dioxide plus carbon dust (5 ppm and 10 mg/m³, respectively). All were experiencing work related respiratory difficulties. Bronchial clearance was measured using radioaerosol inhalations and external detection. Results were variable and no statistically significant changes were observed. One asthmatic showed a complete cessation of clearance during exposure to sulphur dioxide and carbon dust. Bronchial reactivity was found to be significantly raised after exposure to sulphur dioxide but equivocal results were found after exposure to sulphur dioxide and carbon dust. Pronounced changes in pulmonary function were seen only in the two asthmatic subjects. They could not tolerate the levels, indicating that these threshold limit values are too high, at least for these individuals who showed much greater sensitivity to the pollutants than the others.

Most previous work on experimental human exposures to sulphur dioxide (SO₂) or carbon dust has involved healthy volunteers.¹⁻⁴ Nevertheless, since these data relate to industrial threshold limit values (TLVs) it seemed advisable to obtain additional data on exposures from workers who encounter these agents in their everyday environment. With this in mind we chose to study not young healthy volunteers but workers who were experiencing some respiratory difficulties at work. The question was whether these subjects showed responses in mucociliary clearance and pulmonary function similar to the group of healthy volunteers previously studied² or whether they exhibited any altered sensitivity. These subjects were exposed to TLV-short term exposure limit levels of SO₂ alone and SO₂ and carbon dust (5 ppm SO₂ and 10 mg/m³ carbon dust) in acute exposures of 2.5 hours duration. Changes in pulmonary function, mucous clearance, and bronchial reactivity were measured. These measure-

ments were chosen since alterations have been observed in all after exposure to various pollutants. Combinations of measurements have rarely been made in the same subjects, and we wished to see if there were correlations between changes in different measurements and if any one measurement was more sensitive than the others.

Materials and methods

SUBJECTS

Nine individuals from a group of steelworkers who were outpatients at St Joseph's Hospital volunteered for the study. All were employed at the major steel mills in Hamilton and suffered from respiratory difficulties (shortness of breath, pronounced cough or wheeze, or both) which they reported occurred primarily at work. Table 1 shows the age, height and pulmonary function data of the subjects. Table 2 gives a detailed profile of the subjects. Most had never smoked and none was a smoker at the time of the study. Subjects 1-7 felt healthy, with only minor respiratory problems when away from work and

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Table 1 Baseline pulmonary function measurements

Subject	Height (cm)	Age	FEV ₁		FVC		FEF ₇₅₋₂₅		TLC	
			Pred	Obs	Pred	Obs	Pred	Obs	Pred	Obs
1	167	45	3.05	3.60	4.05	4.70	3.60	3.30	6.06	5.66
2	170	44	3.30	3.40	4.35	4.70	3.80	2.75	6.21	6.43
3	163	44	3.15	3.85	4.02	4.50	3.70	4.95	5.74	7.82
4	153	62	2.25	1.80	2.73	3.31	2.70	1.35	4.50	5.51
5	160	46	2.70	1.90	3.40	3.06	3.20	1.25	5.12	5.62
6	178	45	3.40	2.40	4.68	3.90	3.60	1.60	7.00	8.79
7	168	55	2.80	2.70	3.74	3.90	3.00	2.10	5.91	6.65
8	162	26	3.65	2.47	4.30	4.07	4.4	1.19		*
9	187	28	4.10	2.80	5.60	5.35	4.5	1.09		*

*Not available.

they could be described as having "industrial bronchitis" of varying degrees. Smoking probably played a large part in the symptomology of subjects 5, 6, and 8; subjects 8 and 9 were asthmatic and had non-work related wheezing episodes.

Informed consent was obtained from each individual after the procedures had been carefully and completely explained to them.

AEROSOL DEPOSITION AND CLEARANCE MEASUREMENTS

The radioactive test aerosol used to measure clearance was ultrasonically generated from a solution of ^{99m}Tc-albumin in physiological saline. The activity aerodynamic mass median diameter was 3 µm and σ_g 1.6.

A bolus technique described previously¹ was used to achieve reproducible proximal deposition of aerosol in the lung. In each of the present experiments radioaerosol inhalations were performed before exposure to the pollutants and the effects on mucociliary clearance were determined by measuring the changes in lung retention of the radioactivity during a 2.5 hour period. In each experiment inhalations were conducted under carefully controlled conditions and the subjects took 20 aerosol breaths,

each of reproducible volume and flow rate, by mouth.

An Anger scintillation camera was interfaced with a data storage and retrieval system that allowed off line computer data handling.⁵ Measurements of lung retention of activity were made from a 2" × 4" region (inner zone) over the right lung centred at the carina, a middle zone consisting of a crescent around the inner zone terminating at the mediastinum, and an outer zone, a 1" crescent around the middle zone. Lung retention was calculated from the sum of activity in all three zones.

EXPOSURES

Three separate 2.5 hour exposures were carried out for each non-asthmatic individual in the following order on successive weeks:

- (1) placebo (clean air),
- (2) 5 ppm SO₂, and
- (3) 5 ppm SO₂ + 10 mg/m³ carbon dust.

Both asthmatics were first exposed to 5 ppm SO₂, but because of their reaction at this level they were subsequently exposed to 1 ppm. Subject 9 could not be studied with SO₂ + carbon dust because he moved from the area before the final study could be completed.

Table 2 Smoking habits, work history, pulmonary function, and diagnosis of subjects

Subject	Smoking habits	Job (No of years at steel mills)	Pulmonary function	Preliminary diagnosis
1	Non-smoker	Open hearth (14)	Normal	Mild bronchial hyperreactivity
2	Non-smoker	Slag pits (18)	Normal	Normal
3	Non-smoker	Welder (23)	Normal	Mild bronchial hyperreactivity
4	Non-smoker	Welder (28)	FEV ₁ slightly reduced	Minimal airway obstruction, some hyperinflation
5	Ex-smoker for 6 years; 20-pack years previously	Open hearth (20)	FEV ₁ slightly reduced	Minimal airway obstruction
6	Ex-smoker	Basic oxygen furnace (17)	FEV ₁ slightly reduced	Minimal airway obstruction
7	Non-smoker	Open hearth (29)	Normal	Subacute bronchitis, some sputum production
8	Ex-smoker for 6 months; 16-pack years previously	Open hearth basic oxygen furnace (6)	FEV ₁ reduced obstructive	Asthmatic ragweed sensitive, mild chronic bronchitis
9	Non-smoker	Open hearth (3)	FEV ₁ reduced	Asthmatic

Each exposure was started immediately after inhalation of the radioactive aerosol. Initially there was a half hour rest period. In all experiments there was an exercise period of from 0.5 to 1.0 hour consisting of five sessions lasting four minutes, exercising at 50–60% of the maximum predicted heart rate. The four minute exercise sessions were separated by two minute rest periods. Subjects were at rest from 1.0 to 2.5 hours. Both placebo and pollutant exposures lasted a total of 2.5 hours and were carried out in a $2.1 \times 1.8 \times 1.2$ m plexiglass chamber that has already been described.¹ Five ppm SO₂ exposures were achieved as described previously¹ using a controlled flow rate from a 1% SO₂ compressed gas cylinder.

The carbon dust was generated from a Wright dust feeder having been prepared by ball milling coconut charcoal overnight. In samples taken from the exposure chamber the particle size was 1 μ m count median diameter. The dust was compressed in a stainless steel feed cylinder at a pressure of 2000 psi, six successive compressions of 10 second duration being used to eliminate rebound of the material. The dust feeder injected the material into the ducting behind the intake fan of the chamber. When generating dust it was necessary to increase the SO₂ flow by 20% above the flow rate when no dust was present to obtain a 5 ppm reading on the SO₂ analyser, presumably because some SO₂ was adsorbed on to the carbon particles.

In the laboratory air the SO₂ concentration was 0.01–0.02 ppm, particulates were <50 μ g/m³ and the ozone concentration was <0.01 ppm.

The temperature in the chamber was maintained at $22 \pm 1^\circ\text{C}$ and the relative humidity at $50 \pm 5\%$.

Mouth breathing was used in all experiments. To achieve this, the nose was occluded with cotton batting. A small quantity of water was swallowed before each radioactive aerosol retention reading to wash interfering activity from the oesophagus.

Inhaled radioactivity was approximately 50–100 μ Ci per experiment which corresponds to a 1–2 mrad whole body dose.

All measurements of pollutant exposure were compared with control measurements by analysing the retention values at two hours using two tailed paired *t* tests testing for significance at $p = 0.05$ with the *t* value scaled for multiple comparisons.⁶

PULMONARY FUNCTION TESTS

Spirograms were obtained before exposures in each experiment using a spirometer from Vitalograph Medical Instrumentation. Flow volume curves were obtained using a Wedge spirometer. In this way baseline values for vital capacity (VC), one second forced expired volume (FEV₁), forced expired flow

from 75% to 25% of VC (FEF_{75–25}), maximum flow at 50% VC ($\dot{V}_{\text{max}_{50}}$) and at 25% VC ($\dot{V}_{\text{max}_{25}}$) were measured. After exposures were started spirometers and flow-volume curves were taken at 5, 10, 15, 30, 90, 120, and 150 minutes. The average of the best two values from three efforts were used. For the two asthmatic subjects, spirometers were also taken after each four minute exercise session in the 0.5–1.0 hour period.

BRONCHIAL REACTIVITY MEASUREMENTS

Airway reactivity to inhaled aerosolised histamine was measured 15 minutes after the end of exposure to pollutant or placebo using the method modified from Cockcroft *et al.*⁷ Starting with low concentrations (0.03 mg/ml) ten breaths were taken from the controlled breath nebuliser apparatus (see clearance measurements) and the FEV₁ was measured at one, two, three, four, and five minutes after the end of inhalation. If the FEV₁ fell by more than 20% from control, or if subjective irritation was too great, the inhalations were stopped. If not the procedure was repeated with double histamine concentrations until a 20% fall was achieved; the concentration producing this fall was called the threshold concentration. A threshold concentration was determined after the placebo exposure to give a certain percentage fall and then the threshold concentration was administered after each of the other exposures and percentage fall in FEV₁ measured each time.

Paired *t* tests with the *t* value adjusted for multiple comparisons were used to test each of the pulmonary function measures and the bronchial reactivity measurements for significance at the $p = 0.05$ level. Measurements made for experiments entailing exposures to pollutants were compared with measurements at the same time during control experiments.

Results

PULMONARY FUNCTION

Table 3 shows the changes in FEV₁, FEF_{75–25}, $\dot{V}_{\text{max}_{50}}$, and $\dot{V}_{\text{max}_{25}}$. The changes were not dramatic, except for the exposures of subjects 8 and 9, both asthmatics, to 5 ppm SO₂. Apart from these responses $\dot{V}_{50}$ and $\dot{V}_{25}$ decreased in subjects 1, 3, 4, and 7 late in the exposure (2–2.5 h).

Subject 8 had a reduction of 25% in FEV₁ after 30 minutes exposure to 5 ppm SO₂ at rest and, after four minutes of exercise, a reduction of 60% from baseline, at which time the exposure was terminated and a bronchodilator administered. Pulmonary function and clearance measurements were continued until the end of the 2.5 h experiment. This subject was later exposed to 1 ppm SO₂ and to 1 ppm SO₂,

Table 3 Pulmonary function values as a percentage of control

Subject	$\dot{V}_{E1}$				MMFR				$\dot{V}_{50}$				$\dot{V}_{25}$			
	SO_2		$SO_2 + dust$		SO_2		$SO_2 + dust$		SO_2		$SO_2 + dust$		SO_2		$SO_2 + dust$	
	E	L	E	L	E	L	E	L	E	L	E	L	E	L	E	L
1	92	95	103	84	74	92	111	90	80	84	81	75	92	75	85	70
2	100	101	97	97	100	94	93	101	102	101	95	80	88	99	82	70
3	101	99	97	99	100	98	93	99	92	86	95	91	97	90	97	91
4	100	101	104	96	102	107	108	104	104	107	101	104	100	98	107	102
5	89	86	83	83	79	80	76	78	73	74	71	73	71	91	89	89
6	108	115	102	101	108	115	99	96	108	109	109	110	108	111	102	108
7	101	98	97	91	103	101	103	105	96	101	110	90	92	90	95	91
8	41*	79			37*	66*			—	70			—	75		
	93†	90	87	85	91	97	90	82	79	86	77	76	85	87	83	86
9	73†	100			64*	99			76	98			81	101		
Mean	90	96	96	92	86	85	85	94	85	82	92	87	90	92	92	88

*E = Early in the exposure, first half hour average values.

†L = Late in the exposure, 1.5 to 2.5 h, average values.

MMFR = Maximum midexpiratory flow rate.

— Not determined.

*Greater than 30% change.

†1 ppm SO_2 .

plus carbon dust. The results for these exposures are shown separately in table 3 and indicate minimal changes in pulmonary function.

Subject 9 also showed a striking response to 5 ppm SO_2 . After only 15 minutes of exposure to 5 ppm SO_2 at rest, the decrease in FEV_1 was 42% and the SO_2 was shut off for four minutes. The concentration was then re-established at 1 ppm SO_2 which was tolerated well and the FEV_1 began to return to normal, showing a decrease from baseline of 27% after the first exercise period (35 minutes) and 17% (40 minutes) after the second. At this time (40 minutes) the concentration of SO_2 was raised to 2 ppm and the FEV_1 fell again showing a 48% decrease from baseline after the third exercise period (45 minutes). The concentration was then returned to 1 ppm SO_2 and the FEV_1 began to improve again, returning to control levels at the end of the exposure (150 minutes).

CLEARANCE

The figure shows the clearance curves for the nine individuals in the study. The retention of the test aerosol at two hours, expressed as a percentage of the initial lung burden, was used to assess if there had been significant changes during pollutant exposures (table 4). From table 4 it can be seen that the results were mixed with both speeding and slowing of clearance. As may be seen in the figure, subject 8, an asthmatic, showed a complete cessation of clearance after 30 minutes exposure to 1 ppm SO_2 plus carbon dust. It was not possible to expose the other asthmatic to the combination of pollutants. Neither asthmatic showed changes in clearance after exposure to 5 ppm SO_2 when treated with a bronchodilator. Subject 7 showed a considerable slowing

Table 4 Retention of radioaerosol two hours after beginning of exposure

Subject	Placebo	SO_2	$SO_2 + carbon dust$
1	61.0	60.0	35.0
2	29.5	16.0	23.0
3	75.0	80.5	68.0
4	43.0	53.0	39.0
5	58.0	50.0	41.5
6	51.5	51.0	52.5
7	50.5	50.0	62.0
8	22.5	19.0*	45.0*
9	19.5	14.0*	
Mean $\pm$ SD	49 $\pm$ 17†	47 $\pm$ 21†	46 $\pm$ 15†

*1 ppm SO_2 .

†Excluding subject 9.

Table 5 Histamine bronchial reactivity

Threshold concentration Subject	(mg/ml)	Percentage fall in FEV_1		
		Placebo	SO_2	$SO_2 + carbon dust$
1	4	23.0	23.9	40.4
2	1	8.3	13.9	6.9
3	1	10.7	21.0	10.7
4	4	37.0	32.0	29.8
5	1	28.4	31.7	21.6
6	1	20.5	35.6	30.1
7	8	9.2	14.3	8.4
8	0.5	16.7	34.0	47.7
9	0.25	31.0		
Mean $\pm$ SD		19 $\pm$ 10†	26 $\pm$ 9†	24 $\pm$ 15†
p value*			<0.05	0.5

*Exposure measurements compared with control using paired t tests.

†Excluding subject 9.

Lung retention of activity expressed as a percentage of initial lung burden plotted as a function of time. Retention curves are shown for control exposures (—), exposures to 5 ppm SO₂ (---), and 5 ppm SO₂ plus carbon dust (····). Retention curves for subjects 7–9 (group 3). Subject 8 was exposed to 1 ppm SO₂ (---) and 1 ppm SO₂ + carbon dust (····) for entire period and 5 ppm SO₂ (---) for 0.5 hour. Subject 9 was exposed to 1 ppm SO₂ (---) for most of exposure period (see text).

in clearance on exposure to 5 ppm SO₂ plus carbon dust.

BRONCHIAL REACTIVITY

Table 5 shows the threshold concentrations and percentage decrease in FEV₁ when these concentrations were administered after exposure. They indicate that the greatest change occurred on exposure to SO₂, when virtually all subjects had a much greater fall in FEV₁ with the same histamine concentration compared with the exposures to placebos. The

one exception was subject 8, who showed a much greater sensitivity to SO₂ plus carbon dust than to SO₂ alone. Paired *t* tests were used to analyse the data for significant changes. The *p* values at the bottom of the table indicate that changes were significant during exposure to SO₂ (*p* < 0.05) but were not significant during exposure to SO₂ plus carbon dust (*p* < 0.5).

SUBJECTIVE IMPRESSIONS

Virtually all the subjects appeared to find the expos-

ures to SO₂ more irritating than did the young normal subjects of earlier experiments.^{1,2} Most subjects stated that the exposure to SO₂ plus carbon dust was more unpleasant and irritating than to SO₂ alone. During exposure, some subjects coughed occasionally but not to a degree that would be expected to influence the clearance results.

Discussion

The data presented here describe the effects of exposure to SO₂ or SO₂ plus carbon dust in individuals who had some respiratory problems at work. Most other data relate to healthy volunteers or to animal exposures. Previous studies in this laboratory^{1,2} have shown an increase in clearance during the acute exposure of young, healthy, non-smoking subjects to SO₂. Camner *et al* have shown that exposure to carbon dust also increases bronchial clearance³ and so it would seem likely that exposure to SO₂ plus carbon dust in healthy subjects would increase clearance. In the individuals with the best pulmonary function (subjects 1, 2, 3) there was a trend towards faster clearance after exposure both to SO₂ and to SO₂ plus carbon dust. Subject 3 showed slower clearance in response to SO₂ but the result was within the experimental variation. We have suggested previously that increased clearance may be a response to increased mucus production,² resulting from the stimulation of vagal receptors in the upper airway.

Increases in clearance may or may not be beneficial, but decreases in clearance in response to an inhalation insult would probably be detrimental. Impairment of clearance may also allow mucus to accumulate and increase the risk of obstructing airways. In this regard it is noteworthy that two subjects showed a pronounced decrease in clearance during exposure to SO₂ as did three during exposure to SO₂ plus carbon dust. (A pronounced change is one that is greater than the 7% standard deviation found previously for repeat studies.¹) Whether these observations represent an indication of heterogeneous responses to these agents or greater variability in the clearance measurements of these workers than of young healthy subjects cannot be determined with absolute certainty.

Yeates has reported less reproducibility in patients with chronic bronchitis than in normal subjects.⁸ Our subjects were in reasonably good health in that they were all still working and had only limited debilitation and there was no significant difference in clearance from previous control data obtained in normal subjects² by contrast with the observation of Camner *et al* of slower clearance in chronic bronchitis.⁹ Initial deposition and clearance

in the first half hour before pollutant exposures were started were similar for each subject. These facts suggest that our subjects may not have as great a variability as those with chronic bronchitis, but responses could be more varied than observed in a population of normal healthy subjects.

Subjects 8 and 9, the asthmatics, showed fast clearance with retentions of 22.5% and 19.5%, respectively, after two hours, which is faster than that seen in any of the normal subjects in previous studies.² This may be a chance occurrence but it finds a parallel in the data of Wanner *et al*¹⁰ who sensitised dogs to ascaris antigen and showed that the tracheal mucous velocity was 8.6 ± 1.8 mm/minute compared with 4.8 ± 1.0 for controls. Thus in this animal model and in our two asthmatic subjects baseline mucous velocity was faster in the asthmatics than in normal controls.

The response of the two asthmatics to SO₂ was striking and both showed such pronounced reductions in FEV₁ (42% and 60%, respectively) on exposure to 5 ppm SO₂ that the exposures had to be terminated or reduced. The reason that no impairment in clearance was seen at exposures to 5 ppm SO₂ was probably because a bronchodilator, which can increase clearance,¹¹ was administered to subject 8. The exposure level was reduced dramatically for subject 9, perhaps reducing clearance response below a detectable level. Obviously, the generally accepted TLV levels are much too high for these individuals.

Our results are in agreement with those of Shepard *et al*¹² and Jaeger *et al*¹³ who observed that asthmatics showed a greater response to SO₂ than normal subjects. It is also interesting that one of the asthmatics (subject 8) showed a complete cessation of clearance after 30 minutes exposure to 1 ppm SO₂ plus carbon dust; this has not been observed in previous studies of normal subjects. Data could not be obtained for the other asthmatic under these conditions. Even from these limited data it is apparent that asthmatics are particularly sensitive to such irritants.

There were no statistically significant changes in any of the pulmonary function measurements for the set of subjects as a whole, and no changes which were seen after exposures to pollutant occurred only in the two asthmatics. They showed appreciable changes in FEV₁, FEF₇₅₋₂₅, and in $\dot{V}_{50}$ and $\dot{V}_{25}$. In the other subjects $\dot{V}_{25}$ appeared to be the most sensitive indicator of changes possibly suggesting some small airway effects late in the exposures to SO₂ plus carbon dust (table 3).

Our finding of increased bronchial reactivity on exposure to SO₂ agrees well with the data which Ulmer obtained in dogs.^{14,15} We are unable to

explain why bronchial reactivity was closer to control values for exposures to SO₂ plus carbon dust than for SO₂ alone. Possibly some SO₂ was adsorbed on to the carbon dust¹⁶ and deposited more deeply into the lung where there are fewer irritant receptors.¹⁷ This might produce a reduced stimulation of the cholinergic pathways and so might not affect bronchial reaction as much as SO₂ alone. Approximately 20% of the SO₂ was in fact absorbed on to the carbon in the presence of the dust, since the flow of SO₂ into the chamber had to be increased by this amount to maintain a 5 ppm SO₂ concentration in the air.

The subjects we used did not represent a homogeneous group and so it is difficult to generalise from the data. Some subjects appeared to show impairments but, overall, the results indicate that only individuals with a degree of respiratory disease have more variable responses than healthy subjects.

It is clear that asthmatics appear to be at particular risk and their exposure to irritant gases and particles should be limited. Although complete data were only obtained in one asthmatic subject, his striking response indicates that mucociliary clearance may be severely impaired when asthmatics are exposed to relatively low concentrations of SO₂.

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Requests for reprints to: Dr R K Wolff, Inhalation Toxicology Research Institute, PO Box 5890, Albuquerque, NM 87185, USA.

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