DECLARATION

Environmental and host factors associated with persistent lower respiratory tract symptoms or asthma following acute environmental exposure to sulphur dioxide ($S0_2$).

I, Roslynn Baatjies, hereby submit my research report for the degree of Masters in Public Health. I declare that the work on which this research report is based is my original work (except where acknowledgements indicate otherwise), and that neither the whole work nor any part of it has been, is being, or is to be submitted for another degree in this or any other Technikon or University.

26 October 2006

Roslynn Baatjies

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ABSTRACT

Introduction: On the weekend of 16 – 17 December 1995, the community of Macassar was exposed to elevated levels of sulphur dioxide vapours (SO_2) caused by a fire on a nearby stockpile for approximately 21.5 hours. It has been estimated that community members were exposed to levels as high as 200 parts per million (ppm) of this gas as some 15 000 tons of the sulphur stockpile ignited. This resulted in a toxic plume of SO_2 being blown over the Macassar area by the prevailing wind. The aim of this study was to assess the environmental and host factors associated with persistent lower respiratory symptoms among residents of this community six years after being acutely exposed to elevated exposures of SO_2 vapours.

Materials and methods: A case-control study was conducted. The cases and controls were selected from adult residents who reported to the Macassar disaster project clinic for a health assessment in order to lodge a medico-legal claim. Survey instruments included a questionnaire, clinical examination and clinical record review by an expert panel. A case was defined as an adult resident who presented to the clinic for an examination with persistent (at year 1 and 6 after the disaster) lower respiratory symptoms. Controls were chosen from clinic attendees without lower respiratory symptoms at year 1 and 6. Environmental exposure was calculated by using the Industrial Source Complex Short Term Model (ISCST 3) to predict time-averaged concentrations at specified receptor locations. Multiple logistic regression was used to investigate the association between lower persistent respiratory symptoms, host and environmental factors (estimated concentration and duration of exposure to SO_2).

Results: A total of 76 cases and 180 controls were selected. The cases and controls were comparable with respect to age, gender, height and smoking status. The results indicated that a medical history of pulmonary tuberculosis at least one year prior to the fire (OR: 3.5, CI: 1.5-8.4) was significantly associated with having persistent lower respiratory symptoms. Furthermore, subjects with persistent lower respiratory symptoms were nine times more likely to report symptoms of tight chest (OR: 9.9; CI: 5.2-19.1), and twice as likely to report shortness of breath (OR: 2.0; CI: 1.0-4.1) at the time of the fire. None of the exposure metrics (total hours of exposure, cumulative exposure, peak exposure) were significantly associated with persistent lower respiratory symptoms. However, peak SO_2 exposure estimated at hour 15 was significantly associated with persistent lower respiratory symptoms (OR: 1.0; CI: 1.0-1.1).

Discussion: The results of this study are consistent with previous studies reporting lower respiratory tract symptoms after chemical exposure irrespective of age or smoking status. Furthermore, as in other studies respiratory health status was a significant factor in determining susceptibility to SO_2 exposure. Various reports in the literature suggest that exposure > 20 ppm is associated with chronic respiratory symptoms. This however was not demonstrated in this study, using estimates of exposure calculated using the ISCST model suggesting possible exposure misclassification. "Self-selection" bias was an important limitation in this study, since the entire study population was self-referred and as such the study population was not randomly selected. Another limitation is the possibility that there may be potential recall bias operating since the fire incident happened six years ago; however this was considered unlikely as there was non-differential reporting between cases and control. Self reported symptoms on the questionnaires might have been over-reported due to fear, anxiety and stress or secondary

gain related to compensation issues. The lack of association between exposure variables and persistent asthma may have also been due to lack of power (small sample size), although this was thought to be a minor contributory factor.

Conclusion: Host-related factors such as a previous history of pulmonary TB and acute asthma-like symptoms at the time of the fire were important predictors of persistent lower respiratory symptoms reported by residents 6 years after acute exposure to SO_2 vapours emanating from a sulphur fire.

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1.1 INTRODUCTION

During the anti-apartheid trade sanction era the South Africa government found it necessary to stockpile sulphur for the manufacture of sulphuric acid and fertilizer. A chemical company acting as an agent for the government stored the sulphur at its large Somerset West factory in the Western Cape Province. This started in the late 1960's when the surrounding area was largely unpopulated and underdeveloped.[1] However, the geographic and demographic situation subsequently changed to become a developed area occupied by about 30 – 40 000 people at the time of the disaster. On the weekend of 16 – 17 December 1995 approximately 15000 tons of sulphur, stockpiled by AECI ignited. AECI is an explosives factory situated within close proximity to the Macassar community. A sulphur dioxide plume enveloped and blew across the Macassar Township. Based on the plume-model concentration of SO_2 levels in Macassar ranged from 20 - 200ppm.[2] This kind of chemical disaster, namely the burning of a sulphur stockpile, has not been previously reported. The 'Macassar disaster' as it is known today, was the first of its kind. Approximately 3 000 people had to be evacuated to 'safe areas' and many residents endured conditions of extreme discomfort.[2] Batterman et al. estimated that the inhabitants were exposed to high concentrations of smoke and sulphur dioxide, with the main route of exposure being via inhalation of the gaseous sulphur dioxide.[3] White et al. indicated that inhabitants reported several symptoms at the time of the disaster.[4]

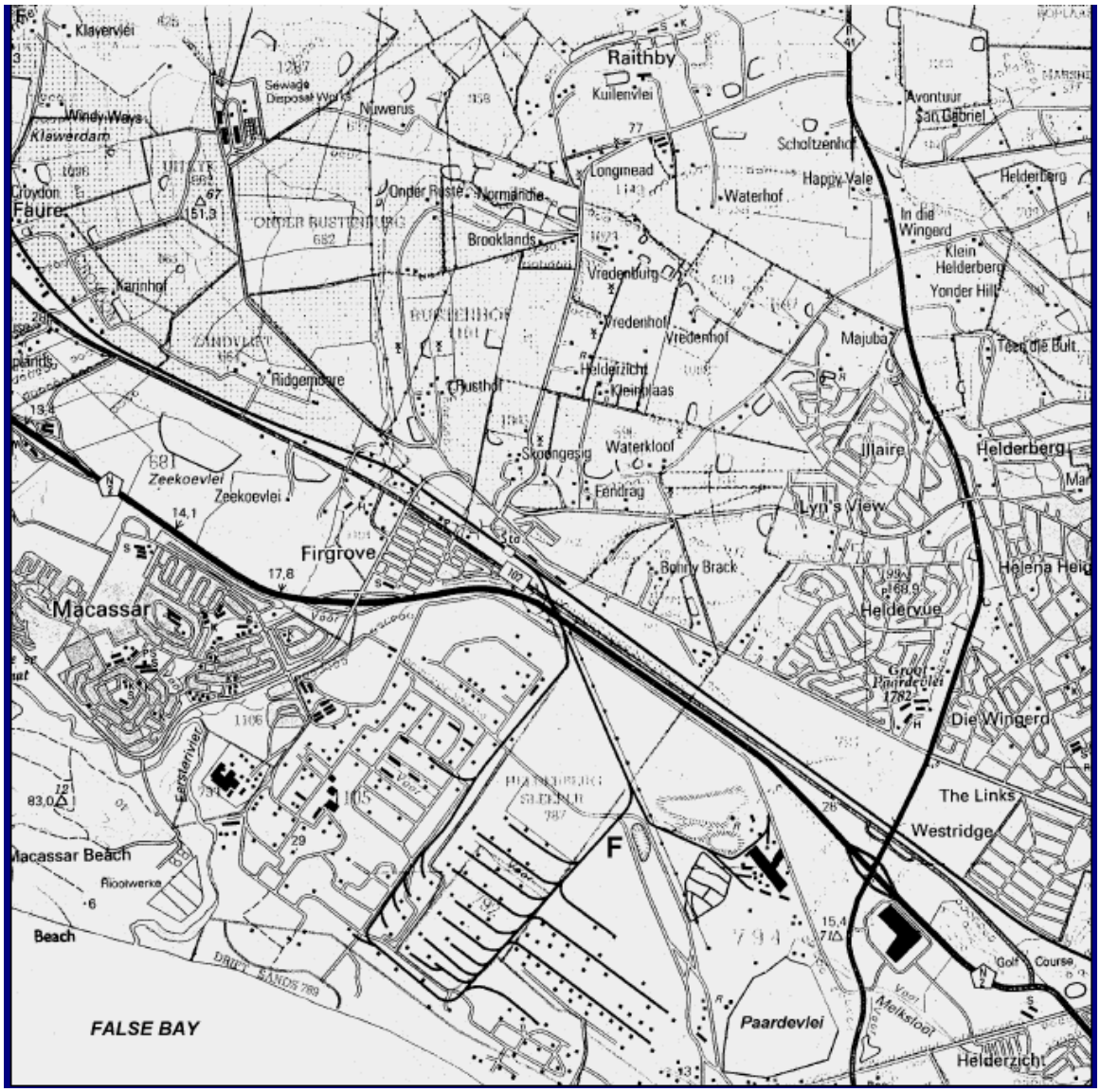

Figure 1. Macassar area and AECI site
Source: Batterman SA

Commonly reported symptoms shortly after the disaster included: coughing (74%), burning eyes (71 %), burning nose and throat (67%), burning chest (62%), anxiety and fear (40%), cramps (36%) and vomiting (21%).[3] The common symptoms present one week after the fire were mainly chest, nose and throat symptoms (90%). Several deaths occurred during the disaster. The precise number of deaths attributed to the fire was disputed; however, Batterman et al. (1999) reported that between 10 – 15 deaths were directly blamed on the fire.[3]

Many of these residents presented themselves to the Macassar disaster project clinic for a medical assessment and evaluation. The medical data collected during this evaluation process formed the basis for the current study.

Figure 2. Macassar fire disaster 1995, Saturday 16 December 1995. High wind speed and constant wind direction
Source: Cape Argus, 1995

Figure 3. Macassar fire disaster 1995, Sunday 17 December 1995. Wind speed became light and variable
Source: Batterman SA

1.2 REVIEW OF THE LITERATURE

In this Chapter sulphur dioxide is defined and its health effects are reviewed. General health effects following exposure to sulphur dioxide, and particularly respiratory health effects, and health protective exposure standards are presented. Epidemiological studies focussing on sulphur dioxide exposure in environmental and occupational settings and host and environmental factors associated with lower respiratory are also reviewed. The Chapter concludes with the aims and objectives of the study.

Environmental disasters as a result of acute sulphur dioxide (SO_2) exposure have not been previously documented although there are numerous contexts in which SO_2 has been associated with adverse health effects.

1.2.1 HEALTH EFFECTS OF SO_2

Sulphur dioxide gas is a severe irritant of the eyes, mucous membranes and skin. Its irritant properties are due to the rapidity with which it forms sulphurous acid on contact with moist membranes. Approximately 90% of all SO_2 inhaled is absorbed in the upper respiratory passages.[5] The summary of general health effects is based largely on a detailed toxicological profile published by the Agency for Toxic Substances and Disease Registry (ATSDR) (Table1.1).[6] In describing the toxicological effects of sulphur dioxide, consideration needs to be given to the route of exposure and the rate at which the exposure has occurred. There are 3 main routes of exposure to sulphur dioxide viz. inhalational, oral and dermal. Rate of exposures can be acute or chronic over a period of time as is the case with general environmental pollutants.

It is clear that in this particular context focus on the toxic effects on humans as a result of acute inhalational exposure to sulphur dioxide, will form the basis of this review.

Table 1.1 Summary of health effects associated with sulphur dioxide exposure

Concentration	Effect
$\geq$ 0.1ppm	• Broncho-constriction in sensitive exercising asthmatics
1-2 ppm	• Lung function changes in healthy non-asthmatic individuals
3 ppm	• Easily detected odour
6-12 ppm	• Upper respiratory irritation and some nosebleeds
20 ppm	• Definitely irritating to eyes • Chronic respiratory symptoms developed at this level
50 – 100 ppm	• Maximum tolerable exposure for 30-60 minutes
$\geq$ 100 ppm	• Immediate danger to life

Source: U.S. Department of Health and Human Services. (1998) Toxicology profile for sulfur dioxide. Agency for toxic substances and disease registry. Atlanta, Georgia 30333

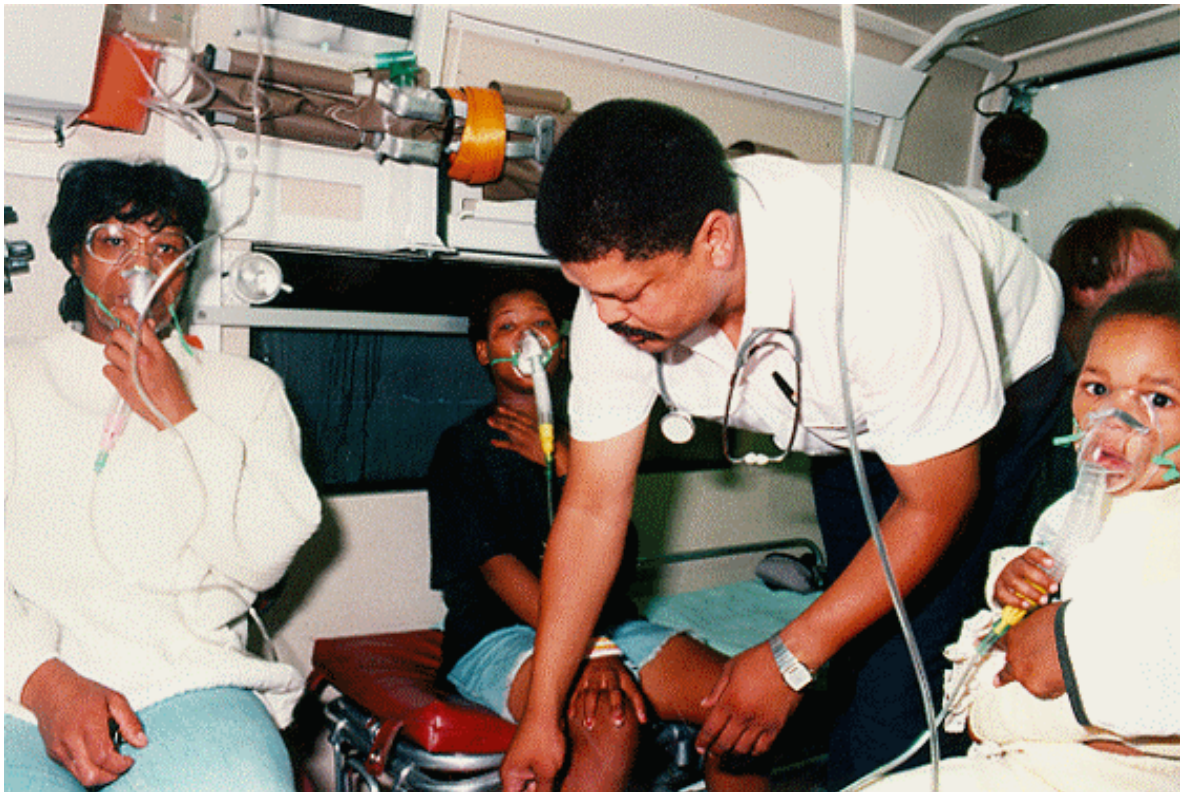

Figure 4. Children receiving oxygen in an emergency response unit
Source: Batterman SA

Most studies investigating adverse health effects have involved small numbers of subjects with accidental or occupational exposure to SO_2. The adverse health effects of SO_2 can be broadly categorized as death, respiratory, ocular, neurological, reproductive, developmental, genotoxic and carcinogenic effects.[7,8,9, 10,11,12,13,14,15,16,17,18,19,20]

1.2.1.1 Respiratory health effects

Available data indicate that the respiratory system is the primary target system for sulphur dioxide toxicity following inhalation exposure at low levels. It can be inhaled by healthy individuals normally for up to an hour with only subjective features arising.[21] However, as soon as deeper breaths occur significant airway resistance develops. This occurs also when the level of SO_2 increases.[22] Numerous controlled studies involving volunteers have documented that acute inhalational exposure to sulphur dioxide causes constriction of the airways, particularly in asthmatics and other sensitive individuals (Table 1.2).[23] It is important to note that there is a distinct difference between natural exposure studies and controlled exposure studies. Controlled studies tend to have higher no observed adverse effect levels (NOAEL) due to the fact that the environment in which the exposure occurs is highly controlled and has no contaminants except for the substance to which exposure is desired. Natural exposure studies tend to have lower NOAEL's due to the fact that the environment in which exposure occurs tends to be contaminated with substances other than the substance under study. When exercise is included in the testing, significant increases in airway resistance occur at concentrations >0.25 ppm.[24,25,26] Bronchoconstriction has even been observed in asthmatics exposed to SO_2 at concentrations as low as 0.1 ppm (Table 1.1).[23] It is notable that the responses between

asthmatics varies greatly.[27,28] In several controlled studies, the testing had to be terminated because of the severity of the pulmonary responses in some individuals whereas others required medical attention. [29,30,31,32,33] Responsiveness to SO_2 is enhanced by exercise and respiratory effects are exacerbated by exposure to cold or dry air and other pollutants such as sulphuric acid, nitrogen dioxide and ozone. Healthy non-asthmatics respond to higher concentrations of sulphur dioxide.[6]

There have been a few studies documenting long term respiratory health effects and symptoms experienced by individuals who were accidentally and acutely exposed to high concentrations of sulphur dioxide (Table 1.3). These studies generally had a small number of subjects. The major health effects reported included obstructive airways disease such as bronchitis, irritant induced asthma (RADS), COPD, as well as restrictive airways disease. [8,9,34] These health effects were observed between 3 months to 14 years after the initial exposure.

Table 1.2 Respiratory health effects and symptoms resulting from the controlled acute exposure of normal human subjects to sulphur dioxide

Author	Exposure level	No. of individuals exposed	Exposure duration	Respiratory abnormality
Schachter et al., 1984.[21]	< 1 ppm	10	40	Slight sore throat and able to taste and smell SO_2.
Anderson et al., 1974.[35]	≥ 1 ppm.	15	1 – 6 hours	Reduced forced expiratory volume and forced expiratory flow. Increase in nasal airflow resistance.
Nadel et al., 1965.[36]	4 – 6 ppm	7	10 minutes	Increased airway resistance.
Frank et al., 1962.[37]	5 ppm	11	10 – 30 minutes	Increased flow resistance. Cough, sense of irritation and increased salivation.

Author	Exposure level	No. of individuals exposed	Exposure duration	Respiratory abnormality
Anderson et al., 1974.[40]	5 – 25 ppm	15	1 – 6 hours	Decrease in nasal mucous flow.
Amdur et al., 1953.[38]	1 – 8 ppm	14	10 minutes	Increased respiratory rate and decreased tidal volume.
Sandstrom et al., 1989.[39]	8 ppm.	22	20 minutes.	Erythema of the trachea and main bronchi. Increase in the inflammatory cells in the bronchoalveolar lavage fluid.

Table 1.3 Long term respiratory health effects and symptoms experienced by individuals accidentally and acutely exposed to high concentrations of sulphur dioxide

Author	**No of subjects**	**Acute symptoms reported.** (This refers to health effects directly after the exposure incident)	**Period elapsed after exposure incident**	**Chronic symptoms reported.** (This refers to health effects that persisted on follow up study)	**Instruments used for evaluation of respiratory health effects**
Charan et al., 1979.[8]	3	Symptoms included soreness of the eyes, nose and throat; tightness of the chest; intense dyspnea; severe conjunctivitis and corneal burns; mild hypoxemia and hypocapnia.	4 months	One subject developed severe, symptomatic, irreversible airway obstruction that was unresponsive to bronchodilators. A second subject developed asymptomatic mild obstructive and restrictive disease. A third subject was asymptomatic with normal pulmonary function.	Spirometry
Rabinowitch et al., 1989.[11]	2	Intense burning of the eyes, nose and throat; diffuse precordial and retrosternal chest pain; nausea; vomiting; urinary incontinence; skin irritation. Evidence of severe airway obstruction, hypoxemia, markedly reduced exercise intolerance, ventilation – perfusion mismatch and active inflammation.	2 years	Partial improvement of pulmonary function and exercise performance. Airways obstruction gradually improved but did not completely resolve. COPD also resulted from the acute exposure.	Chest x-rays, ventilation – perfusion lung scans, gallium lung scans, spirometry

Author	**No of subjects**	**Acute symptoms reported.** (This refers to health effects directly after the exposure incident)	**Period elapsed after exposure incident**	**Chronic symptoms reported.** (This refers to health effects that persisted on follow up study)	**Instruments used for evaluation of respiratory health effects**
Harkonen et al., 1983.[9]	7	Decrease in forced vital capacity (FVC), forced expiratory volume (FEV) and maximal midexpiratory flow (MEF) within 1 week of the event. Spirometric findings were obstructive in six and restrictive in one subject. Lung function improved within 3 months but never reached the pre-accident levels.	4 years	Reversible obstruction of the bronchi, positive histamine challenge test indicated bronchial hyperactivity persisted	Spirometry, histamine challenge testing, chest x-rays
Piirila et al., 1996.[45]	7	Decrease in forced vital capacity (FVC), forced expiratory volume (FEV) and maximal midexpiratory flow (MEF) within 1 week of the event. Spirometric findings were obstructive in six and restrictive in one subject. Lung function improved within 3 months but never reached the pre-accident levels.	13 years	2 individuals showed obstructive spirometry; 3 individuals with obstructive and restrictive spirometry which indicates ventilatory impairment. 4 individuals had positive histamine challenge test. This bronchial hyperactivity proved to be persistent. 1 individual could not perform the histamine challenge test because of bronchial obstruction. 4 patients showed signs of chronic bronchitis. 5 individuals were characterized as having RADS.	Spirometry, histamine challenge testing, chest x-rays

1.2.1.2 Irritant induced asthma

There are several chronic respiratory health outcomes that might arise subsequent to an acute exposure to sulphur dioxide or any other chemical irritant. It is well documented that bronchial hyper-reactivity can develop following a single exposure to very high concentrations of SO_2.[46,47,48] In most instances exposure to an irritant produces bronchoconstriction, probably by inducing acute airways inflammation. As a result, these irritants induce asthma usually through non-immunological mechanisms. RADS (Reactive Airway Dysfunction Syndrome) or irritant induced asthma is the best example of this type of asthma (Table 1.4).[49] Irritant induced asthma (RADS) is usually the result of inflammatory bronchial hyperactivity caused by a single exposure to high concentrations of an irritant. Piirila et al. (1996), demonstrated that the bronchial hyperactivity seen in irritant induced asthma (RADS) can develop into a permanent pathological state. A case-series (n=10) investigated by Brooks found that irritant induced asthma (RADS) could lead to chronic airway disease (mean duration of follow up of 35.8 months). Four out of the ten subjects had airway obstruction (FEV_1/ FVC<70%) at the end of the follow-up period.

Table 1.4 Criteria for irritant induced asthma (RADS)

1	Exposure to high concentration of a gas, smoke, fume or vapour that had irritant qualities
2	Symptoms consistent with asthma, cough, wheeze, and dyspnea
3	Onset of symptoms within 24 hours after the acute exposure and persistence of symptoms for at least 3 months
4	Possibly airflow limitation on pulmonary tests
5	Airway hyperresponsiveness on methacholine challenge
6	Documented absence of preceding respiratory complaints
7	Other types of pulmonary disease excluded

Source: Tarlo S, (2000) Occupational Medicine: State of the Art Reviews. Workplace respiratory irritants and asthma. 15(92): 471-483

1.2.1.3 Epidemiological studies of chronic respiratory symptoms associated with acute SO_2 exposures

Sulphur dioxide forms part of the general outdoor pollution in various countries and has been investigated not only for its effects on the respiratory system but also its effects on the cardiovascular system and the role it plays as an atopic sensitisation agent.[50,51] Some studies deal with SO_2 from a specific source that leads to environmental contamination e.g. petrochemical manufacturing (school children experienced more respiratory symptoms and asthma conditions than the control group). An intervention study was conducted where the sulphur weight in petrol was reduced in the petrol for the duration of a weekend. This automatically led to a reduction of SO_2 in the environment and a decline in the respiratory symptoms experienced by the subjects of the trial.[52,53]

Since Reactive Airway Dysfunction Syndrome usually occurs as a result of accidental circumstances, it is difficult to perform studies to estimate the true prevalence of the condition. However, Blanc attempted to estimate the prevalence of RADS / IIA by reviewing literature and pooling various studies including three cohort investigations (n=1138). This study found the prevalence to be 7.2% (95% confidence interval 6.8-7.6) but not without referral, selection and publication bias.[54]

With regard to chronic respiratory symptoms caused by acute level exposures studies are scant (Table 1.3), hence good estimates of the disease burden could not be calculated.

1.2.1.4 Environmental and host factors associated with irritant induced asthma

There are no known risk factors influencing the onset of irritant induced asthma (RADS), but some environmental and host factors do play a role. The concentration of the inhaled agent is probably the main factor responsible for developing irritant induced asthma (RADS). As stated previously mild concentrations could induce irritant symptoms whereas high concentrations could lead to pulmonary lesions and even death.[55,11] Farm workers exposed to high concentrations of SO_2 (ranging between 106-721 ppm) during a sulphurisation process of apricots experienced acute mucosal irritation and a decrease in pulmonary function after one hour of exposure.[56] In a case control study, Savić studied workers (n=190) with chronic exposure to sulphur dioxide (those with a higher concentration of sulphites in their urine). The study found that this group of workers experienced more symptoms than the control group (the unexposed). The symptoms included coughing (94.2%), dyspnoea (91.0%) and burning in nose, eyes and throat (74.7-83.7 %).[57]

In a study of nine men who were accidentally exposed to SO_2 for 20-45 min because of an explosion in a pyrite mine, seven of the men were followed up for four years. It was found that reversible bronchial obstruction was still present in three cases and four had a positive reaction to the histamine challenge test. Thirteen years after the disaster six of these men were followed up and all were found to display an altered bronchial response. None of these subjects had a previous history of asthma or atopy. The study concluded that bronchial hyper-responsiveness appeared to persist for years in subjects exposed to high concentrations (level not reported) of sulphur dioxide.[45]

With regard to *host factors*, a previous study by Demeter reported clinical findings of nineteen irritant induced asthma (RADS) cases after exposure to an inhaled irritant (type not mentioned) and followed nine of them up for a mean of nine years.[58] None of the cases had recovered from their airway hyper-responsiveness and symptoms completely. In one individual with a previous history of asthma, aggravation of this condition was reported. The subjects' smoking history or age at time of the disaster did not influence the pattern of these findings.[58]

However, a series of studies conducted amongst 8 – 17 year olds and healthy male seniors concluded that respiratory health status, and not age, was the primary factor in determining susceptibility to SO_2.[59,60] These studies also found that in addition to asthmatics, asymptomatic adolescents were also more susceptible to SO_2.

1.2.2 Environmental exposures to SO_2 during the Macassar disaster

Batterman et al. (1999) used the Industrial Source Complex Short Term Model version 3 (ISCST3) (version 93109; US EPA) to estimate hourly and 24 hour average sulphur dioxide concentrations.[3] This is a conventional and well-validated Gaussian plume type model. The investigators used a second model, SCREEN3 (version 96043; US EPA) to perform their sensitivity analysis. To estimate the ambient sulphur dioxide concentrations in Macassar during the sulphur fire a 6 x 6 km grid on 250 m centers was established. A 30 x 30 km grid on 1250 m centers was used to evaluate the regional ambient concentrations of sulphur dioxide.

Model predictions showed that the highest hourly concentrations of sulphur dioxide in Macassar ranged between 20 – 200 ppm. A large section of the Macassar community exceeded the 100 ppm level.

This 100 ppm level is the immediately dangerous to life and health level (IDLH) as specified by NIOSH.[61] This concentration level is the maximum level to which a healthy worker can be exposed to for up to 15 – 30 minutes without suffering irreversible health effects. Their results further indicated that the second highest hourly concentration, which is often used in such an analyses, ranged from 10 – 40 ppm.

These 1 – hour concentrations were all found to exceed the health guidelines. The investigators reported the 24 – hour ambient sulphur dioxide concentrations in the Macassar community to range from 1 – 15 ppm. This sulphur dioxide level is far in excess of the protective WHO guideline of 0.06 ppm. Clearly, residents of the Macassar community experienced a short-term exposure to very high concentrations of sulphur dioxide.

1.2.3 Exposure standards for SO_2

A number of agencies have regulated or established guideline concentrations for the control of sulphur dioxide, these include the World Health Organization, the United States Environment Protection Agency, the United States based National Institute for Occupational Safety and Health (NIOSH), the Occupational Safety and Health Administration (OSHA) and the American Conference of Governmental Industrial Hygienists (ACGIH). Table 1.5 lists exposure concentration limits specified by these agencies for specific exposure duration to sulphur dioxide.

The OSHA, ACGIH, and NIOSH concentration limits mentioned in Table 1.5 refers strictly to occupationally exposed workers. The other regulated exposure concentrations mentioned, including the WHO guidance and EPA-NAAQS standards, have relevance to

the general population. The current standards in South Africa (and most other countries) is 2 ppm and is based on a consideration of acute and reversible effects but not potentially irreversible chronic effects.[62]

Table 1.5 Concentration standards or guidelines applicable to sulphur dioxide (adapted from the ATSDR (1998)

Regulating Agency	Sampling duration (minutes / hours)	Exposure concentrations limits (ppm)
WHO	10 minute exposure limit	0.2 ppm
WHO	1– hour exposure limit	0.13 ppm
WHO	24 – hour exposure limit	0.04 – 0.06 ppm
WHO	Annual arithmetic mean	0.015 – 0.023 ppm
EPA-NAAQS	24 – hour exposure limit	0.14 ppm
EPA-NAAQS	Annual arithmetic mean	0.03 ppm
OSHA	PEL TWA (8 hour work day)	5 ppm
ACGIH	TLV TWA	2 ppm
NIOSH	REL TWA	2 ppm
NIOSH	STEL	5 ppm

NOTE:
WHO = World Health Organization; NIOSH = National Institute for Occupational Safety and Health; EPA = Environment Protection Agency; NAAQS = National Ambient Air Quality Standard; OSHA = Occupational Safety and Health Administration; PEL = Permissible Exposure Limit; REL = Recommended Exposure Limit; STEL = Short Term Exposure Limits; TLV = Threshold Limit Value; TWA = Time-Weighted Average.

The above review demonstrates that environmental exposure to SO_2 is an important risk factor for the development and persistence of respiratory health effects (mainly obstructive airways disease), years after exposure has occurred. Host factors such as smoking and age do not appear to influence the pattern of these findings. However, a previous history of respiratory problems appears to be an important risk factor for the development of pulmonary effects following environmental exposure to SO_2. These host and environmental factors were further investigated in this study of residents exposed to SO_2 levels estimated to be between 20-200 ppm over a 21-hour period.

1.3 AIM

To determine the environmental and host factors associated with persistent lower respiratory symptoms or asthma attributable to SO_2 vapours from a sulphur fire among Macassar residents exposed to the disaster.

1.4 OBJECTIVES

- To estimate the hourly and peak concentrations of SO_2 vapours experienced by Macassar residents in the defined geographical area.
- To identify and measure the following parameters as risk factors for persistent (6 years post exposure) lower respiratory symptoms or asthma:

  a) Host factors
  - Age
  - Gender
  - Cigarette smoking status
  - Acute symptoms experienced at the time of the fire

b) Environmental factors

- location at time of disaster (inside / outside the dwelling)
- peak exposure level to SO_2
- duration of exposure SO_2
- cumulative exposure to SO_2

CHAPTER TWO

METHODOLOGY

In this Chapter the methodology employed in this study is explained. The study design, population and sampling, data collection and data management and analysis are presented in detail, and methods employed to ensure quality, reliable data is described. The Chapter ends with an explanation of the important ethical considerations and how these were addressed.

2.1 Study Design

A case control study was conducted over a period of 24 months (May 2001– May 2003). Selection of cases and controls underwent a rigorous 2-step process, which included the administration of a screening questionnaire (step 1) and evaluation by the medical reference panel (MRP) (step 2). On the basis of this process, cases and controls were selected. Cases were referred to a pulmonologist to validate the diagnosis made by the MRP on the basis of the presence and nature of respiratory symptoms obtained from the questionnaire For efficiency, cost and time, controls were not evaluated by the pulmonologist as the MRP's opinion was considered to be sufficient as confirmed by the pulmonologist opinion.

Definition of cases

1. Residents of the Macassar area during the fire disaster (16 / 17 December 1995) and exposed to SO_2 as a result thereof.
2. Eighteen years or older at the time of exposure.
3. Presented themselves to the Macassar disaster project clinic for medical evaluation.

4. Free of persistent lower respiratory symptoms, asthma and other chronic respiratory illnesses such as pneumonia, chronic obstructive pulmonary disease at the time of the disaster and TB at least one year prior to and after the disaster.

5. Must have had persistent (at year 1 and 6 years after the fire) respiratory symptoms / asthma which in the opinion of the medical panel (MRP) was a result of sulphur dioxide vapours arising from the fire.

Definition of control

Similar to criteria 1-4 but free of persistent lower respiratory symptoms and asthma following the incident (criteria 5).

Definition of persistent lower respiratory symptoms attributable to the fire

Persistent lower respiratory symptoms attributable to the fire included wheeze, tight chest, irritant induced asthma (RADS), asthma aggravation and chronic obstructive airways disease present at year 1 and 6 years post exposure.

2.2 Study Population

The study population consisted of all 4 000 residents who suffered acute health effects (mainly upper and lower respiratory symptoms) due to acute exposure to SO_2 vapours at the time of the fire. More than 95% of the residents in Macassar attended the health facility set up as part of a medico-legal process to assess eligibility for compensation payouts. Residents presented with respiratory and other health problems (ocular-nasal, psychological, skin, and reproductive). Among this group there were 120 (3%) residents who reported persistent lower respiratory symptoms 6 years after the initial exposure incident.

2.3 Sample size and procedure

Power calculations were conducted using STATA version 8 statistical software. Based on these calculations a sample size of 76 cases and 180 controls was selected for conducting a two-sample comparison of proportions. This was based on having >80% power and 95% confidence and a background exposure prevalence of 25% and 50% among cases and controls respectively. The selection of cases and controls was in accordance with a predetermined definition applied to a sampling frame constructed on the basis of attendance at the Macassar disaster project clinic. A database of all attendees was maintained. All cases and a random sample of controls were selected.

2.4 Data collection

The data collection process involved obtaining information on the following parameters:

- demographics
- medical history
- health outcomes
- environmental exposure
- the Medical Reference Panel's (MRP) opinion, and
- the pulmonologist evaluation and the spirometry findings where appropriate.

The data collection tools included:

- questionnaire Appendix 1: Questionnaire
- clinical examination by occupational health nurse
- decision of panel (medical reference panel) Appendix 5a & 5b
- lung function (spirometry) and pulmonologist diagnosis
- environmental exposure grid

Questionnaire: The main data collection tool was a structured interviewer – administered questionnaire consisting of mainly close-ended questions to reduce interpretation bias. This hour long interview was used to obtain data pertaining to demographics, exposure history and health symptoms experienced prior to – and after the disaster. The questionnaire was developed using background knowledge on symptoms suffered due to SO_2 exposure from the literature. Pre-testing was done on the questionnaire in order to refine the tool and to assess the time it took to complete it, among residents who attended the clinic.

Once the instrument was refined, it was translated into Afrikaans and back translated to ensure validity and reliability. Recording of observation and answers was done in a systematic and accurate manner to ensure reliability and consistency over time. A trained occupational health nurse with experience in data collection conducted all the interviews thereby excluding interviewer variation that may affect the reliability of the data collection process. In a study of this nature re-call bias might be present as subjects need to re-call medical symptoms over the past six years. Since the interviewees were unaware of the hypothesis of the study they were unlikely to answer the questions according to the expected outcome.

Clinical examination*:* In order to ensure uniformity, the same occupational health nurse responsible for the interviews performed all the measurements. The clinical examination focussed on the respiratory system.

***Discussion of medical dossier by MRP**:* A panel of at least 3 experienced occupational health medical practitioners reviewed the data obtained on questionnaire and clinical examination to assess the presence of chronic respiratory symptoms requiring further investigations by a pulmonologist for spirometry (Appendix 5a & 5b).

***Spirometry and pulmonologist diagnosis**:* The pulmonologist made a final diagnosis on subjects with chronic symptoms after obtaining an independent detailed history, examination and investigations e.g. chest x-rays and lung function testing. The spirometry was performed according to American Thoracic Society [ATS] guidelines.[63] This data was used to validate that a large proportion of the cases has asthma related symptoms (Reactive Airways Dysfunction Syndrome and asthma aggravation).

SO_2 exposure estimates

a) Environmental exposure grid

The Industrial Source Complex Short Term Model version 3 (ISCST3) (version 93109; US EPA, 1995a) was used to predict hourly and 24-hour average SO_2 concentrations ($\mu g/m^3$) at specified receptor locations and averaging times.[64,65] The estimation of the concentrations using this model was conducted by H Amsterdam, M Tech student and Prof E Cairncross, from Peninsula Technikon. Concentrations were then converted to ppm. This model is a conventional and well-validated steady-state Gaussian plume model, i.e. dispersion parameters such as meteorological conditions and emission rate were assumed constant while the plume was en route from source to receptor. The model is widely used in regulatory, risk assessment, and other applications, and is suitable for predicting ambient air quality concentrations, surface depositions, and other results from various types of emission sources over distances up to 100 km and averaging times from

1 hour to 1 year. It is generally used to analyse both continuous and time-varying emission sources, and it can account for multiple sources and receptors, varied land use, averaging times from one hour to one year, flat or elevated terrain, building downwash effects, and other effects.

Modeling methodology

Parameters necessary to perform the modeling simulations were obtained from exposure estimate model on levels of exposure done shortly after the disaster.[2] The parameters described the emission rate, temperature, location and extent (geometry) of the sulphur fire. Release rates were then determined as a function of time based on the sequence of the fire. Since emissions occurred over an extended spatial area, 16 release points were selected to represent the source's area and shape. A subsequent analysis indicated that concentration impacts at the downwind distance of interest (>1 km) were not sensitive to the source configuration.

Development of receptor grid

Concentrations were divided into a 21 x 21 receptor grid representing a 4 km x 2 km area, centred over the Macassar area. No height or topographic adjustments were made for the receptors. Source and receptor coordinates were then determined in relation to each other with the aid of a Somerset-West map.[66]

Meteorological data

Meteorological data for Somerset West were obtained from the South African International Weather Station (Rustenhof base) for the duration of the fire (21hours). These data ranged from hour 17 on Saturday, 16 December 1995 to hour 14 on Sunday,

17 December 1995. Because of nearby mountains, it was necessary to rotate the wind data by 30 degrees; this yielded predictions that coincided with observations that the sulphur vapours and smoke most directly affected the Macassar area, as well as predictions from Eulerian general circulation models for the same site and time.

b) Calculating specific SO_2 exposure concentrations based on exposure grid model

For the current study, concentrations resulting from the fire were obtained for 441 receptor locations (i.e., 21 x 21 locations) over the 4 x 2 km grid for each of the 21 hours of the fire. Firstly, the reported location at the time of the fire was established and pinpointed on the exposure grid. Secondly, exposures for each individual were taken as the concentrations of the receptor nearest to residence or reported location at the time of fire. Thirdly, the exposure concentration was determined as the average concentration for each hour at the receptor nearest to the residence or reported location at the time of the fire using a map of the area and the receptor grid developed for this purpose (Table 2.1).

c) Calculation of exposure metrics: peak exposure, cumulative exposure and total hours of exposure

The peak exposure was determined as the highest exposure concentration over the 21 hours of the fire based on exposure concentrations obtained for each specific individual. The total hours of exposure was determined by adding the number of hours each individual was present in Macassar and consequently exposed to the SO_2 vapours using data from the questionnaire (question 3.2). Cumulative exposure was determined by multiplying the exposure concentration by the duration of exposure.

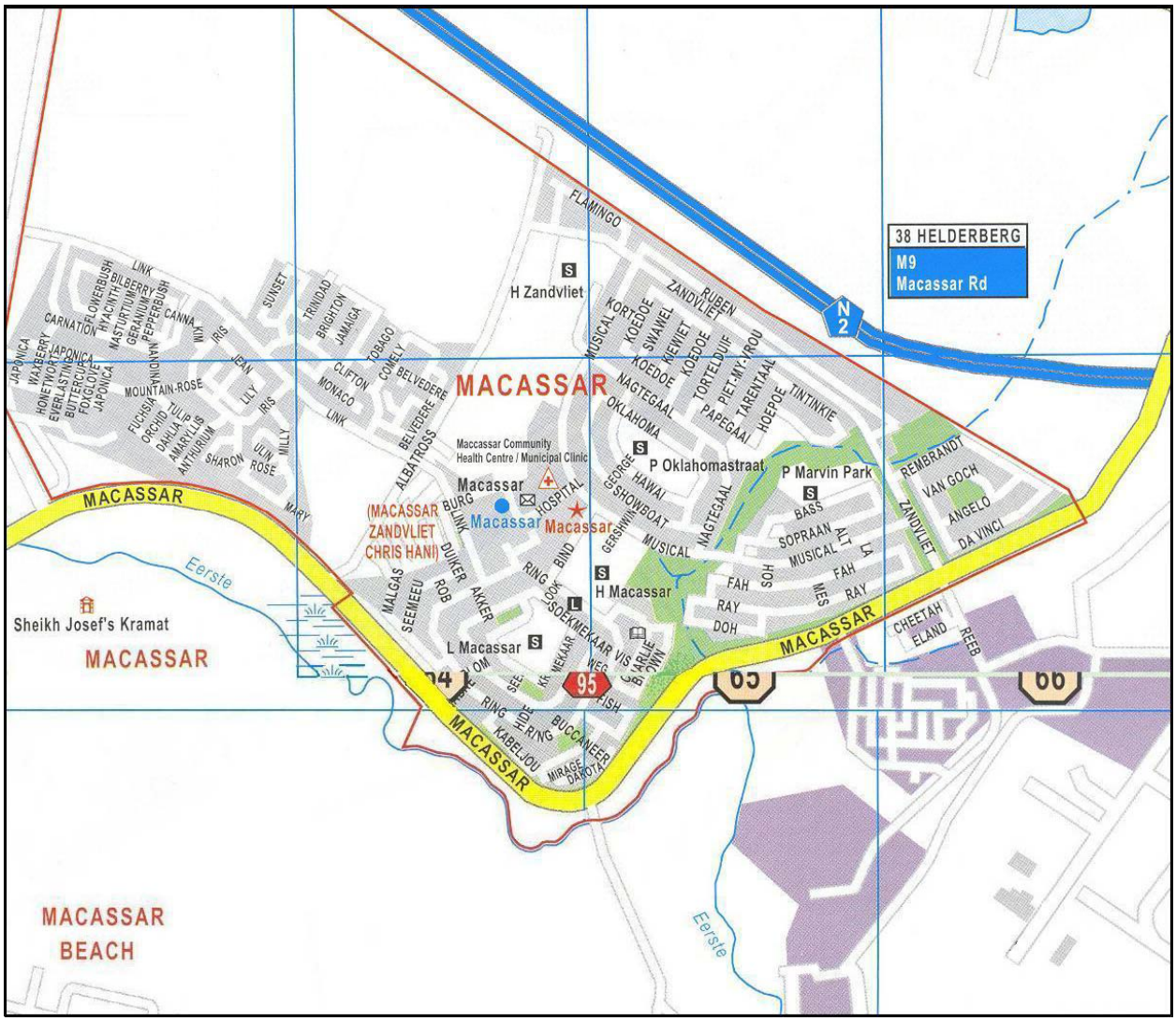

Figure 5. Street map of Macassar used to plot hourly concentration of SO_2

Table 2.1 Example of the exposure grid used to predict SO_2 exposure concentration for each hour of exposure

Location 17-24			
Date	**Hour**	**Time**	**Conc ppm**
16.12.1995	1	5-6pm	1.2219
16.12.1995	2	6-7pm	2.7465
16.12.1995	3	7-8pm	1.2710
16.12.1995	4	8-9pm	3.6753
16.12.1995	5	9-10pm	1.2456
16.12.1995	6	10-11pm	4.7216
16.12.1995	7	11-12pm	2.8910
17.12.1995	8	12-1am	134.5376
17.12.1995	9	1-2am	
17.12.1995	10	2-3am	
17.12.1995	11	3-4am	
17.12.1995	12	4-5am	
17.12.1995	13	5-6am	
17.12.1995	14	6-7am	0.0000
17.12.1995	15	7-8am	0.0000
17.12.1995	16	8-9am	13.3461
17.12.1995	17	9-10am	
17.12.1995	18	10-11am	
17.12.1995	19	11-12am	0.0001
17.12.1995	20	12-1pm	5.1828
17.12.1995	21	1-2pm	0.0000
17.12.1995	22	2-3pm	0.0000

2.5 Data management and analysis

The Information Technology Services at the University of Cape Town captured the questionnaires from a data capture sheet (Appendix 2: Data capture sheet). All questionnaires were stored in confidential files until the completion of the study. The questionnaire and spirometry data were entered and analysed using Stata 8.[67] Descriptive statistics such as means and proportions were used to summarize the data and odds ratios were calculated to compare cases and controls across the predictor variables of interest. The odds ratio was compared using p-values and confidence internals. Generalized linear models were used for multivariate logistic analyses with individual dichotomous outcomes and categorical and/or continuous exposures and covariates. All models were formulated using the saturated model approach when adjusting for confounders to enable comparison across various exposure metrics. Key associations of interest involved investigating relationships between exposure variables (total hours of exposure to SO_2, peak exposure and cumulative exposure to SO_2, host factor attributes) and health outcomes based on a summary dichotomous variable (persistent lower respiratory symptoms attributable to the fire, yes/no). Other dependent variables of interest included the pattern of baseline spirometry (primarily FEV1/FVC ratio, FEV_1 % of predicted, and FVC % of predicted). For the statistical analysis of SO_2 exposure concentrations descriptive univariate statistics were generated for cases and controls. The data followed a log-normal distribution, thus the natural logarithm of the measured exposure was used as the independent variable.

2.6 ETHICS

Obtaining sensitive medical information for medico-legal purposes posed a threat to the client's right to privacy. Subjects have the right to expect that any information collected during the course of the study would be kept in strictest confidence. In order to safeguard the rights and welfare of clients or their next-of-kin, the process of obtaining information and collecting data for research was explained and written informed consent obtained.[68] Oral presentation provided opportunities for greater elaboration and for subjects to ask questions as they are entitled to full disclosure. The study could not replace names with numbers to secure anonymity as some of the clients may have needed to be referred for further medical evaluation. The project could only ensure confidentiality but not anonymity. All records were kept locked in a cabinet in a secure facility. Any agreement made between the researcher and the subjects, including adherence to the procedure outlined in advance was honoured. This especially pertained to informing subjects on the outcome of their medical condition in writing. All clients referred to the specialist were informed in writing with regard to their diagnosis and treatment recommendations. Any subject found to have medical abnormalities by the panel of doctors were referred to the appropriate medical facilities for treatment and follow up treatment. The protocol was submitted to the Research Ethics Committee of the University of the Western Cape for approval (Appendices 3, 4 & 6).

CHAPTER THREE

RESULTS

In this Chapter the findings of the study are presented. The results are presented in chronological order commencing with basic descriptive statistics (means, percentages) and following with more complex statistics (logistic regression analysis). Given the study design (case-control study), it is important that the data is presented for both cases and controls to highlight similarities and differences. Key associations of interest involved investigating relationships between exposure variables (total hours of exposure to SO_2, peak exposure and cumulative exposure to SO_2, host factor attributes) and health outcomes (persistent lower respiratory symptoms). Other dependent variables of interest included the pattern of baseline spirometry (primarily FEV1/FVC ratio, FEV_1 % of predicted, and FVC % of predicted).

3.1 Demographic characteristics

The demographic characteristics of the cases and controls are outlined in Table 3.1. A total of 76 cases and 180 controls were selected. The cases and controls were comparable with respect to age, gender, height and smoking. A slightly higher proportion of controls (29%) were current smokers, whilst the proportion of ex-smokers was slightly higher among cases. Seventeen percent (17%) of the cases and 10% of the controls had a previous history of tuberculosis more than one year prior to the fire and after the disaster.

Table 3.1 Demographic characteristics of study population exposed to SO_2 during the Macassar incident in 1995

Demographic characteristics	Cases	Controls
	n = 76	**n = 180**
Age (yr)	43±12	41± 13
18 – 30	15 (20%)	39 (22%)
31 – 40	21 (28%)	57 (32%)
41 – 50	19 (25%)	36 (20%)
>51	21 (28%)	48 (26%)
Sex: no. (%)		
- Males	23 (30%)	63 (35%)
- Female	53 (70%)	117 (65%)
Height (cm)	162 ±10	162± 9
Smoking status: no. (%)		
- Non	32 (43%)	73 (41%)
- Ex	29 (31%)	55 (31%)
- Current	14 (19%)	52 (29%)
Pulmonary TB*	13 (17%)	10 (6%)

Note: Categorical variables – number (%), Continuous variable – mean ±S.D
*Pulmonary tuberculosis diagnosed more than 1 year prior to and after the disaster

3.2 Medical diagnosis of cases

The medical diagnosis of cases after assessment by a specialist physician is outlined in Figure 6. The majority of the cases were diagnosed with irritant induced asthma (RADS) (64%) and Reactive Upper airway Dysfunction Syndrome (RUDS) (46%). Thirty two percent (32%) of the cases were diagnosed with asthma aggravation, and 15% with rhinitis aggravation. A similar proportion (34%) of the cases had co-existing irritant-induced upper (RUDS) diagnoses.

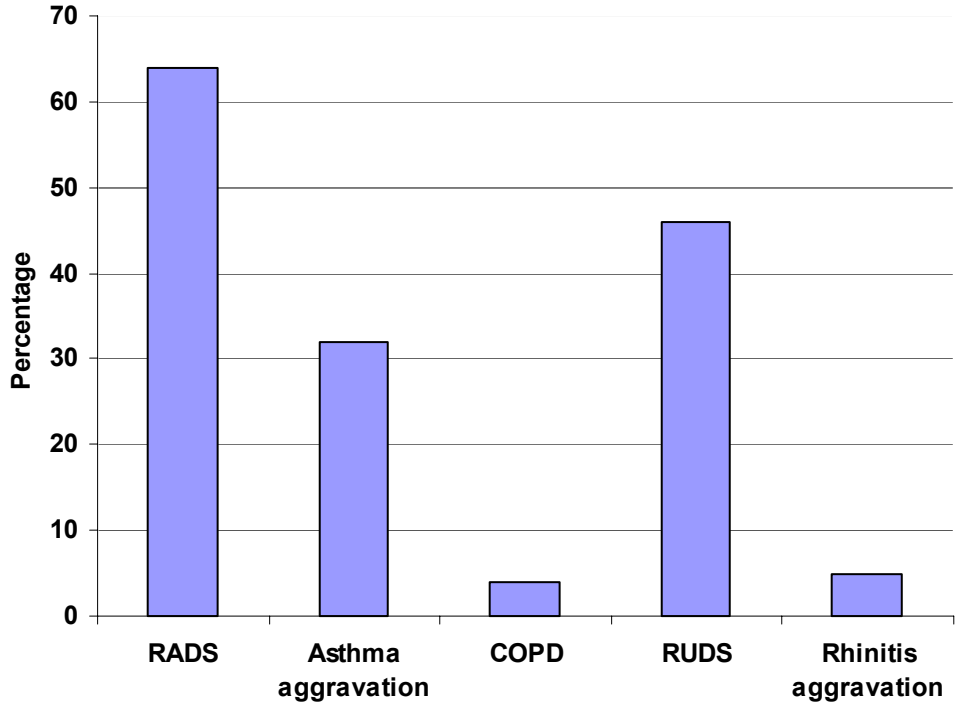

Figure 6. Final diagnosis of cases (subjects with persistent lower respiratory symptoms) exposed to SO_2 during the Macassar fire incident in 1995

*Note upper and lower respiratory symptoms/disease may be present per subject (n=76)
RADS-Reactive Airway Dysfunction Syndrome, **RUDS**- Reactive upper airway dysfunction syndrome, **COPD**-Chronic obstructive pulmonary disease /Chronic obstructive airway disease **(COAD)**

3.3 Spirometry results

The results of spirometry performed on cases are presented in Table 3.2. A large proportion (84%) of the cases had sub-optimal lung function (FEV_1 < 80% predicted), whilst 51% of the cases had evidence of airway obstruction on baseline spirometry. A total of 41% of the cases demonstrated evidence of bronchial reversibility suggestive of asthma (FEV_1 ≥ 12%). These abnormalities were more common among males than females.

Table 3.2 Current spirometry results of cases (n=76) exposed to SO_2 during the Macassar fire incident in 1995

Result	Mean ± S.D	Range
All Cases (n=76)		
No (%) FEV_1/FVC ratio<=80%	39 (51%)	-
No (%) FEV_1< 80% predicted	64 (84%)	-
- Mild: 61-80% predicted	31 (41%)	-
- Moderate: 51-60 % predicted	13 (17%)	-
- Severe: <50% predicted	20 (26%)	-
No (%) FEV_1 with >=12% reversibility	31 (41%)	-
Males (n=23)		
FEV_1 (L) (baseline)	2.05± 0.83	0.69-3.72
FVC (L) (baseline)	2.86±0.99	0.87-4.38
FEV_1 / FVC ratio (baseline)	72±16	39-100
No (%) FEV_1/FVC ratio<=80%	17 (74%)	-
No (%) FEV_1< 80% predicted	21 (91%)	
No (%) FEV_1 with >=12% reversibility	9 (39%)	
Females (n=53)		
FEV_1 (L) (baseline)	1.67±0.55	0.73-3.18
FVC (L) (baseline)	2.10±0.69	0.90-4.32
FEV_1 / FVC ratio (baseline)	80±13	54-100
No (%) FEV_1/ FVC ratio<=80%	22 (42%)	-
No (%) FEV_1< 80% predicted	43 (81%)	-
No (%) FEV_1 with >=12% reversibility	22 (42%)	

Predicted values: European Community for Coal and Steel (ECCS)

3.4 Host factors associated with persistent lower respiratory tract symptoms

Host factors

In the unconditional logistic regression statistical models of the various host factors in relation to the outcome of interest indicated that none of the demographic characteristics (age, sex, smoking status) were significantly associated with persistent lower respiratory symptoms attributable to the fire Table 3.3.

Previous medical history

The results revealed that subjects with persistent lower respiratory symptoms attributable to the fire were three times more likely to have a medical history of pulmonary tuberculosis more than one year prior to and after the fire (OR: 3.5, CI: 1.5-8.4) Table 3.3.

Self reported acute symptoms at the time of the fire

Self-reported headache symptoms (p=0.026) were more prevalent among controls at the time of the disaster, whilst lower respiratory symptoms such as wheeze (p=0.007) and tight chest (p<0.001) were significantly more prevalent among cases than controls. A borderline association was demonstrated for shortness of breath (p=0.066) (Figure 7). In the unconditional logistic regression models cases (those with persistent lower respiratory symptoms) were nine times more likely to report tight chest symptoms (OR: 9.9, CI: 5.2-19.1), and almost twice as likely to report shortness of breath (OR: 1.9, CI: 0.9-4.1) at the time of the fire. The association demonstrated for shortness of breath was however not statistically significant (p=0.07).

Table 3.3. Host factors as predictors for chronic lower respiratory symptoms for subjects (cases=76, controls =180) exposed to SO_2 during the Macassar fire incident, 1995 as determined by unconditional logistic regression

Predictor	O.R	95% C.I	p-value
Age (as continuous variable)	1.0	0.99-1.03	0.458
Sex			
Female=1 & Male =0	1.2	0.70-2.21	0.464
Smoking status (compared to non-smokers)			
Ex-smokers	1.2	0.65-2.21	0.554
Current smokers	0.6	0.30-1.26	0.186
Previous medical history			
Pulmonary T.B*	3.5	1.46-8.35	0.005
Self reported acute symptoms			
Ocular-nasal			
Burning eyes	0.8	0.45-1.33	0.345
Burning / sore nose	0.9	0.50-1.66	0.770
Burning / sore throat	0.9	0.49-1.79	0.836
Lower respiratory symptoms			
Burning / sore chest	1.5	0.79-2.74	0.218
Shortness of breath	1.9	0.95-4.09	0.070
Cough	1.2	0.65-2.09	0.602
Tight chest	9.9	5.15-19.11	<0.001
Constitutional symptoms			
Headache	0.3	0.08-0.92	0.036
Gastro-intestinal symptoms			
Diarrhoea	0.8	0.08-7.69	0.837
Vomiting and nausea	0.6	0.25-1.45	0.257

***Pulmonary TB diagnosed more than 1 year prior to and after the fire**

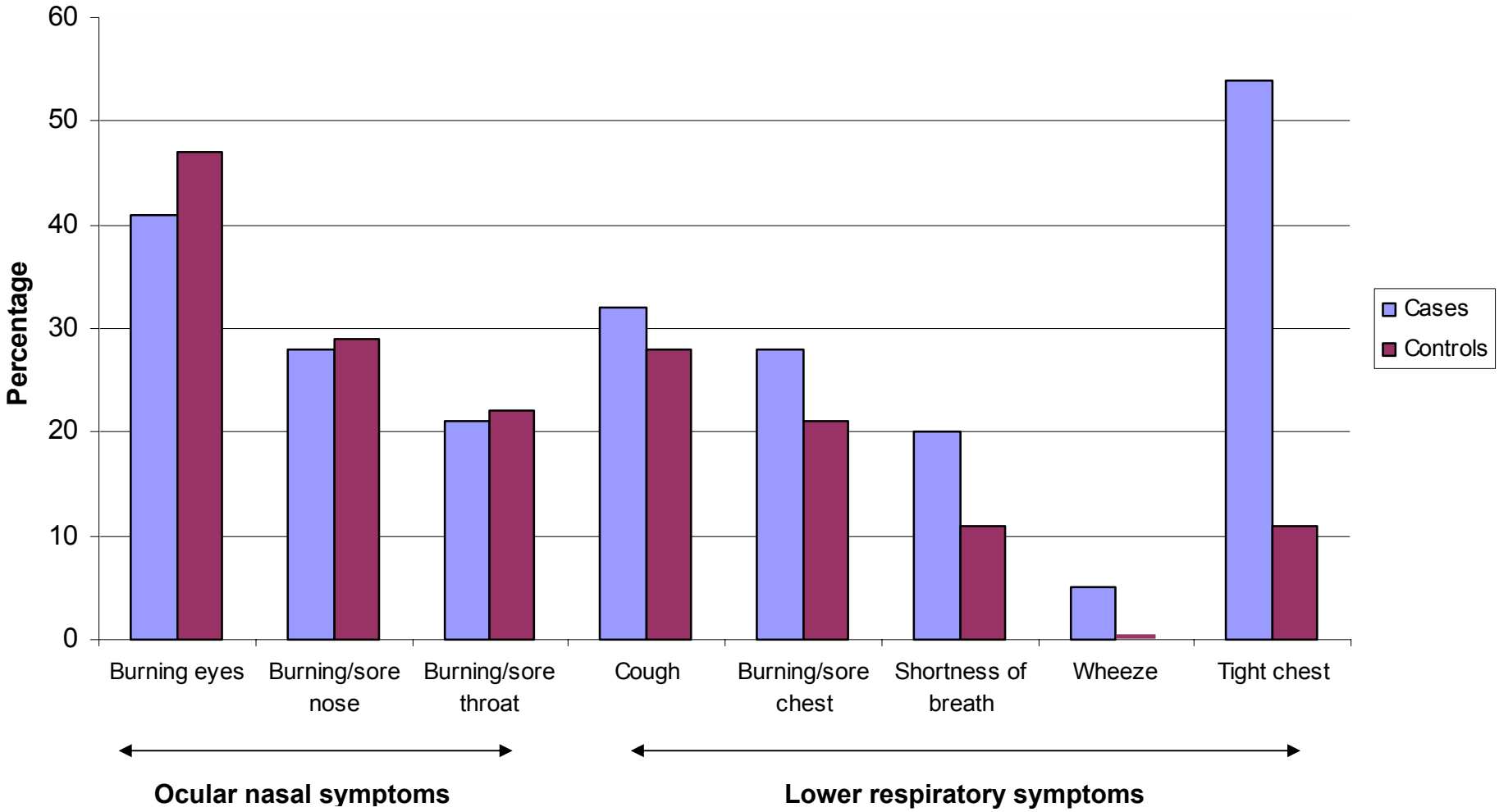

Figure 7. Acute self reported upper and lower respiratory symptoms experienced by cases and controls exposed to SO_2at time of the Macassar fire incident in 1995

3.5 Environmental factors associated with persistent lower respiratory tract symptoms

Summary descriptive exposure metric data for cases and controls are outlined in Table 3.4. The mean total hours of exposure were similar between cases and controls. Overall the cases had higher peak exposure and cumulative exposure concentrations (ppm/hr) to SO_2, compared to controls, however this was not statistically significant ($p>0.05$). The geometric mean hourly SO2 concentration for cases and controls are presented in Tables 3.5.1 and 3.5.2. During the first 8 hours of the fire, a much greater proportion of cases and controls were exposed to SO_2. During the 21-hour exposure period, two peaks of exposure were observed. The first peak occurred in the first 8 hours of the fire before the evacuation process and the second peak occurred in the latter 6 hours (Figure 8). Analysis of the mean hourly exposure concentration between cases and controls revealed that the cases had a significantly higher SO_2 exposure concentration at hour 15 in comparison to controls ($p=0.04$) (Figure 8).

Table 3.4 Total hours, peak exposures, cumulative (ppm/hr) exposure and time weighted averages exposures to SO_2 levels and location at time of the Macassar fire incident in 1995 for cases and controls.

	Cases (n=76)				Controls (n=180)				
	Mean± S.D	Range	Median	IQR	Mean± S.D	Range	Median	IQR	p-value
Total hours of exposure	8.43±6.33	1-21	6	6.5	8.54±6.11	1-21	6	7	0.896
Peak exposure (ppm)	46.46±86.67	0-444.06	6.94	64.51	40.63±95.91	0-540.64	4.01	41.17	0.649
Cumulative exposure (ppm*hrs)	104.22±168.46	0-821.97	13.37	163.78	101.40±187.70	0-884.23	7.74	106.95	0.910
Outside/ Inside dwelling at the time of the fire	26 (34%)				63 (35%)				0.904

T-test for continuous variable, Chi-Square test for categorical variable

Table 3.5.1 Hourly exposure to SO_2 concentration (ppm) experienced by cases (n=76) during the Macassar fire incident in 1995 according to the Industrial Source Complex Short Term Model

Hour No.	No. of persons exposed	SO_2 concentration			
		A.M.	G.M.	G.S.D.	Range
1	76	5.02	2.16	10.51	0-22.04
2	71	10.53	4.48	8.25	0-51.97
3	64	21.31	7.52	10.80	0-84.72
4	53	23.34	5.10	15.96	0-98.51
5	50	16.41	4.67	15.87	0-81.36
6	38	23.50	6.69	14.59	0-90.83
7	22	96.01	78.07	9.11	0-444.06
8	18	0	-	-	-
9	18	0	-	-	-
10	17	0	-	-	-
11	16	0	-	-	-
12	16	0	-	-	-
13	15	0	-	-	-
14	16	0	0.02	-	0-0.02
15	17	17.86	4.12	16.78	0-80.01
16	20	0.01	0.17	-	0-0.17
17	20	0	-	-	-
18	21	0.01	0.06	1.39	0-0.08
19	24	3.36	1.52	15.33	0-18.47
20	24	0	0.07	-	0-0.07
21	25	0	-	-	-

Note: **A.M:** Arithmetic Mean, **G.M:** Geometric Mean, **G.S.D:** Geometric Standard Deviation.
Hour no.1 = 6pm on the 16 December 1995, Hour no. 21 = 2pm on the 17 December 1995

Table 3.5.2 Hourly exposure to SO_2 concentration (ppm) experienced by controls (n=180) during the Macassar fire incident in 1995 according to the Industrial Source Complex Short Term Model

Hour No.	No. of persons exposed	SO_2 concentration			
		A.M.	G.M.	G.S.D.	Range
1	175	4.70	1.72	12.06	0-22.04
2	173	9.92	3.15	12.30	0-40.43
3	156	19.98	4.44	17.29	0-84.72
4	126	24.13	6.46	12.30	0-98.51
5	106	20.22	4.78	14.29	0-81.36
6	84	26.14	7.42	10.80	0-91.85
7	56	80.72	8.95	44.70	0-540.64
8	46	0.59	27.28	-	0-27.28
9	40	0	-	-	-
10	38	0	-	-	-
11	36	0	-	-	-
12	38	0	-	-	-
13	40	0	-	-	-
14	43	0	-	-	-
15	50	7.46	0.82	17.99	0-53.86
16	51	0	-	-	-
17	54	0	-	-	-
18	57	0.04	2.26	-	0-2.26
19	59	2.77	0.93	15.03	0-19.46
20	61	0.61	18.6	0	0-18.6
21	64	0	-	-	-

Note: **A.M:** Arithmetic Mean, **G.M:** Geometric Mean, **G.S.D:** Geometric Standard Deviation.
Hour no.1 = 6pm on the 16 December 1995, Hour no. 21 = 2pm on the 17 December 1995
Note: at hour no. 1, the number of controls exposed was only 175, as some residents may not have been in Macassar at that specific point in time (6pm), but may have returned to Macassar at some point during the 21 hour period of the fire.

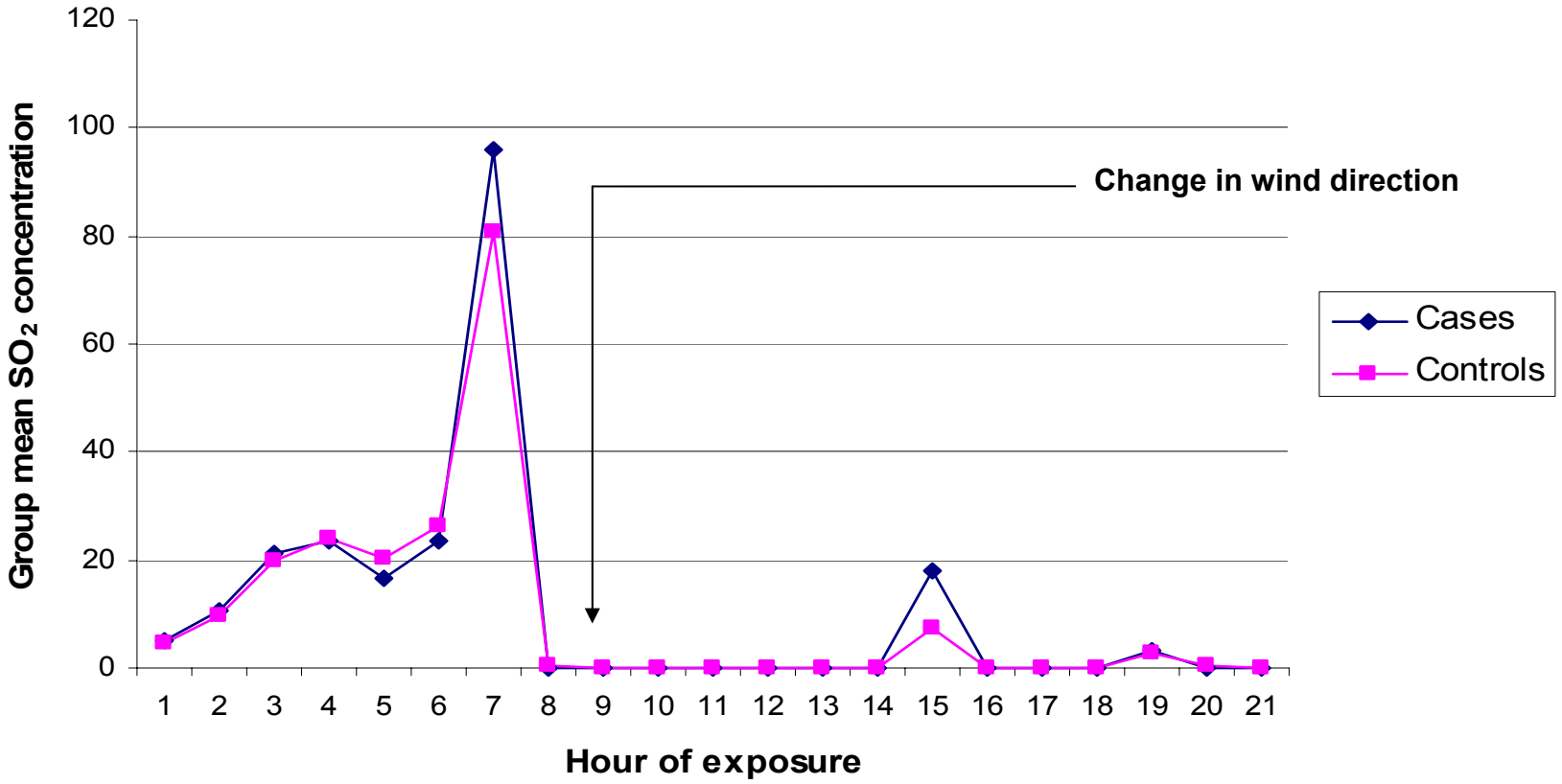

Figure 8. Mean hourly exposure to SO_2 experienced by study subjects during the Macassar fire incident according to the Industrial Source Complex Short Term Model

3.5.1 Total hours of exposure

Analysis of the total hours of exposure to SO_2 as a categorical variable indicated no significant trend (p=0.878) in relation to persistent lower respiratory symptoms (Figure 9).

3.5.2 Peak exposure

There was also no significant trend between peak SO_2 exposure (p=0.275) and the likelihood of having persistent lower respiratory symptoms (Figure 10). These results follow a similar pattern to that of the total hours of exposure. However regression analysis revealed an increased risk of persistent lower respiratory symptoms with increased peak exposure (peak exposure >20 ppm versus <2 ppm, OR: 1.4), though not statistically significant.

3.5.3 Cumulative exposure

Cumulative exposure to SO_2 was calculated for cases and controls. Analysis of cumulative exposure as a continuous variable showed no significant association with persistent lower respiratory symptoms. Categorical variables were constructed for the cumulative exposure over the twenty-one hour duration of SO_2 exposure. Trend analysis revealed no significant exposure response relationship for cumulative exposure (p=0.310) (Figure 11). However, there appeared to be an increased risk of having persistent lower respiratory symptoms for cumulative exposure >50 ppm*hr (OR: 1.4) over the 21 hour exposure duration, although this finding was not significant.

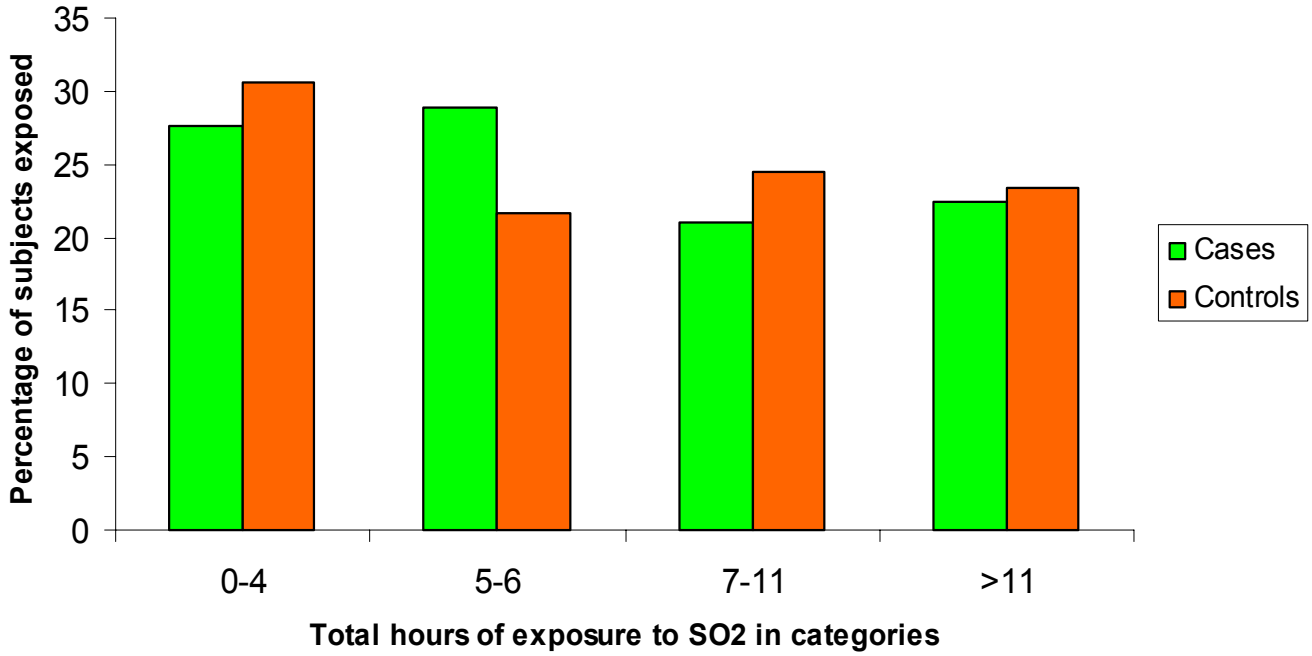

Figure 9.Total hours of exposure to SO_2 by cases and controls during the Macassar fire incident in 1995 according to categories

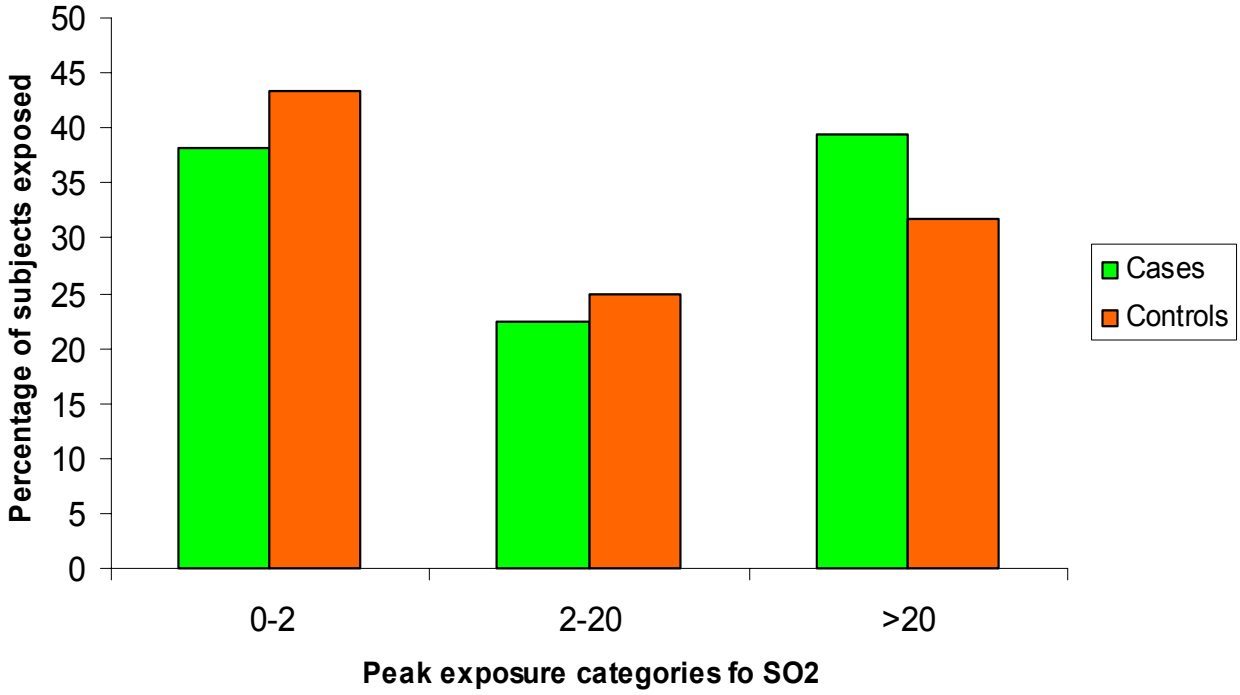

Figure 10. Peak exposures of SO_2 for cases and controls during the Macassar fire incident in 1995 according to categories

Note: Peak exposure of SO_2: 1 = 0-2 ppm, 2 = 2-20 ppm, 3 = >20 ppm

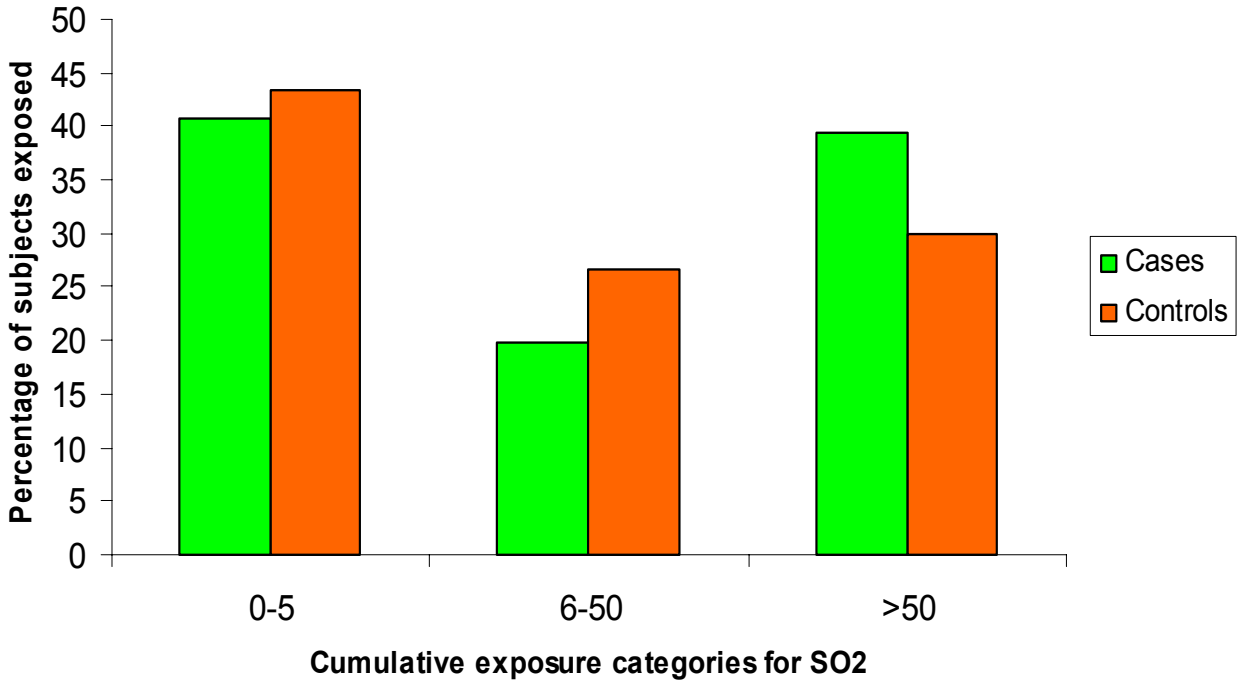

Figure 11. Cumulative exposure (ppm*hr) to SO_2 for cases and controls during the Macassar fire incident in 1995
Note: Levels of exposure: 1 = 0-5 ppm*hr, 2 = 6-50 ppm*hr, 3 = >50 ppm*hr

3.5.4 Log-transformed (base2) continuous, cumulative, peak exposure variables

No significant association was found between the log-transformed (0.5 added to exposure variables / log2) exposure variables (peak exposure and cumulative exposure) and persistent lower respiratory symptoms in the regression models (Table 3.6).

Table 3.6 Environmental factors as predictors for persistent lower respiratory symptoms for cases and controls exposed to SO_2 during the Macassar fire incident in 1995, determined by logistic regression

Predictor	O.R.	C.I.	p-value
Peak exposure (ppm)	1.1	0.96-1.14	0.266
Cumulative (ppm*hr)	1.0	0.96-1.11	0.405

3.5.5 Exposure metrics as predictors lower respiratory symptoms – final model

The logistic regression results for the various exposure metrics are outlined in Table 3.7**.** None of the exposure metrics (total hours of exposure, cumulative exposure, peak exposure) were significantly associated with persistent lower respiratory symptoms attributable to the fire. However, SO_2 exposure concentration at hour 15 after adjusting for previous history of TB more than one year prior to and after the fire was significantly ($p = 0.022$) associated with an increased risk of having persistent lower respiratory symptoms attributable to the fire (OR: 1.04, CI: 1.00 – 1.07)

Table 3.7 Environmental factors (categories) as predictors for persistent lower respiratory symptoms for cases and controls exposed to SO_2 during the Macassar fire incident, 1995 as determined by logistic regression

Predictors	O.R.	95%C.I	p-value
Unadjusted models			
Location at time of incident			
Outside v/s inside	0.97	0.55-1.70	0.904
Total hours of exposure (hrs[a])			
5-6 hrs	1.48	0.72-3.05	0.291
7-11 hrs	0.95	0.44-2.04	0.900
>11	1.06	0.50-2.26	0.880
Cumulative exposure (ppm*hours[b])			
6-50 ppm	0.79	0.39-1.61	0.509
> 50 ppm	1.40	0.76-2.57	0.282
Peak exposure (ppm, hours[c])			
2-20	1.02	0.50-2.01	0.964
>20	1.42	0.77-2.62	0.267
Exposure at hour 15	1.03	0.99-1.06	0.060
Adjusted for previous history of TB			
Exposure at hour 15	1.04	1.00-1.07	0.022

Note: [a]Compared to <5 hours of exposure, [b]Compared to <6 ppm, [c]Compared to <2 ppm.

CHAPTER FOUR

DISCUSSION

The aim of this study was to assess the environmental and host factors associated with persistent lower respiratory symptoms or asthma attributable to the fire among residents six years after being acutely exposed to elevated SO_2 vapours during a sulphur fire. Despite the well-known irritant effects of SO_2, limited information is available about the long-term health effects of the accidental exposure to this substance. Macassar residents with persistent lower respiratory symptoms attributable to the fire (at least 64% having irritant induced asthma) 6 years after the sulphur fire were more likely to have a history of TB more than one year before the fire and more likely to present with acute asthma-like symptoms (tight chest) at the time of the fire. Exposure to peak sulphur dioxide at hour 15 of the fire was also associated with an increased risk of having persistent symptoms attributable to the fire.

Thirty four percent (34%) of the cases had co-existing irritant-induced upper (RUDS) and lower respiratory (RADS) diagnoses. It has been suggested that respiratory irritants can lead to asthma and rhinitis through interaction with chemical irritant receptors in the airway, leading to release of substance P from sensory nerves and neurogenic inflammation. Demeter et al showed that chronic rhinosinusitis symptoms requiring treatment may be paralleling the course of asthma in RADS.[58] This observation supports the concept of "one airway, one disease".[69]

In this study the host factors associated with persistent lower respiratory symptoms attributable to the fire was also investigated. Analysis revealed that none of the

demographic characteristics (age, sex, smoking status) were significantly associated with persistent lower respiratory symptoms attributable to the fire. However, subjects with persistent lower respiratory symptoms attributable to the fire were three times more likely to have a medical history of pulmonary tuberculosis more than one year prior to the fire (OR: 3.5, CI: 1.5-8.4). This finding is consistent with the results of a recent national survey in South Africa, which showed that a history of tuberculosis was an independent predictor of both recent wheeze (OR: 3.4; 95% CI 2.5-4.7] and asthma diagnosis (OR: 2.2; 95% CI 1.5-3.2).[70] Airways obstruction has been a well documented long term sequela of pulmonary tuberculosis.[71,72] The association of past tuberculosis with asthma diagnosis is difficult to explain, and may be the result of post tuberculous lung disease being misdiagnosed as asthma.[70] This was considered unlikely in this study since all cases were evaluated by a specialist pulmonologist using spirometry as confirmation and active pulmonary TB excluded on clinical examination. The study also demonstrated that subjects with persistent lower respiratory symptoms attributable to the fire were nine times more likely to report tight chest symptoms (OR: 9.9), and almost twice as likely to report shortness of breath (OR: 1.9) at the time of the fire. This is consistent with previous studies in which lower respiratory symptoms occurred after chemical exposure irrespective of age or smoking status, while respiratory health status was found to be a significant factor in determining susceptibility to SO_2 exposure.[45,58,59]

Among these residents with persistent lower respiratory symptoms attributable to the fire, objective diagnostic clinical examination by an experienced pulmonologist demonstrated that the majority of the cases had newly diagnosed irritant induced asthma (64%), whilst 32% had experienced aggravation of their asthma after the fire. Smoking status was not significantly associated with having persistent lower respiratory symptoms attributable to

the fire, thus it would appear that the majority of the cases of chronic symptoms could be attributed to the fire. Furthermore a large proportion (84%) of the cases had sub-optimal lung function (FEV_1 < 80% predicted), whilst 51% of the cases had evidence of airway obstruction on baseline spirometry. A total of 41% of the cases demonstrated evidence of bronchial responsiveness ($FEV_1 \geq 12\%$) confirming the persistent asthma. The findings of this study is consistent with the results demonstrated by Piirilä that reversible bronchial obstruction was still present after four years and altered bronchial response after 13 years following SO_2 exposure.[45] Brooks also demonstrated that irritant induced asthma (RADS) preceded chronic obstructive pulmonary disease with 40% of subjects having $FEV_1FVC<70\%$ at follow up examination (mean duration 35.8 months).[46]

Various exposure variables were created to assess environmental exposure as a predictor for persistent respiratory symptoms attributable to the fire. None of the exposure metrics (total hours of exposure, cumulative exposure, peak exposure were significantly associated with persistent lower respiratory symptoms attributable to the fire. However, SO_2 exposure concentration at hour 15 after adjusting for previous history of TB (more than one year prior to and after the fire) was significantly ($p = 0.022$) associated with an increased risk of having persistent lower respiratory symptoms attributable to the fire (OR: 1.04, CI: 1.00 – 1.07). The attribution of the persistence of symptoms to exposure to the relatively small secondary exposure at 15 hours is probably not plausible given the fact that the initial exposure was longer and more intense. There was a suggestion that there may be some threshold effects operating, but the trends were not consistently significant. Regression analysis revealed an increased risk of persistent lower respiratory symptoms attributable to the fire with increased peak exposure (peak exposure 2-20ppm, OR: 1.02; peak exposure >20ppm, OR: 1.42), and there appeared to be an increased risk

of having persistent lower respiratory symptoms attributable to the fire for cumulative exposure >50 ppm*hr (OR: 1.39), although this finding was not significant. Various reports in the literature suggest that exposure > 20 ppm is associated with chronic respiratory symptoms.[56,11] However, this could not be convincingly demonstrated in this study. There are various reasons for this lack of association observed. Both the length and intensity of SO_2 exposure determine dose, and both factors varied considerably during the fire making it difficult to generate precise exposure estimates. Ambient SO_2 levels over the 21-hr period varied temporally and spatially. Furthermore, a person's dose depends on many factors, e.g. location, the sheltering effect of a building or vehicle, breathing rate, and any protective measures undertaken. Residents who were outdoors or evacuated and crossing the fire's plume may have been exposed to the highest SO_2 concentrations. Most residents remained indoors in shut houses, partly sheltered from the SO_2 plume. Batterman et al suggest that a better understanding of exposures and health effects requires additional information on demographics (population density), housing characteristics (air exchange rate and locations), and activity patterns (location, time outdoors, etc.).[3] Alternatively, theoretical assumptions made in the modelling of exposure may have resulted in exposure misclassification, and therefore, an inability to demonstrate an association.

In considering the findings of this study it is important to bear in mind the following limitations. It is well documented that there is a strong relationship between persistent lower respiratory symptoms and exposure to chemical respiratory irritants, including sulphur dioxide which was the putative agent in the Macassar fire. Lack of statistical power may have been one of the reasons for the current study failing to demonstrate a dose-response relationship. This was considered to be a minor contributory factor.

Several other factors restrict the interpretation of results, especially the quantitative aspects. Firstly, "self-selection" bias was an important limitation in this study, since the entire study population was self-referred and as such the study population was not randomly selected. The study population (clinic attendees) may therefore not necessarily be viewed as being representative of the entire Macassar community. It is also important to note that the prevalence of symptoms obtained could not be viewed as the true prevalence of symptoms within the exposed population, as some residents may have presented to other health services for treatment and therefore potentially excluded from the sampling frame. Another possible limitation is the possibility of recall bias operating since the fire incident happened six years ago; however this was considered unlikely as there was non-differential reporting between cases and control. Self reported symptoms may have been over-reported due to potential secondary gain since the cases were drawn from a medico-legal process to assess eligibility for compensation payouts. This may have created greater expectations among those residents with minimal symptoms, such as the controls prompting them to exaggerate their symptoms thereby diluting possible associations present. Finally, since the exposure measures were not directly measured but inferred from an experimental exposure model, this may have introduced exposure misclassification and further contributed to the failure to demonstrate an association between exposure level and respiratory symptoms reported.

In conclusion this study confirmed the findings of previous studies suggesting that pre-morbid respiratory health status (pulmonary TB more than one year prior to the fire) is an important factor predicting chronicity of acute asthma-like symptoms associated with SO_2 exposure. The study also demonstrated that bronchial responsiveness persists in a large proportion of affected individuals 6 years after the initial exposure to high levels of SO_2.

It is recommended that future studies consider alternative assumptions when modeling exposure to derive more reliable estimates of exposure making it possible to explore dose-response relationships in a more meaningful manner. Future studies need to explore the association between pulmonary TB and the development of asthma – whether this may be due to post TB structural damage of the airways or the result of altered cytokine production following mycobacterial infection producing immunomodulatory effects on the airways thereby increasing the likelihood of developing asthma.

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