CHAPTER FIVE

5. RESULTS

The results of the studies were grouped into four categories according to the study phases previously outlined.

5.1 PHASE I – LUNG FUNCTION STUDIES

5.1.1 Exploratory lung function study

5.1.1.1 Objective

An initial study on lung functions of workers in higher risk occupations (including boilermakers and welders) was done. The lung function results were analysed with respect to the suitability of Bouhuys and Cavitron predictions as a basis for screening lung function results; the early diagnosis of airway disease and the suitability of "peak flow" in the pre-employment screening of potential employees.

5.1.1.2 Introduction

In the late 1970's and early 1980's when this study was done the Golden Standard for lung function evaluation (Spirometry) in the mining industry in Southern Africa was the Peak Expiratory Flow Rate measurement (PEFR). Rapid development in the field of computerised lung function apparatus combined with consensus statements (standarised spirometry) by authoritative scientific bodies such as the American Thoracic Society (ATS)[266,267] necessitated the replacement

of peak flow measurements with spirometry or flow volume measurements.

Lung function testing was beset with controversy about the transfer of reference ranges across racial lines and with the concept of normality. The transfer of "accepted" scientific norms to the occupational health arena was problematic, mainly because of the potential impact on compensation payments.[264]

The introduction of new methods had to be evaluated and agreed with the management team of the mine. It was decided to purchase a Cavitron Spirometric Computer and to use both the Cavitron predicted values as well as Bouhuys reference values.

5.1.1.3 Method

Details of height, weight, age, sex and ethnic group were collected from a sample of initially 342 and later 946 Rössing employees. Latest lung function results, obtained from the Cavitron Spirometric Computer in the Medical Centre were recorded. Predicted lung function values were obtained from three sources: the Cavitron Computer, tables of norms published by Bouhuys and a computer programme operating on the ICL computer at Rössing which calculated Bouhuys norms and minima.

* Cavitron Predictions

The Cavitron predictions comprised three sets of lung function "norms". Actual lung function was measured as a percentage of the predicted norms associated with:

FVC	Forced Vital Capacity
FEV_1	Forced Expired Volume in one second

FEV_1/FVC Ratio of these two lung function parameters

* Bouhuys Tables (Norms)

The set of tables comprised predicted lung function "norms" for varying ranges of age, height, weight, age and ethnic group. The predictions included norms associated with:

FEV_1

FEF_{50} Forced Expired Flow at 50% of lung capacity

FEF_{75} Forced Expired Flow at 75% of lung capacity

PF Peak Flow

* Bouhuys Programme (Norms and Minima)

This computer programme, developed for the Rössing ICL computer, produced predicted norms and predicted lung function minima based on 95% probability points within expected normal distributions of lung function parameters. The predictions included norms and minima associated with: $FVC, FEV_1, FEV_1/FVC, FEF_{50}, FEF_{75}$, PEFR

5.1.1.4 Analyses

Two predictive techniques had been developed whereby it is possible to identify non-normal lung function. Both techniques were dependent on details of age, height, weight, ethnic group and sex to calculate appropriate predicted lung function. The Bouhuys technique is based on experience with South African indigenes and the Cavitron is based on experience with American indigenes. Clearly an indication was required of which was most appropriate to Namibia.

The Cavitron predictions were limited to the norms of three lung function parameters only. The comparison was, by necessity,

therefore limited to corresponding Bouhuys predictions and actual lung functions associated with them. Findings were that the Bouhuys FVC norm was a significantly better predictor than the Cavitron norm at the 99% level of significance.

The selective criteria used to identify abnormal lung function on the basis of Bouhuys minima were applied in two parts:

Table 15 – Bouhuys Minima

FEV_1	<Bouhuys minimum
FEV_1/FVC	<Bouhuys minimum
PF	<Bouhuys minimum
FEF_{50}	<Bouhuys minimum
FEF_{75}	<Bouhuys minimum

The selection criteria currently used to identify candidates for further investigation were as follows:

Table 16 – Bouhuys Norms

FEV_1	<90% Bouhuys norm
PF	<90% Bouhuys norm
FEV_1/FVC	<0.75 (75%)
FEF_{50}	<90% Bouhuys norm
FEF_{75}	<90% Bouhuys norm

* Peak Flow as a Single Measure of Abnormality

The following tables represent a summary of the results obtained when applying peak flow minima as the sole criterion for determining lung function abnormality.

Table 17 – Abnormalities according to method used

	Normal	Abnormal	Total
Bouhuys Minima	284	58	342
90% of Bouhuys Norms	194	148	342
Peak Flow	328	*14	342

5.1.1.5 Application

Having eliminated the Cavitron predictions in the diagnosis of early airway disease because (a) they comprise only limited lung function parameters (b) they incorporate only norms and (c) the predictions appear to be no better than the corresponding Bouhuys predictions, the diagnosis of early airway disease involved the comparison of two methods both of which employed Bouhuys prediction.

The first method involved the application of a fixed percentage to tables of Bouhuys norms to obtain minimum permitted values. If actual lung function results were below such minimum permitted values, the appropriate employees would be referred for further investigation.

The second method, which was incorporated into an additional computer programme, involved the application of calculated Bouhuys minima (based on 95% significance levels) to actual lung function results. Diagnostics were given in two parts – those relating to airway abnormalities and those relating to vital capacity abnormalities.

Findings were as follows:

Of the 342 employees examined, 148 exceptions (43%) were identified using method 1 and 58 (17%) using method 2.

It is likely that a significant number of employees have been accepted as medically fit for employment at Rössing when their overall lung function was impaired.

The following table represents a summary of the lung function diagnosis exercise employing 946 readings:

Table 18 – Comparing Different Criteria for Abnormal Lung Function

Criterion	Normal	Abnormal	Total
Bouhuys minima	342	74	946
90% Bouhuys norms	561	385	946
PF	930	*16	946

5.1.1.6 Recommendations

Recommendations are made in three parts, to coincide with the objectives of the study.

* **The use of "Peak Flow" in screening**

The use of only peak flow readings in the determination of lung function abnormality has been advocated for some time. Rössing has in fact selected peak flow as the prime indicator of normal/abnormal lung functions in the screening of potential employees.

One of the aims of this exercise was to compare the effectiveness of peak flow as a single indicator of abnormality with the two previously defined alternatives – method 1 (indicating airflow abnormalities only) and method 2 (indicating airflow and vital capacity abnormalities).

It is recommended that the use of the single lung function parameter peak flow in the screening of potential employees be replaced by a

more comprehensive test. Of the 342 people examined only 4% were considered to have abnormal peak flow readings compared with a 17% abnormality rate when applying the full spectrum of lung function minima.

* **Early diagnosis of airway disease**

It is recommended that the Bouhuys tables currently in use be abandoned. The tables are limited to airflow measurement of males only. They are printed in steps of 5 kilograms for weight and 5 centimetres for height and may therefore produce only approximations to norms. In addition the norms do not lend themselves to valid mathematical manipulation for the calculation of minima.

Finally, it is recommended that at some point in the future a control group should be established to determine whether the lung function of the Rössing work force is "normally" distributed. Little point is served in establishing a set of "norms" and "minima" based on normal distribution when the lung functions used to calibrate them are not normally distributed. (It is conceivable that a skewed distribution may be obtained from such an exercise as Rössing employs a large number of staff whose lung function may well have been affected by their previous and current mining working environments.)

5.1.2 Exploratory Cross-Sectional Lung Health Study

5.1.2.1 Objective

To evaluate and standardise equipment, to evaluate predicted values for lung function parameters and to identify high-risk groups.

5.1.2.2 Introduction

Although the exposure time was short (approximately eight years), higher than prescribed exposure levels of dust and, sometimes, radiation were experienced during the initial phases of the operation. The workforce was fluctuating and the continued existence of the mine was sometimes in jeopardy. Safety and environmental control received the highest priority but results came only with time and effort.

5.1.2.3 Study Population

During the first eight years of production, manpower levels fluctuated with a high-annualised percentage turnover complicating the selection of a representative sample.

Table 19 – Manpower and Number of Starters and Leavers

Year	Manpower	Annual % Labour Turnover	Number of Leavers	Number of Starters
1977	2950	26.6	NA	NA
1978	2901	30.1	NA	NA
1979	3115	23.5	NA	NA
1980	2999	27.4	849	730
1981	3164	24	751	916
1982	3048	19.2	606	490
1983	2906	12.9	369	106
1984	2643	14	226	79

The study population was selected out of a fluctuating workforce of approximately 3000 employees. Inclusion criteria included length of service of two years and more, accurate personal information (the date of birth being the biggest problem) and acceptable lung functions (as discussed under the heading "Methodology"). A random selection was done.

Table 20 – Ethnic Distribution of Population

	Total Population	Study Population	Percentage
Total	2985	1485	49.75%
Caucasians	833	337	40.46%
Mixed Races	547	260	47.53%
Blacks	1605	888	55.33%

Table 21 – Ethnic Distribution of Smokers

	Ethnicity			Total
	Caucasian	Mixed	Black	
Number	337	260	888	1485
Smokers	203	171	238	612
Percentage	60	66	27	41
Mean Age (Years)	38	31	31	33.3
Caucasians were statistically significantly older than mixed races and blacks				

5.1.2.4 Methods for demonstrating early small airway involvement

For the purposes of this project, an ideal test should be capable of fulfilling several criteria:

* It should not be patient-dependent. The more sensitive tests are, by and large, unable to satisfy this requirement. A capable and experienced technologist can however, for the most part, overcome these difficulties.
* It should not be time consuming.
* The cost of an individual test should be relatively low.
* The acquisition and collation of data should be readily practicable.
* There should be rapid reproducibility of data and results and an acceptable control (calibration) should be possible.
* Repeatability within minutes, days or years is important.

* The tests should strike the right balance between sensitivity and specificity.

The following tests were considered for the early detection of small airway disease:

- Initially the frequency dependent compliance test would prove to be the most sensitive test for small airways disease. This test is, however, relatively difficult to perform and does not lend itself for application to a study of this nature.
- The measurement of forced maximal expiratory flow following the inhalation of air and the helium mixture has been advocated by some authorities. Such tests of density dependent airflow are however not very simple to interpret and are, relatively costly.
- Tests that reflect the inhomogeneity of gas distribution, such as the single breath nitrogen washout curve (also known as the single breath oxygen curve) can also be employed. Once the necessary apparatus for this test has been constituted, it is capable of satisfying nearly all the requirements for this type of study.
- The closing volume of the lung and the closing volume/vital capacity ratio are useful parameters of small airway disease and can be derived from the same nitrogen washout manoeuvre.
- At a given lung volume maximal flow is in direct relationship to the elastic recoil of the lungs and is inversely proportional to the airway resistance of the non-compressible airways during a forced expiration. In cases of established, clinically recognisable chronic bronchitis and emphysema, the expiratory flows are reduced at all lung volumes and the flow/volume curve does not provide much more information than the FEV_1 alone. Histological studies on autopsy material and lung tissue obtained at lobectomy have established a correlation between histological changes in the small airways and the flow at 50% of

expired vital capacity. The measurement of maximal flow at 50% and 75% of expired forced vital capacity is simple and it is relatively accurate provided that attention is paid to the continuation of expiration down to residual volume. Under these circumstances, the variables described reflect changes in the small airways. This measurement is especially indicative of early disease when it yields abnormal results in the presence of a normal FEV_1 peak flow rate and flow at 25% of forced expiratory vital capacity.

* **Predicted Normal (Reference) Values**

When lung function tests are used primarily to evaluate clinically advanced disease, or to ascertain the response to treatment, the calculation of the predicted normal values (reference values) is not of critical importance. However, when early signs of abnormality and the natural history of such changes require to be studied, as is the case in this study, the predicted normal value is of critical importance. The influence of age, sex, body-weight, height and ethnic grouping are well recognised. Various formulae exist for the calculation of predicted normal values but these formulae yield results that differ greatly from one another. Guided by experience at the Tygerberg Hospital, it was decided to employ the following formulae for the various measurements:[34]

Table 22 –Reference Values used by Tygerberg Hospital – 1983

1.	Schoenberg-Bouhuys formulae for the calculation of predicted normal values for FVC, FEV_1, FEV_1/FVC ratio, FEF_{50}, FEF_{75} and peak expiratory flow. Supplementary values for FEF_{25} were obtained through extrapolation and a modified formula of Bass was utilised to predict peak inspiratory flow.
2.	Formulae of Grimby for the calculation of the predicted normal values of the lung volumes and their ratios.
3.	The formulae of Buist and Ross for the predicted normal values for N_2% per litre (a slope of phase 3 of the single breath N_2 washout curve) and the closed volume/vital capacity ratio.
4.	Morris' formula for the calculation of the predicted normal value for flow between 75% and 85% of the expired forced vital capacity (FEF_{75}% to 85%).

It could hardly be considered acceptable, simply to apply formulae which have been constituted in the USA to a group of individuals in the Namib Desert, who could certainly not be described as typical Americans, without prior critical evaluation of such formulae. This evaluation was indeed undertaken by calculating the predicted normal values for members of the various ethnic groups and comparing these values statistically with the actual measured values obtained in a number of individuals representative of each of the various groupings. (Table 25 showing the means, standard deviation, coefficient of variation and 99% confidence limits).

With the exception of the residual volume and the peak inspiratory flow in blacks, an acceptable correlation was found in respect of all lung function measurements. It is probable that the low inspiratory flow in blacks is a true representation, considering the fact that the flow volume contour in this ethnic group is otherwise also suggestive of a restrictive flow pattern.

Table 23 – Percentage Abnormal Lung Functions

Total no of subjects	1485	
Total no of smokers	612	41%
Total no of abnormals (FEF_{50} and FEF_{75})	288	20%
Total no of abnormals(FEF_{50}, FEF_{75} and FEV_1)	140	9%
Total no of abnormals (FEV_1 alone)	30	2%

Table 24 – Ethnic Distribution of Study Population

Totals	Ethnic	Smokers	Abnormal L/F
337	Whites	203 (60%)	87 (26%)
888	Blacks	238 (27%)	151 (17%)
260	Mixed Races	171 (66%)	49 (19%)

* Statistically significant difference (95% confidence level) between the percentage of abnormals among whites and that obtained for both mixed races and blacks.

** No statistical difference between mixed races and blacks.

*** Average Age: Whites 38
Mixed Race 31
Blacks 31

Whites were statistically significantly older than either mixed races or blacks.

Table 25 – Mean Values of Lung Function Parameters in Various Ethnic Groups

Lung Function	Statistic	Whites	Mixed Races	Blacks
FVC	Mean	92	110	100
	S.D.	13	16	12
	VX	15	14	12
	99% Conf	87	104	99
FEV_1	Mean	95	110	101
	S.D.	11	13	11
	VX	12	12	11
	99% Conf	91	105	97
FEV_1/FVC	Mean	101	98	100
	S.D.	6	11	6
	VX	6	11	6
	99% Conf	99	94	97
FEF_{50}	Mean	92	104	100
	S.D.	22	29	24
	VX	25	28	24
	99% Conf	84	92	94
FEF_{75}	Mean	90	104	106
	S.D.	29	25	28
	VX	32	24	26
	99% Conf	79	94	99
PEFR	Mean	91	93	116
	S.D.	17	23	19
	VX	19	25	17
	99% Conf	85	84	109
PIFR	Mean	110	96	73
	S.D.	17	20	18
	VX	15	21	25
	99% Conf	104	88	66

Table 26 – Distribution of Abnormal Lung Functions according to Work Area for Caucasians

Caucasians	Admin & Personnel	Open Pit	Crushers	Leaching	CIX/SX	Final Product Recovery	Acid Plant	Operators & Drivers	Mine Mainten	Boilermakers & Welders	Outside Services	Total
Groups	1	2	3	4			5	6				
Number of Smokers	78 58%	25 56%	14 82%	10 56%	6 38%	8 80%	9 75%	1	43 63%	10 73%	5 71%	203 60%
FEV_1 Abnormality Only	3 2%	2 5%	0 0%	0 0%	2 13%	0 0%	2 17%		3 4%	1 8%	0 0%	13 4%
Number of Abnormals FEF_{50} & FEF_{75}	44 33%	6 15%	6 35%	4 22%	3 19%	2 20%	2 17%		15 22%	4 33%	1 14%	87 26%
FEV_1 & FEF_{50} & FEF_{75} Abnormal	25 19%	4 10%	6 35%	3 17%	1 6%	0 0%	2 17%		10 15%	2 17%	0 0%	53 16%
Total	135	41	17	18	16	10	12	1	68	12	7	337

Table 27 – Distribution of Abnormal Lung Functions according to Work Area for Blacks

Blacks	Admin & Personnel	Open Pit	Crushers	Leaching	CIX/SX	Final Product Recovery	Acid Plant	Operators & Drivers	Mine Mainten	Boilermakers & Welders	Outside Services	Total
Groups	1	2	3	4			5	6				
Number of Smokers	54 25%	59 28%	20 33%	22 22%	9 37%	8 22%	11 29%	4 14%	39 29%	7 41%	5 22%	238 27%
FEV_1 Abnormality Only	2 1%	7 3%	1 2%	0 0%	0 0%	0 0%	3 6%	0 0%	3 2%	0 0%	0 0%	16 21%
Number of Abnormals FEF_{50} & FEF_{75}	37 16%	42 20%	9 15%	19 19%	6 25%	6 17%	2 5%	5 18%	18 14%	5 29%	3 14%	152 17%
FEV_1 & FEF_{50} & FEF_{75} Abnormal	17 8%	18 8%	3 5%	12 12%	2 8%	5 14%	2 5%	2 7%	12 9%	1 6%	1 5%	95 81%
Total	216	212	61	101	24	36	38	28	133	17	22	888

The average age of the abnormal subjects who smoke is statistically significantly higher than that of normals who smoke.

The average age of abnormal non-smokers is statistically significantly higher than the average age of normal non-smokers.

Table 28 – Distribution of Abnormal Lung Functions according to Work Area for Mixed Races

Mixed Races	Admin & Personnel	Open Pit	Crushers	Leaching	CIX/SX	Final Product Recovery	Acid Plant	Operators & Drivers	Mine Mainten	Boilermakers & Welders	Outside Services	Total
Groups	1	2	3	4			5	6				
Number of Smokers	49 57%	23 62%	7 64%	11 69%	16 80%	11 65%	5 83%	2 33%	29 69%	9 90%	9 100%	171 66%
FEV_1 Abnormality Only	1 1%	0 .5%	0 0%	0 0%	0 0%	0 0%	0 0%	0 0%	0 0%	0 0%	0 0%	0 0%
Number of Abnormals FEF_{50} & FEF_{75}	19 22%	7 19%	2 18%	3 19%	2 10%	3 18%	1 17%	3 50%	5 12%	2 20%	2 22%	49 19%
FEV_1 & FEF_{50} & FEF_{75} Abnormal	4 5%	0 0%	1 9%	1 6%	1 5%	0 0%	1 17%	1 17%	1 2%	1 10%	1 15%	12 5%
Total	86	37	11	16	20	17	6	6	42	10	9	260

Among the mixed races the average age of abnormals who smoke is statistically significantly higher than that of the normals who do not smoke.

5.2 PHASE II – PILOT STUDIES

5.2.1 Alpha-1-Antitrypsin Study

5.2.1.1 Objective

To determine the prevalence of various Pi- phenotypes in the Rössing workforce in order to exclude high-risk individuals from high risk work areas.

5.2.1.2 Introduction

Alpha-1-antitrypsin (AAT), a defense glyco-protein synthesized in the liver, is one a group of proteolytic enzyme inhibitors, which suppresses immunological and inflammatory reactions. It has an effect on various proteolytic enzymes and should rather be called "Alpha-1- protease inhibitor (alpha-1-antitrypsin). [140]

Alpha-1-antitrypsin has the molecular weight of approximately 50 000. It has a single poly peptide chain of 394 amino acids with three carbohydrate side chains. It is manufactured in the liver and macrophages and lymphocytes produce a small amount. Its half-life is ± 7 days and it is catabolysed by the lysosomes in the liver. Fifty-five percent of alpha-1-antitrypsin is found in extra vascular tissue and secretions (lymph, sputum, tears).[141]

As an acute phase protein, its concentrations rise rapidly during acute inflammatory conditions, pregnancy, tumour activity and with oestrogen and corticosteriod therapy. Smokers exhibit higher than normal levels of alpha-1-antitrypsin, which is thought to be associated with a chronic low-grade inflammatory response.

Abnormal levels of alpha-1-antitrypsin are associated with abnormalities such as emphysema, liver abnormalities, connective tissue diseases, uveitis, contact dermatitis, urticaria and

glomerulonephritis. Low levels of alpha-1-antitrypsin could be due to genetic disorders or can be acquired.[140]

5.2.1.3 Genetics

Although Jackson (1837) and Fuller (1862) recognised the importance of familial factors in the development of emphysema, it was only in the 1960's that Eriksson and co-workers published evidence of its hereditary association. Alpha-1-antitrypsin is coded for by a pair of co-dominant allele at a single autosomal locus, known as the Pi (Protease inhibitor). It is not known which chromosome carries the gene, but chromosome 2 and 14 are under intense investigation. Alfalpha-1-antitrypsin manifests as an extensive genetic polymorphism. More than 30 alleles have been determined electrophoretically for alpha-1-antitrypsin; each identified by a letter of the alphabet. The most common are M, S and Z. Sub-types are indicated with numerical values.[140,141,142]

P1M1 (M1, M2, and M3) is the most common phenotype and regarded as normal and present in 90% of people. PIZ phenotype is associated with low plasma concentrations of alpha-1-antitrypsin and emphysema (more common in Scandinavia).

The abnormal PiZ allelic gene is characterised by a point mutation, producing a protein substituting glumatic acid for lysine at position 342. Point mutations in the S protein leads to amino acid substition glumatic acid to valine at position 264. These individuals have deficient levels of alpha-1-antitrypsin with resultant inefficient proteolytic protection of especially lung elastin against protease.

Homozygote of the Z allele (PiZ) has subnormal levels of alpha-1-antitrypsin (15% of normal values). This leads to unopposed phagocytic elastase mediated destruction of lung tissue with the subsequent development of emphysema.[142]

5.2.1.4 *The Role of Smoking and Environmental Pollution*

Alpha-1-antitrypsin is responsible for 90% of the anti-elastase effect in blood and lungs. Elastase is a neutral protease found in PMNL (polymorphonuclear leukocytes) together with collagenase and catepsine G. Elastase has proteolytic activities and also changes the elasten - connective tissue adhesion, which is found in patients with emphysema.

PMNL and alveolar macrophages increase in numbers when exposed to cigarette smoking and the oxidative metabolism of PMNL and alveolar macrophages were increased in smokers, which might contribute towards a protease/anti protease disequilibrium.

Cigarette smoke contains free radicals and oxides of nitrogen (NOX) which in turn can react with H_2O_2 produced by lung phacolytes to produce even stronger free radicals. Oxidants produced by cigarette smoking, industrial gases and lung phagocytes, oxidises alpha-1-antitrypsin. It appears that it is the Tio ester group in the Metionite residue Met 358 and Met 351, that is sensitive to oxidation (both are found in the active part of the alpha-1-antitrypsin molecules.[141]

5.2.1.5 *Clinical Aspects*

The lung disease most commonly associated with abnormal levels of alpha-1-antitrypsin is emphysema. The elasten in the alveoli is destroyed though unopposed action of proteolytic enzymes. 70 to 80% of patients with the homozygotic variant of alpha-1-antitrypsin deficiency develop airflow limitation lung diseases that account for 1 to 2% of all emphysema.

It is well established that smoking is responsible for the majority of emphysema cases and it is reported on to be of the sentrilobular type. Panlobular (aciner) type of emphysema is thought to be associated with A-1-anti protease deficiency. The pathological differentiation is, however, disputed by others.

Carrel, *et al*[142] predicts that patients with the homozygotic type of alpha-1-antitrypsin who smoke, have double the risk of developing emphysema before the age of 40, with a 20 year reduction in life expectancy. Environmental pollution likewise increases the risk to develop premature emphysema.

The pathogenesis of emphysema in heterozygotic Z individuals are open to dispute. The clinical importance of the heterozygote state is, however, not clear, but consensus points towards a slightly increased risk for the development of emphysema (PiMZ 60% and PiSZ 35% of normal alpha-1-antitrypsin values). The combined effect, however, of a heterozygotic genetic profile with exposure to environmental agents, passive and active cigarette smoking is believed to have an increased risk of emphysema.

The protective role of female progesterone is believed to be responsible for the lower rate of emphysema in both smoking and non-smoking females.[142]

5.2.1.6 Method

Blood samples were taken from Rössing workers who were employed in high-risk work areas and or whom had lung function abnormalities detected during routine occupational medical examinations. Analyses were done by the Department of Genetic Studies in Pretoria (Dr HW Hitzeroth).

Both quantitative analyses (normal values 1.1 to 2.4 gram/L) and phenotyping for alpha1-antitrypsin was done. The PI- phenotyping was performed by iso-electric focusing on commercially available poly-acrylamide gels.

5.2.1.7 Results

A total of 163 sample were examined. All the quantitative results were normal as was the majority (151) of the phenotyping (M variant 126, M1-M2=25). Ten cases were heterozygotic for the defective variant "S" (M1S and M2S). They exhibit sensitivity for lung abnormalities. Two workers were homozygotic for the more serious type of alpha1-antitrypsine defect (SZ and M1Z). The "Z"-variant is strongly associated with lung emphysema and these workers must be regarded and high-risk individuals.

5.2.1.8 Conclusion

The frequency of abnormal PI-variants in the study population is regarded by Dr Hitzeroth to be significant and higher than expected. Those with abnormal lung functions should routinely be investigated for abnormal phenotypes of alpha-1-antitrypsin. Routine pre-employment screening could be introduced to assist with the correct placing, counseling and protection. Those with the detected abnormalities should be employed in low-risk areas, encouraged not to smoke and followed up.

5.2.2 Uranium Lung Burden Study – In Vivo Measurement of Uranium in the Human Chest

5.2.2.1 Objective

To determine the lung burden of uranium in the lungs of Rössing workers in order to reduce their risk of lung cancer.

5.2.2.2 Introduction

Exposure of the general population to uranium dust is limited, but workers in the mining and recovery of uranium are exposed to radioactive dust and gases. Inhalation is the most important pathway and excessive exposure to uranium and its daughter products are

associated with health problems that are well documented. It is an accepted fact that workers' exposure to radioactive substances should be limited, and that the workers should be evaluated regularly.

When uranium particles are inhaled they come into contact with the biological milieu of the inner lung. The soluble portion of the uranium (uranium hexafluoride and uranyl nitrate) enters the bloodstream via the capillary system. It is bound to proteins or carried as a bicarbonate complex. It disassociates at the level of the convoluted tubules and the bicarbonate ions (the carrier complex) is re-absorbed. A small amount is deposited in the epithelium cells of the tubules and can lead to kidney disease if exposure is excessive and prolonged. The insoluble portion of the radioactive materials such as the oxides of uranium (UO_2, UO_3 and U_3O_8), tetra fluoride (UF_4) and ammonium diuranate are either exhaled or removed by the lung's clearing mechanisms. A portion of these insoluble compounds might find their way into the lymphatic system of the lung where they radiate the lung for a long time. These insoluble compounds have a biological half-life of up to 800 days, and do not only contribute to the radiological hazard over a long period, but cannot be readily detected by the excretion analysis.[62]

5.2.2.3 Environmental Monitoring

The purpose of environmental monitoring is twofold. It ensures that the environmental agents do not exceed the safe limits and individual exposure can be calculated through indirect methods such as the determination of the annual limit intake (A.L.I.), or via direct methods such as in vivo measurement of uranium in the lungs.

5.2.2.4 *Annual Limit Intake*

The lung model of the ICRP provides three clearance classes, namely D (day); W (week); and Y (year) for the respiratory retention of inhaled radioactive particles and aerosols. In this model, radioactive materials with a biological half-life time in the pulmonary region in the range of less than ten days are classified as class "D", in the range of 10 to 100 days class "W", and with more than 100 days in the class "Y". In general most hexavalent uranium compounds belong to class "W" and most tetravalent uranium compounds to class "Y". Exceptions are the U-halides and urinyl compounds that are arranged in the next higher solubility class. In order to calculate the body burden of uranium in the lungs, it is necessary to know the solubility, size and biological clearance rates of the possible contaminants. According to the ICRP's calculations, the lowest possible lung burden would be 20,8 mg natural uranium. The next solubility class, class "W", gives a responding value of 233mg for a biological Th for fifty days. Natural uranium is composed of mainly three isotopes with ^{238}U as the major constituent. The annual limit intake for each component must be calculated and a combined A.L.I. can then be found.[320]

5.2.2.5 *In Vivo Lung Burden Measurements*

In 1960, R E Cofield[321] from Oakridge, Tennessee, reported the direct in vivo method for the measurement of uranium within the human lung, utilising the detection of syntillation spectroscopy of the gamma radiation accompanying alpha release from uranium. He used sodium iodate crystal to detect the 186keV gamma associated with ^{235}U and the peaks around 90keV associated with ^{231}Th and ^{234}Th, the daughter products of ^{235}U and ^{238}U respectively. Scott and West, as well as Bogen *et al* who proved the techniques by using a "phoswich"

(phosphate sandwich) scintillation detector consisting of a sodium iodate crystal and caecium iodate phoswich crystal. The application of this type of phoswich detector has been established in several laboratories, for example in Pelindaba and Tygerberg Hospital. The detection levels are normally expressed as a fraction of the maximum permissible lung burden (MPLB). The maximum permissible lung burden of ^{235}U in natural uranium is 180 micrograms, equivalent to a mass of 25,6mg of natural uranium. This limit is derived from the maximum safe radiation dose to the lungs as determined by the ICLP. It is an international accepted recommendation that workers should not be exposed to more than 0,3 MPLB, i.e. approximately 8 mg of natural uranium in the lungs. This is often found to be an impossible target to achieve, and unrealistic, if compared with the principle of A.L.I which sets the lowest target at 20mg of uranium. There are a number of problems associated with the measurement of uranium retained in the lungs. The alpha emissions from the uranium are not detectable because the thorax wall absorbs them. The signal measured is therefore the low energy gamma rays from either ^{235}U or ^{234}Th or ^{238}U. It is often difficult to distinguish these low signals from ambient radiation background levels, as well as from the natural occurring radioactivity of human beings (40k and 137 caecium). Efficient shielding is required to reduce background radiation to a level where it is not a predominant factor. In order to estimate the uranium burden of an exposed person, the relation of count range obtained from exposed and unexposed individuals is used. The technique involves the gamma counting of unexposed individuals, and empirically deriving a statistical equation for predicting the number of counts expressed in the energy regions of gamma rays emitted by uranium and its short-lived daughters. There is a linear relationship for areas between 90keV and 300keV with high counting tempos of at 90 and 186keVs as an indication of the amount of uranium present.[321,322,323,324,325]

5.2.2.6 Method

* Apparatus

Four round NaI (Tl) crystal detectors of 150mm diameter, mounted on moveable arms and housed in a specially constructed low background counting chamber built with steel plates that were specially produced to ensure low levels of radioactive contaminants (pre-World War 2 steel). The steel plates are 150mm thick and covered with a 3mm lining of high purity lead to shield against compton scatter, arising from the interaction of cosmic rays with the steel shield. The signal processing is done by a Nuclear Data ND68-MCA system.[323,325,327]

* Calibration

The solution (50 cm^3) was prepared from a weighed (± 50mg U) amount of uranyl acetate. It was sealed in a plastic container surrounded with saline bags to give a rough simulation of the absorption properties of the chest wall. Results suggested that in vivo uranium could be counted to approximately 25% of MPLB.

An adjustable chest phantom was constructed at Rössing to simulate various chest dimensions. (Bogen *et al's* example).[322] The ribs, breastbone and vertebrae were simulated by 3mm aluminium and the tissue by a 20mm thick paraffin wax layer. It was put in a wooden framework with one fixed and on moveable layer, built up out of aluminium and wax. Liquid examples of natural uranium, from Rössing Uranium, of various concentrations between 50ppm and 5000ppm were used to calibrate the apparatus. The shoulders were placed in the perspex plate in the phantom half way between sets of crystals. Baseline measurements were done on unexposed medical students from Namibia. It was accepted that they would have different diets,

near ideal body mass, but it was the best that could be done. The volunteers were counted in the same configuration as was used for the chest phantom and the gamma spectrum obtained from 30 minute counts were stored on disc and later analysed.[323,324]

5.2.2.7 *Measuring Rössing Uranium Mine Personnel*

During the next couple of years, a large group of uranium miners were flown to Cape Town and the following selection criteria was used, because the cost of doing these test were astronomical.

* Workers had to come from as many as possible different working positions, i.e. open pit, crushers, final product recovery etc.
* As far as possible, those who had the longest service with the mine were included.

A diverse group was also done just after a major maintenance operation of the final product recovery and one person with suspected lung cancer was also counted.[325]

5.2.2.8 *Results and Discussion*

The uranium decay series has only a few gamma emitters that peak at ± 90 keV and 186 keV. The 90 keV region of the background spectrum of the whole body counting system was perfectly usable, but the 186keV peak fell within the high background region of the spectrum. Calibrations were done for both regions.
The following measurements were obtained.

Solutions at 90 keV	=	6,1 c/m/mg U
Solutions at 186 keV	=	2,0 c/m/mg U

This can be expressed as the minimum detectable activity (MDA) as

MDA at 90 keV : 2,8 mg U
MDA at 186 keV : 6,8 mg U

Results with the chest phantom

The counting sensitivity showed:

	90 keV	-	5,55	c/m/mg U
	186 keV	-	2,4	c/m/mg U
MDA	90 keV	-	2,9	c/m/mg U
	186 keV	-	6,8	c/m/mg U

The above results represent the case where the uncontaminated background is known and was calculated for a 99,7% confidence limit as is normally the case in whole body counting.

5.2.2.9 *Prediction of Uncontaminated Count Rates*

There is a relationship between the whole body potassium content and body mass. We therefore set out to try and prove a correlation between the background count rate at 90 keV and 186 keV and body mass. We were able to do so with the help of the counts that were performed on the uncontaminated medical students. The following results were obtained:

90 keV	y	=	2,413x	+	3,58,19	- 1
	r	=	0,852			
186 keV	y	=	1,17x	+	334,9	- 2
	r	=	0,83			

It is known that the main contributor to the background count-rate for persons living in the Southern Hemisphere is ^{40}K. We thus also investigated the relationship between the 90 keV background count-rate and the ^{40}K count-rates. This produced the following equation:

$$y = 2,49 + 437,5 - 3$$
$$r = 0,847$$

The above results show that there was a good correlation between the presence of 40K in the body on the one hand and the lower energy background count-rates on the other, between body mass and the background count-rates in the group of volunteers measured. The final evaluation of our results was made using equation 1. We were now in a position to predict the background count-rate with a certain degree of accuracy. Since the correlation is not 100% the standard error of estimate was calculated to give an indication of the uncertainty of a prediction. Using the 95% confidence level and taking into consideration the standard error of estimate, we recalculated the MDA to be 3,7mg uranium. Due to the nature of our uranium burden calculations, this value also gives an indication of the possible error in calculated values.[325,326,327]

5.2.2.10 Rössing Personnel

The only two persons, in whom measurable amounts of uranium could be found, were working in the final recovery plant. Up to the time of measurement they had been working there for six and eight years respectively.

All but one of the persons counted had some uranium in their lungs. The uranium contents varied from 3,9mg (the limit of our detection ability) to a substantial 18,5mg. The relatively high concentrations of uranium are probably due to extensive maintenance of the final recovery plant and the fact that these persons had been employed in their current position for periods of up to 10 years. The exception to

the above is Mr J E Louw who accompanied both groups as a supervisor. We repeated his count on the second occasion. It was approximately the same as the first, thus reflecting favourably on the reproducibility of the counting procedure.

5.2.2.11 Conclusion

Though none of the workers counted exceeded the MPLB of 25,6mg uranium, we have definitely shown that there existed lung burdens of at least up to 50% of the MPLB. It also appeared that it is primarily the workers at the final recovery plant that are at risk. We suggested that a repeat count be performed on the persons with the higher burdens. This would indicate whether there is a decrease in the lung burdens during normal operations.[325,326,327,328]

5.2.3 Sputum Cytology

5.2.3.1 Objective

To investigate whether sputum cytology can be used to monitor epithelial cell changes in groups of workers at high risk for lung cancer from exposure to radioactive dust and radon.

To investigate whether sputum cytology can be used as a marker for lung cancer in high-risk groups.

5.2.3.2 Discussion

Several studies confirmed the causal association between radon, uranium mining, smoking and the increased rates of lung cancer.[10-20] Of the four common cell types of primary lung cancer, small cell undifferentiated cancer dominates in uranium workers. Small cell,

large cell and adeno-carcinoma develop from cells deeper in the lung and are best detected radiologically.[334] Squamous cell carcinoma is also found in uranium workers and arises from surface epithelium. It is best detected by analysing changes in exfoliated cells. These changes vary from moderate to marked atypia (twice as high in uranium workers than in control groups) and take between three to five years to develop. Saccomanno has shown in prospective studies that the slow progression of the bronchial mucosal cells could progress over 15 to 20 years to cancer in situ which, in turn, precedes cancer by four to five years.[329,330,331,332,333,334,335,336]

Malignant cells have been found in up to 10.3 % of cases in the absence of lung cancer (usually due to infection or due to asthma) mild degrees of atypia are believed to be reversible, but according to Saccomanno[332] *Severe atypia may represent an irreversible step in the progression to cancer.* Contradictory reports on the reversibility of atypia lead to the recognition of inter- and intra-observer errors. Experts disagree up to 9.3% on the degree of cell atypia with an average of 1.3% false positive and 5% false negative rate. Sensitivity increases with repeated examinations and where the tumour is in the main bronchi whilst specificity points towards inter-observer differences. With the dismal prognosis of primary lung cancer, sputum cytology was introduced as a screening test. It provides a simple and resourceful method for the diagnosis of pre-neoplastic lung conditions during the asymptomatic stage and it is non-evasive.[331,332,333,334,335,336,337,338,339,340,341,342,343]

5.2.3.3 Sputum Cytology Programme

a) Pilot Studies

A number of uranium mining and processing facilities published studies on sputum cytology and its usefulness. Based on information available in early 1980, Rössing also launched a sputum cytology programme. Sputum was treated locally (stripper and modified Saccamano technique) and sent to the Cytology Department (Dr J Deale) at the Tygerberg Hospital in Cape Town (R.S.A.). Samples were classified "suitable" if "dust cells" were found in the specimen.

The specimens were subdivided into two sets of 120 and were processed and reported on as part of a pilot study. The results were as follows:

Table 29 – Sputum Sample Results	First Twenty		Second Twenty	
Not suitable	51	(42,5%)	35	(29%)
Inflammatory	41	(34,1%)	63	(52%)
Metaplasia (normal)	21	(17,5%)	18	(15%)
Metaplasia (atypical)	4	(3,2%)	2	(1,6%)
Metaplasia (Squamous)	3	(2,5%)	2	(1,6%)

Technical problems were solved and "not suitable" were redone and a larger study was launched.

b) Results of Larger Study:

* Of the 1500 samples taken, 1392 were "suitable" samples. (W=1392).
* The median age of the participants was 38,09 years (18 - 65) with a mean employment of 5,8 years.
* There were 486 smokers and 193 had an allergic tendency (atopy).

* No cases of cancer were reported with:

-	Not suitable	=	108
-	Normal and/or	=	693
-	Inflammatory	=	190
-	Normal metaplasia	=	365
-	Atypical metaplasia	=	12
-	Squamous epithelium atypia	=	2
-	Parakeratose	=	7
		=	2
	Total		**1392**

Of the total of 1392, only 16 were "abnormal". Ten of the 16 were smokers (with four of this group having fibrotic changes on x-ray and ten had abnormal lung functions.) Of the group of 16, two had both normal chest x-rays and normal lung functions.

5.2.3.4 Conclusion

Newly published data gave disappointing overall results. The combined Mayo, Hopkins and Sloan-Kettering study on sputum cytology (30 000 participants) made their findings available. Reports from all institutions were consistent.

* The detection rate for sputum cytology was 23%.
* The detection rate for x-ray screening was 58% (most sensitive) and 40% (lowest).
* Combined sputum/x-ray screening yielded another 19% detection rate.
* Sputum cytology was most sensitive for squamous cell carcinoma even when radiologically occult (18% of all cancers) but was of little value in detecting small cell carcinoma (26% of incidence cases).

* Initially the estimated five year survival probability was 40 to 45% (against 12 to 15%) in the general population. Curative surgical resection rate was possible in 52% versus 32% in the control group.
* Follow up analysis, however, showed the disappointing effect that survival rates were the same in all groups studied and failed to identify differences in overall mortality rates.
* The final conclusion was that cytological screening had no impact on population survival rates.

Benbassat reviewed all available data on the predictive value of sputum cytology in 1987 and stated that:

* Exfoliative sputum cytology is not a definitive diagnostic test for lung cancer.
* Cytological abnormalities found in high-risk groups have a strong positive predictive value for cancer (sensitive and specific).
* Early diagnosis of lung cancer does not reduce the mortality rate of the disease and screening for lung cancer is therefore not specifically recommended.

Recently there has been a resurgence of interest in sputum cytology as a preventative tool. Much attention was focused on exfoliated cell micronucleus assays (a relative cytogenic technique). Micronuclei are small cytoplasmatic bodies that contain deoxyribonucleic acid (DNA). During cell division small parts of chromosomes are left outside the nucleus. The frequency of micronuclei is an indication of increased frequency of structural and or numerical chromosome aberrations.

Studies done by Stich *et al* in 1984 and Sarto *et al* in 1987 positively correlated the increased frequency of micronuclei with increased exposure to cigarette smoking and ionising radiation. In a study done

in 1990 by Loomus, Saccamanno *et al* they failed to demonstrate the same effect as " higher radon progeny exposure nor cigarette smoke had any appreciable effect on the prevalence of cells with micronuclei."

5.3 PHASE III – MAIN STUDIES

The purpose of these studies was to assess the respiratory health status of the study population after at least ten years exposure. To achieve this objective two separate studies were launched. The first step was to develop predictive equations for the lung functions of the specific study group, to publish the results and to invite scientific discussion. The second step was to assess the respiratory health status of the work force after a significant period of time (more than ten years of continuous service).

5.3.1 Cross-Sectional Study of Uranium Mine Workers to Develop Predictive Equations for Lung Functions with reference to Chronic Obstructive Pulmonary Disease

In this study such serial monitoring of lung functions was undertaken to discover early lung disease and to study the etiology and natural history of such disease. The first step was to find the best-suited formula for prediction of the normal values for the workers under study at the Rössing uranium mine.

5.3.1.1 Study population

This group consisted of 1467 subjects of which 60(4%) were women. It was decided to exclude the women from all analysis and all further results therefore refer to the initial group of 1407 male workers. The mean age of the group was 32.8 years with a standard deviation of 8.5 years. The youngest subject was 19 years old. We are thus dealing with an adult population. The median age was 31 years with an inter-

quartile range of 11 years. Of the males 306 (22%) were Caucasian, 225 (16%) of mixed race and 876 (62%) black.

5.3.1.2 Smoking Profile

Smokers included current smokers and those who stopped for less than two years. Non-smokers included never-smokers and those who stopped smoking for more than two years. Table 29 shows the percentage of men who were smoking or had smoked. The mixed group contained the highest percentage of smokers (70%) while the black group contained only 29%. For comparative purposes between the ethnic groups, it was decided to concentrate on the non-smokers. The findings in the smokers are also given but for any relevant comparisons the quantity and duration of the smoking habit must be taken into consideration.

TABLE 30 – SMOKING HABIT FREQUENCY AND PERCENTAGE SMOKERS IN THE THREE ETHNIC GROUPS

	ETHNIC GROUP		
	CAUCASIAN	MIXED GROUP	BLACK
Non-smokers	112	67	620
Smokers	192	158	256
% Smokers	63	70	29

5.3.1.3 Analysis of lung function values

Box plots of the different measurements of lung function as registered were drawn for the different ethnic groups and separated into smokers and non-smokers **(Figs 3 - 10).** The median values for FVC and FEV_1 **(Figs 3 and 4)** were larger for the Caucasians than for the blacks, with the mixed group in between. The same was true for the PEFR for the non-smokers **(Fig 5),** but for the smokers the median of the PEFR of the mixed group was similar to that of the blacks. The PIFR median of

the Caucasians was also larger than that of the blacks, but not so pronouncedly different from the mixed group in the non-smokers although larger in the smokers **(Fig 6).** The difference in the medians of the FEF_{25} was not so obvious in the various ethnic groups **(Fig 7)**. There was no pronounced difference between the ethnic groups as regards the medians of the FEF_{50} and FEF_{75} values **(Figs 8 and 9).** The median of the FEF_{75} in the Caucasian smokers was slightly lower than the same medians in the mixed group of smokers and black smokers. It is of interest that the mean of the FEV_1/FVC ratio was lower for the Caucasians than for the workers of the mixed and black groups (P<0,001) **(Fig 10)**.

5.3.1.4 Evaluation of the Schoenberg standardisation formulae for lung function test in non-smokers

The lung function measurements of the Caucasians were standardised as a percentage of the predicted values evaluated by the regression of the predicted values calculated by the regression formulae provided by Schoenberg *et al*. The non-Caucasians (black and mixed groups) were grouped together and their lung functions were standardised according to the regression equations for blacks from Schoenberg *et al*. These authors made no distinction between the mixed and blacks groups and it was assumed that their "black" group included both. The validity of this standardisation for height, weight, and age in general for this mining community was investigated in various ways. The decision to use the regression constants for blacks from Schoenberg *et al* to standardise the lung function of the mixed group was also evaluated. **Figs 11 - 13** show the composition of the samples with regards to the three prediction variables (age, height and weight). In all three groups the age distribution **(Fig. 11)** shows that there were younger subjects (<35 years old).

Caucasians were the tallest, followed by the blacks, and the mixed group **(Fig 12)**. Caucasians weighed the most, but the weights of the blacks and the mixed group were comparable **(Fig 13)**. It is evident that the body dimensions of the mixed group and the blacks differed from each other in a special way and that both of them differed from the Caucasian group.

We considered our sample to be an adult one because 99% of workers were aged 20 years or over (the remainder being 19 years old). For this reason it was only necessary to consider the comparison with the transformation for the adult group suggested by Schoenberg *et al*. The measurements expressed as a percentage of the predicted value were drawn as box plots for the different ethnic groups, separating smokers from non-smokers **(Figs 14-20)**. The sufficiency of their standardisation formulae was evaluated in different ethnic groups by trying to predict 'percentage of prediction' by means of height, weight and age. Stepwise multiple regression was used and whenever one of these three predictors entered the regression equation, this meant that the standardisation of Schoenberg *et al* was lacking in this respect. If their standardisation formulae were sufficient in all respects for these ethnic groups, the predictor variables (height, weight and age) would not enter the regression equation. The sign of the coefficient associated to the predictor variable in specific instances showed in which way their formulae were lacking. When R2 (squared multiple correlation) was near to 0 it indicated that the standardisation formulae of Schoenberg *et al* fitted the present data reasonably well, but when R2 was greater than 0,05 (5%) we regarded their formulae as lacking in some respects. The results for the standardisation FVC are summarised in **Table 30**. This table deals with the predicted functions and the effect of dividing the sample into a younger and older group by using 30 as a cut-off point (the age of 30 was chosen arbitrarily with

the aim of dividing most subgroups in half). Differences between the ethnic groups are shown in **Table 30** in terms of the predictability of the standardised FVC as measured by R2.

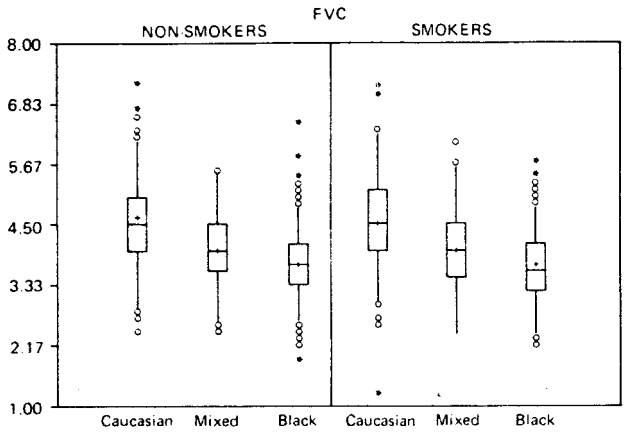


Fig. 3. Box diagram of the observations of FVC separated according to ethnic group and smoking habit.

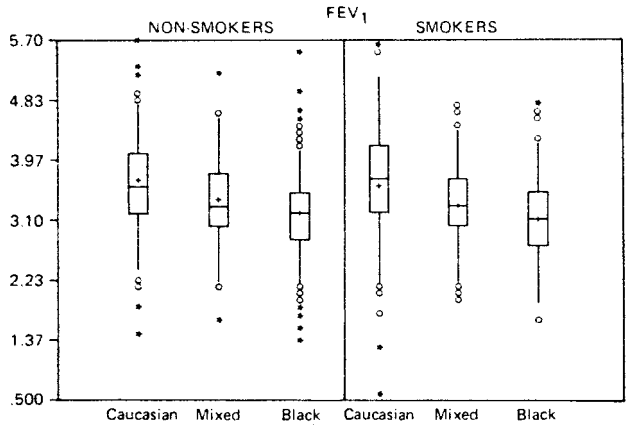


Fig. 4. Box diagram of the observations of FEV_1 separated according to ethnic group and smoking habit.

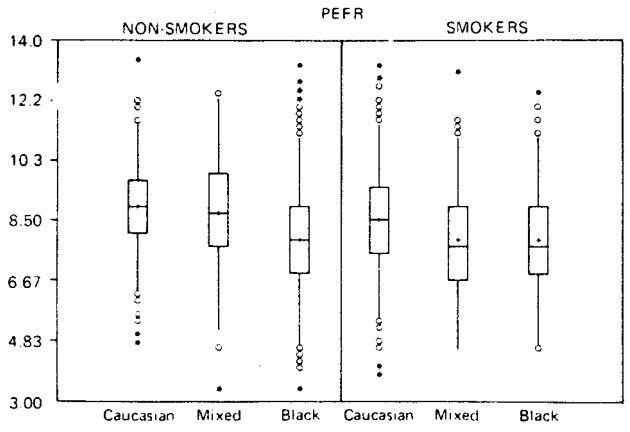


Fig. 5. Box diagram of the observations of PEFR separated according to ethnic group and smoking habit.

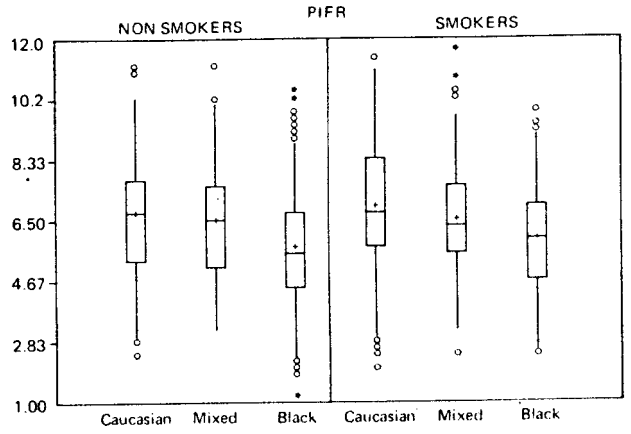


Fig. 6. Box diagram of the observations of PIFR separated according to ethnic group and smoking habit.

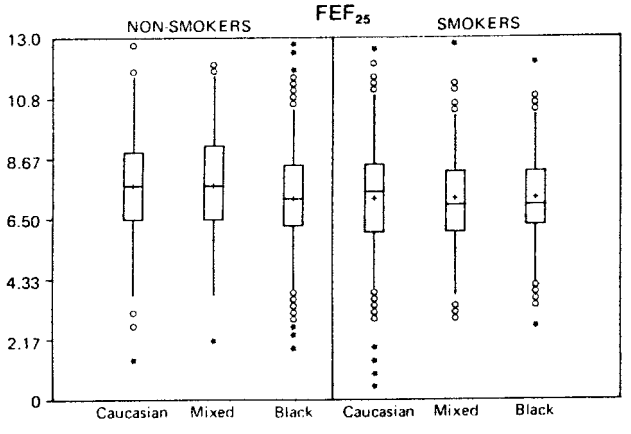


Fig. 7. Box diagram of the observations of FEF_{25} separated according to ethnic group and smoking habit.

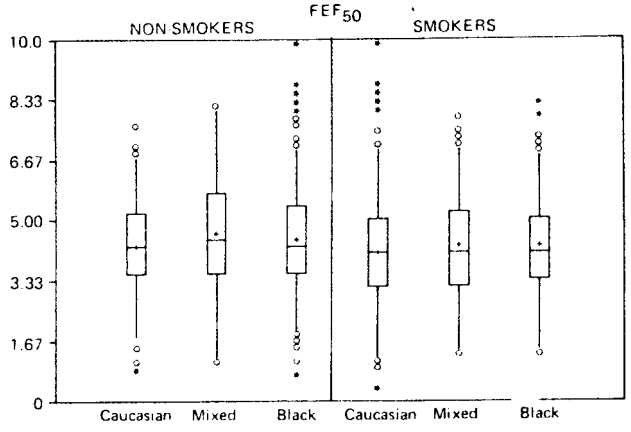


Fig. 8. Box diagram of the observations of FEF_{50} separated according to ethnic group and smoking habit.

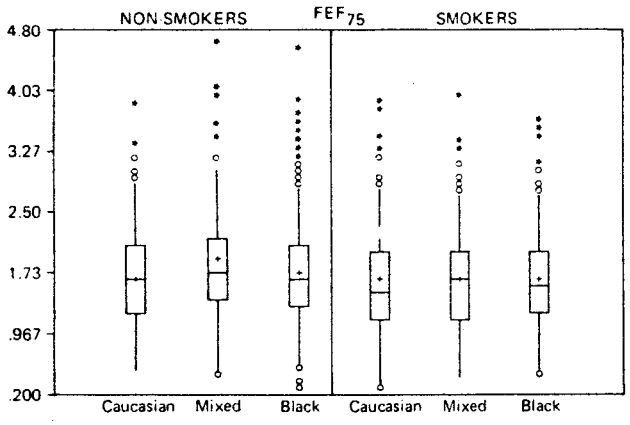


Fig. 9. Box diagram of the observations of FEF_{75} separated according to ethnic group and smoking habit.

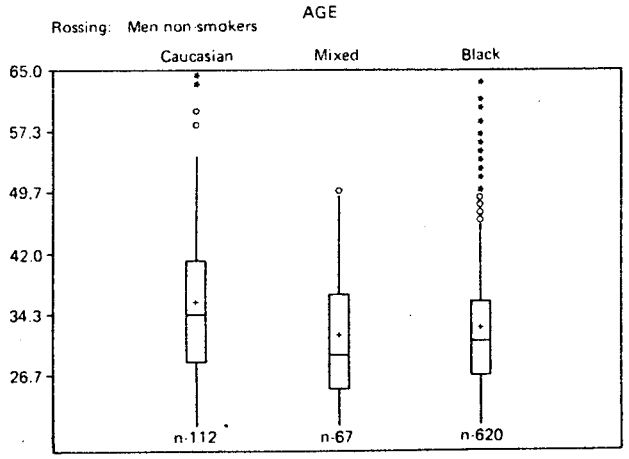


Fig. 11. Box diagram of age for non-smoking males divided into the three ethnic groups.

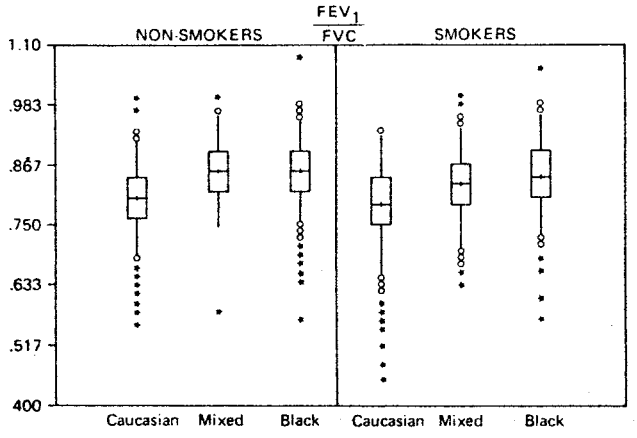


Fig. 10. Box diagram of the observations of FEV_1/FVC ratios separated according to ethnic group and smoking habit. The Caucasian ratios are significantly lower than the ratios of the non-Caucasians ($P < 0{,}001$).

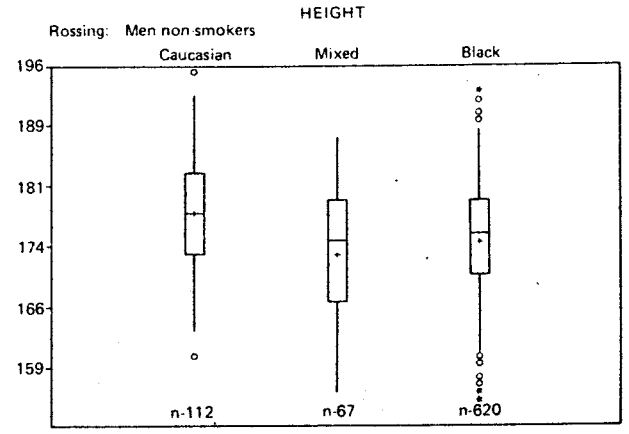


Fig. 12. Box diagram of height for non-smoking males divided into the three ethnic groups.

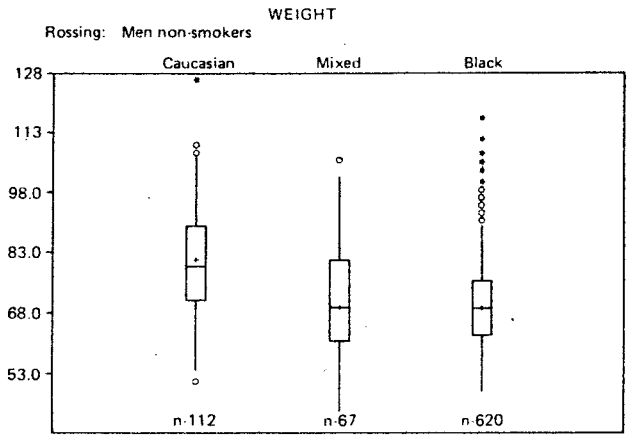


Fig. 13. Box diagram of mass for non-smoking males divided into the three ethnic groups.

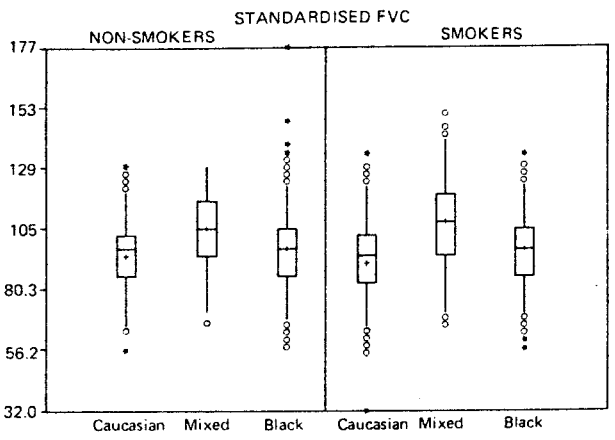


Fig. 14. Box diagram of the observations of standardised FVC according to Schoenberg *et al.*, separated according to ethnic group and smoking habit.

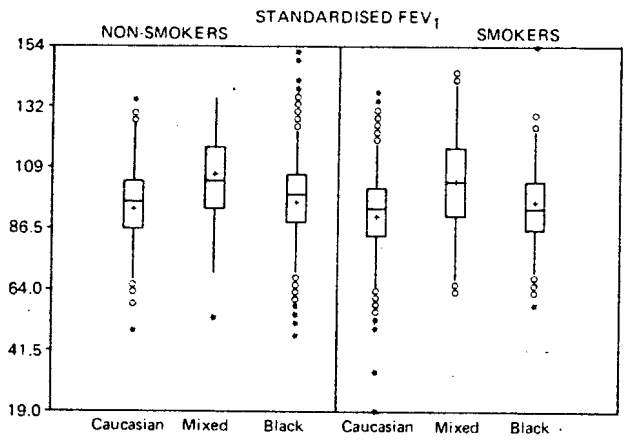


Fig. 15. Box diagram of the observations of standardised FEV_1 according to Schoenberg *et al.*, separated according to ethnic group and smoking habit.

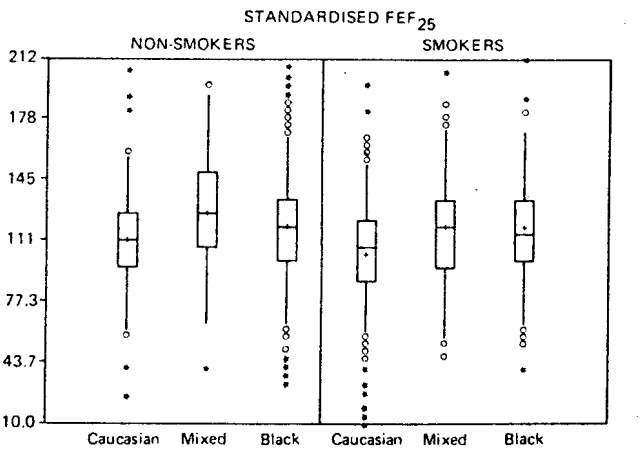


Fig. 18. Box diagram of the observations of standardised FEF_{25} according to Schoenberg *et al.*, separated according to ethnic group and smoking habit.

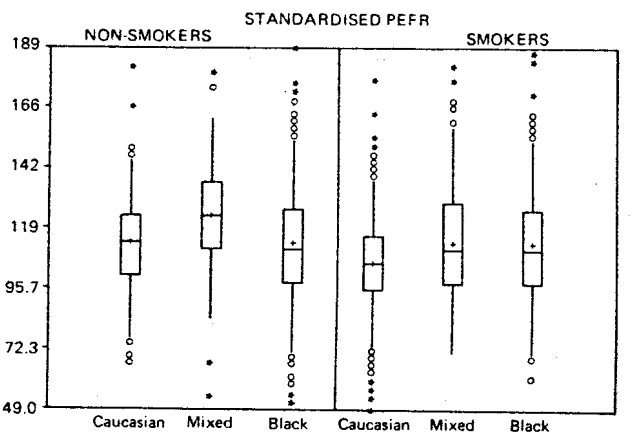


Fig. 16. Box diagram of the observations of standardised PEFR according to Schoenberg *et al.*, separated according to ethnic group and smoking habit.

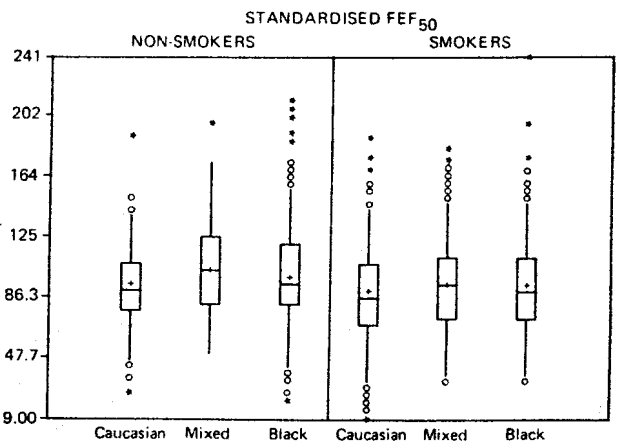


Fig. 19. Box diagram of the observations of standardised FEF_{50} according to Schoenberg *et al.*, separated according to ethnic group and smoking habit.

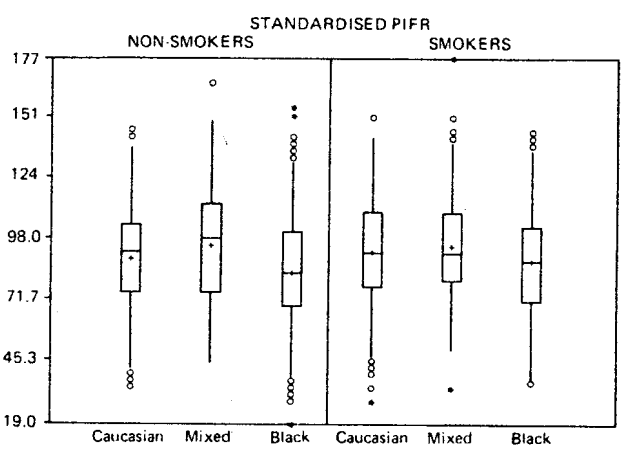


Fig. 17. Box diagram of the observations of standardised PIFR according to Schoenberg *et al.*, separated according to ethnic group and smoking habit.

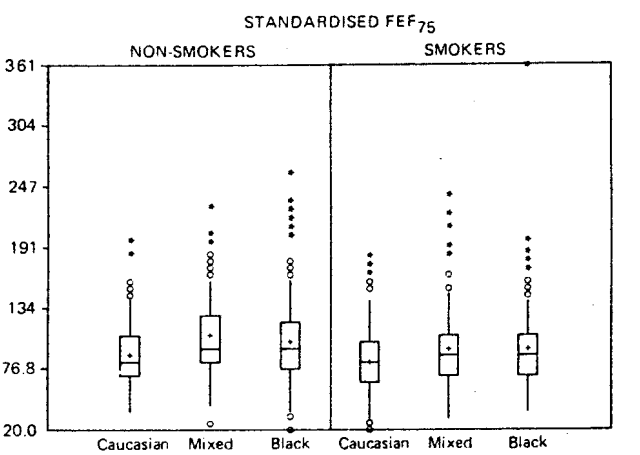


Fig. 20. Box diagram of the observations of standardised FEF_{75} according to Schoenberg *et al.*, separated according to ethnic group and smoking habit.

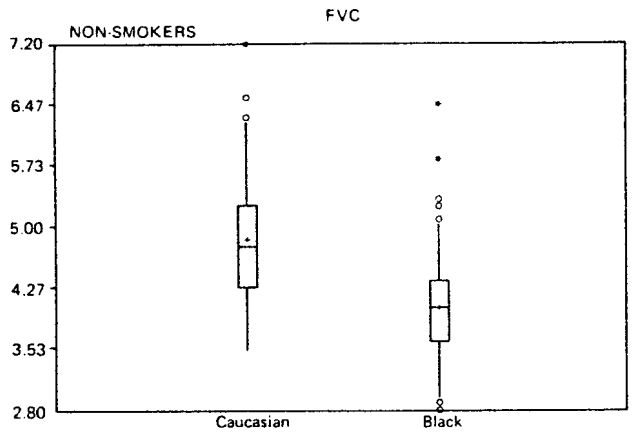


Fig. 21. Box diagram comparing the FVC between comparable groups of Caucasians (62) and blacks (125). FVC in Caucasians is significantly higher than FVC in blacks ($P < 0{,}0001$).

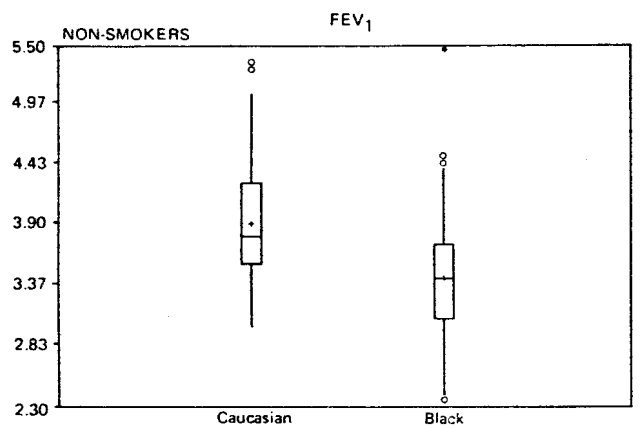


Fig. 22. Box diagram comparing the FEV_1 between comparable groups of Caucasians (62) and blacks (125). FEV_1 in Caucasians is significantly higher than FEV_1 in blacks ($P < 0{,}0001$).

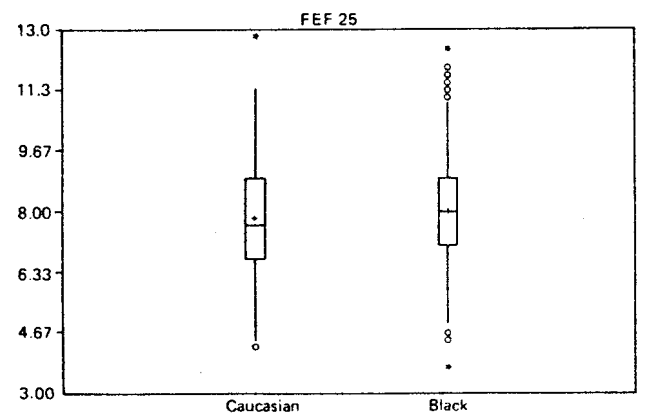


Fig. 23. Box diagram comparing the FEF_{25} between comparable groups of Caucasians (62) and blacks (125). The difference is not statistically significant ($P > 0{,}05$).

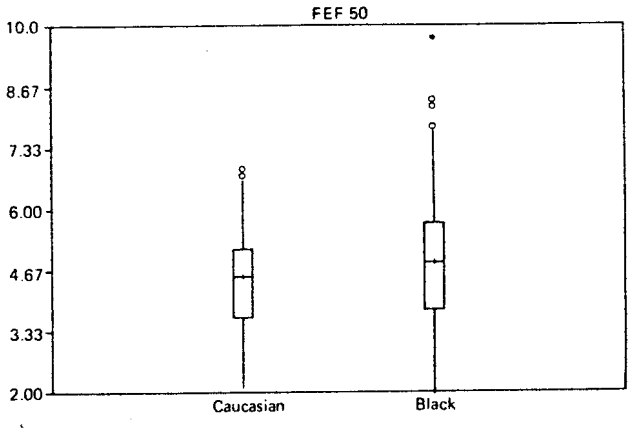


Fig. 24. Box diagram comparing FEF_{50} between comparable groups of Caucasians (62) and blacks (125). The difference is not statistically significant ($P > 0{,}05$).

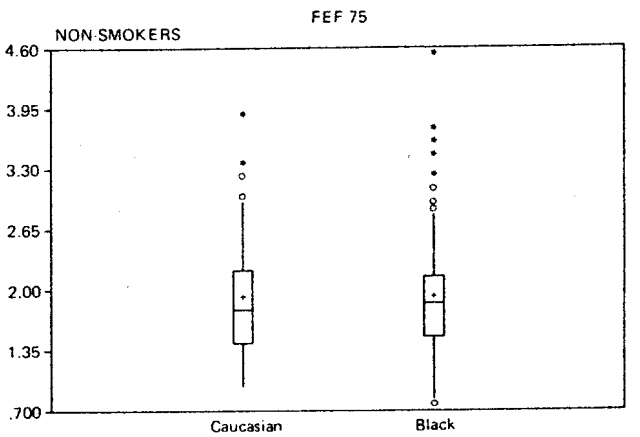


Fig. 25. Box diagram comparing FEF_{75} between comparable groups of Caucasians (62) and blacks (125). The difference is not statistically significant ($P > 0{,}05$).

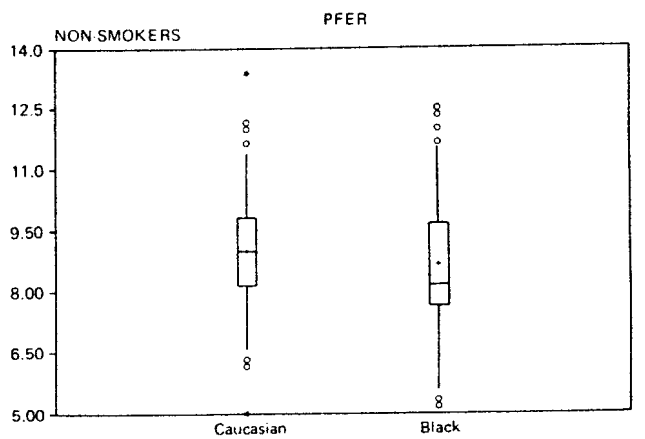


Fig. 26. Box diagram comparing PEFR between comparable groups of Caucasians (62) and blacks (125). The difference is not statistically significant ($P > 0{,}05$).

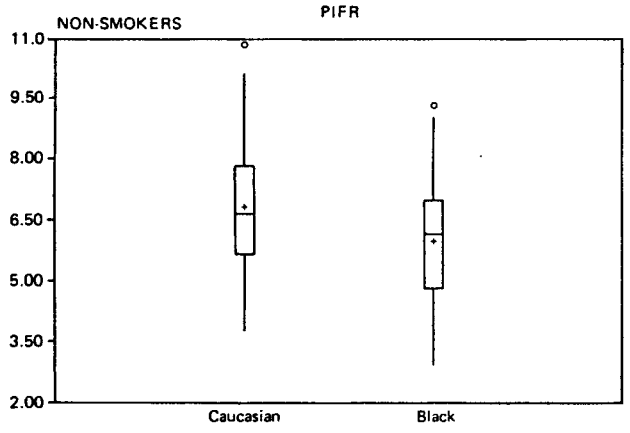


Fig. 27. Box diagram comparing PIFR between comparable groups of Caucasians (62) and blacks (125). PIFR in Caucasians is significantly higher than PIFR in blacks ($P < 0{,}0002$).

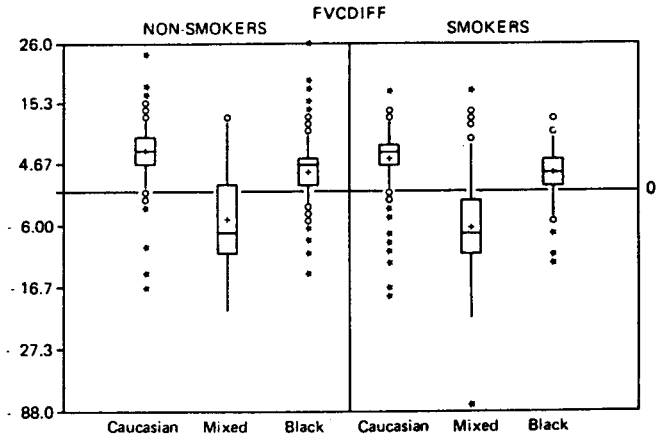


Fig. 28. Box diagram of the difference in the percentage of predicted of the FVC according to the formula described and the formula of Schoenberg *et al.*, separated according to ethnic group and smoking habit.

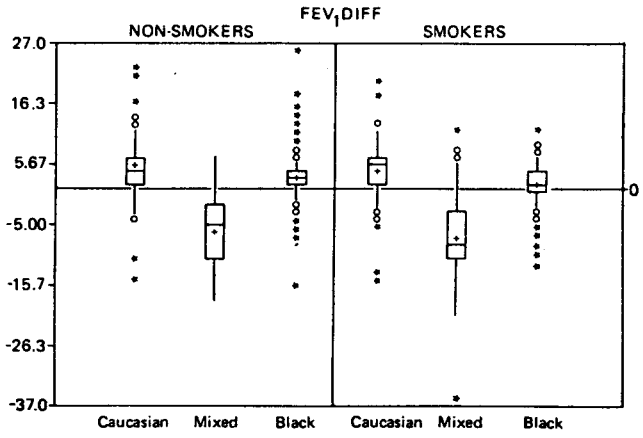


Fig. 29. Box diagram of the difference in the percentage of predicted of the FEV_1 according to the formula described and the formula of Schoenberg *et al.*, separated according to ethnic group and smoking habit.

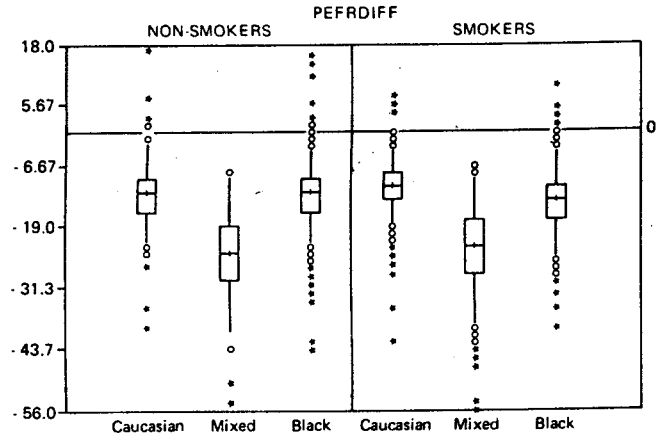


Fig. 30. Box diagram of the difference in the percentage of predicted of the PEFR according to the formula described and the formula of Schoenberg *et al.*, separated according to ethnic group and smoking habit.

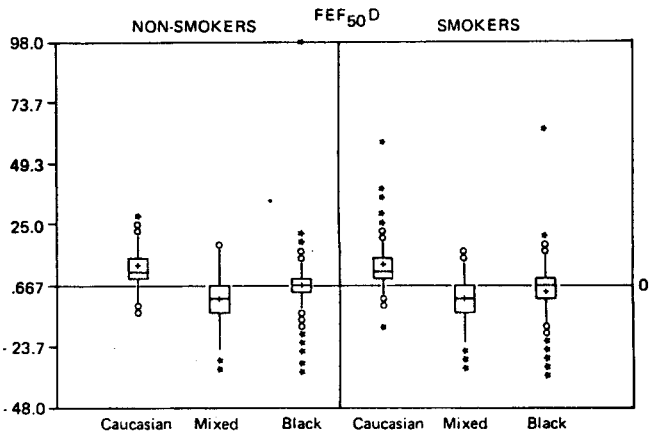


Fig. 32. Box diagram of the difference in the percentage of predicted of the FEF_{50} according to the formula described and the formula of Schoenberg *et al.*, separated according to ethnic group and smoking habit.

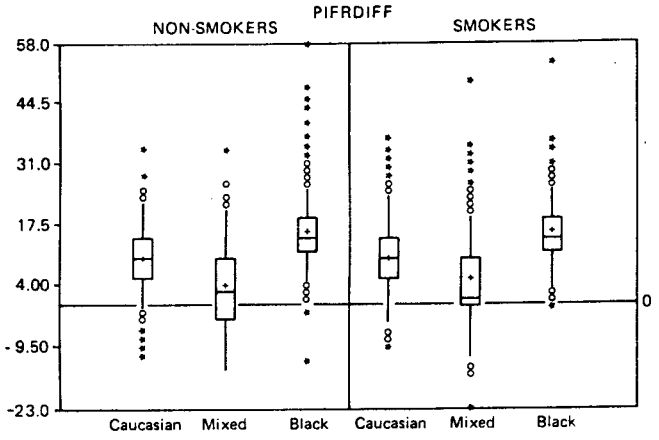


Fig. 31. Box diagram of the difference in the percentage of predicted of the PIFR according to the formula described and the formula of Schoenberg *et al.*, separated according to ethnic group and smoking habit.

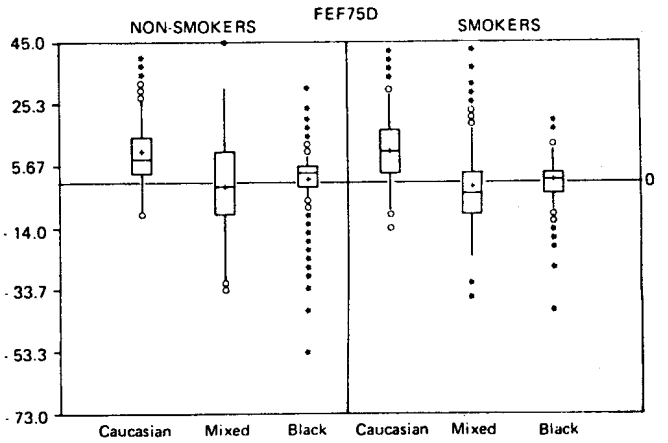


Fig. 33. Box diagram of the difference in the percentage of predicted of the FEF_{75} according to the formula described and the formula of Schoenberg *et al.*, separated according to ethnic group and smoking habit.

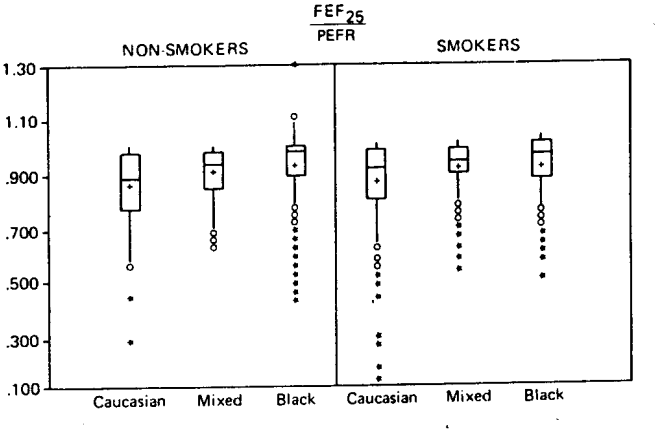


Fig. 34. Box diagram of the observations of FEF_{25}/PEFR ratio separated according to ethnic group and smoking habit. The ratio in blacks is significantly higher than that in Caucasians ($P < 0{,}001$).

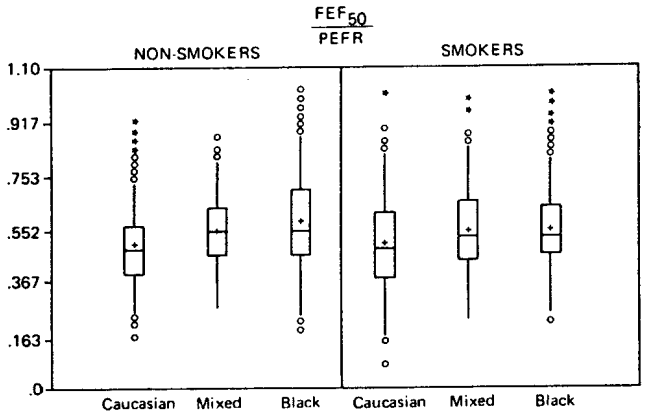


Fig. 35. Box diagram of the observations of FEF_{50}/PEFR ratio separated according to ethnic group and smoking habit. The ratio in blacks is significantly higher than that in Caucasians ($P < 0{,}001$).

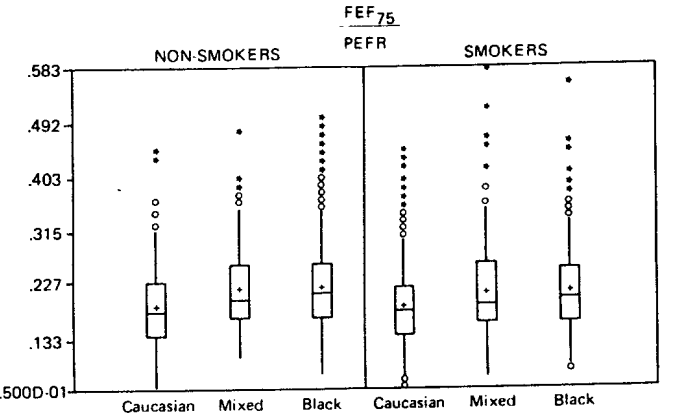


Fig. 36. Box diagram of the observations of FEF_{75}/PEFR ratio separated according to ethnic group and smoking habit. The ratio in blacks is significantly higher than that in Caucasians ($P < 0{,}001$).

Table 31			
RESULTS FROM A STEPWISE REGRESSION TO PREDICT THE STANDARDISED FVC OF NON-SMOKERS IN THE THREE ETHNIC GROUPS BY MEANS OF HEIGHT, MASS AND AGE			
SAMPLE SIZE		VARIABLES	R2
NON-SMOKING CAUCASIAN MALES:			
GROUP	112	NONE	-
< 30 YRS	32	AGE	0.12
> 30 YRS	78	NONE	-
NON-SMOKING MALES OF MIXED GROUP:			
GROUP	67	AGE	0.10
< 30 YRS	34	NONE	-
> 30 YRS	33	AGE	0.12
NON-SMOKING BLACK MALES:			
GROUP	619	AGE	0.02
< 30 YRS	266	NONE	-
> 30 YRS	353	NONE	-

Forward selection of variables was used in selecting the variables in the regression equations, and on each application the same conventions were applied. An important point that must be stressed is that the sample was inspected for severe outliers (values that differed by a factor of 10 or more and were grossly out of keeping with the regression), which were then excluded because their presence could have seriously influenced the parametric method of multiple regression used. It was possible, but unlikely, that a value could have been an outlier in its age subgroup (< 30 years or > 30 years) without being an outlier in the group as a whole. Such a value would be excluded from the subgroup but not from the group as a whole. Because of this, the sample size of the two age subgroups within an ethnic group may not necessarily add up to the sample size of the whole group.

The sufficiency of the standardisation for FVC can also be evaluated from **Table 31**. The standardisation was adequate for the Caucasian non-smokers, except when the sample was divided into a younger and

older group. In the younger group the variable age provided added predictability for the standardised FVC. Age entered the stepwise multiple regression function for the mixed group of workers as a whole. The predicting variable entered indicated in which respect the standardisation according to Schoenberg *et al* was lacking. For blacks the standardisation of FVC appears to be sufficient. Although age entered the regression equation, it improved the predictability only slightly. The sufficiency of the standardisation did not need to stay the same for other lung functions. **Table 32** shows that the standardisation formula of Schoenberg *et al* for FEV_1 was sufficient with respect to the predicting variables of height, weight and age. In the whole of the black group only age entered, but explained only 0,01 (R2) of the variation of the standardised FEV_1.

TABLE 32			
RESULTS FROM A STEPWISE REGRESSION TO PREDICT THE STANDARD FEV_1 OF NON-SMOKERS IN THE THREE ETHNIC GROUPS BY MEANS OF HEIGHT, MASS AND AGE			
SAMPLE SIZE		VARIABLES	R2
NON-SMOKING CAUCASIAN MALES:			
GROUP	112	NONE	-
< 30 YRS	34	NONE	-
> 30 YRS	78	NONE	-
NON-SMOKING MALES OF MIXED GROUP:			
GROUP	66	NONE	-
< 30 YRS	33	NONE	-
> 30 YRS	33	NONE	-
NON-SMOKING BLACK MALES:			
GROUP	618	AGE	0.01
< 30 YRS	353	NONE	-
> 30 YRS	265	NONE	-

Tables 33 and **34** show that the standardisation for FEF_{50} and FEF_{75} is adequate. **Tables 35** and **36**, however, indicate that the standardisation for PEFR and PIFR (especially in the Caucasians under 30 years and the mixed group over 30 years) is insufficient.

TABLE 33			
RESULTS FROM A STEPWISE REGRESSION TO PREDICT THE STANDARDISED FEF_{50} OF NON-SMOKERS IN THE THREE ETHNIC GROUPS BY MEANS OF HEIGHT, MASS AND AGE			
SAMPLE SIZE		VARIABLES	R2
NON-SMOKING CAUCASIAN MALES:			
GROUP	111	NONE	-
< 30 YRS	34	NONE	-
> 30 YRS	77	NONE	-
NON-SMOKING MALES OF MIXED GROUP:			
GROUP	67	NONE	-
< 30 YRS	34	NONE	-
> 30 YRS	32	NONE	-
NON-SMOKING BLACK MALES:			
GROUP	617	NONE	-
< 30 YRS	266	HEIGHT, AGE	0.05
> 30 YRS	351	NONE	-

TABLE 34			
RESULTS FROM A STEPWISE REGRESSION TO PREDICT THE STANDARDISED FEF_{75} OF NON-SMOKERS IN THE THREE ETHNIC GROUPS BY MEANS OF HEIGHT, MASS AND AGE			
SAMPLE SIZE		VARIABLES	R2
NON-SMOKING CAUCASIAN MALES:			
GROUP	110	NONE	-
< 30 YRS	34	NONE	-
> 30 YRS	77	NONE	-
NON-SMOKING MALES OF MIXED GROUP:			
GROUP	66	NONE	-
< 30 YRS	34	NONE	-
> 30 YRS	27	NONE	-
NON-SMOKING BLACK MALES:			
GROUP	612	NONE	-
< 30 YRS	266	AGE	0.02
> 30 YRS	347	NONE	-

TABLE 35			
RESULTS FROM A STEPWISE REGRESSION TO PREDICT THE STANDARDISED PEFR OF NON-SMOKERS IN THE THREE ETHNIC GROUPS BY MEANS OF HEIGHT, MASS AND AGE			
SAMPLE SIZE		VARIABLES	R2
NON-SMOKING CAUCASIAN MALES:			
GROUP	111	NONE	-
< 30 YRS	33	MASS	0.17
> 30 YRS	77	NONE	-
NON-SMOKING MALES OF MIXED GROUP:			
GROUP	65	NONE	-
< 30 YRS	33	NONE	-
> 30 YRS	33	NONE	-
NON-SMOKING BLACK MALES:			
GROUP	618	AGE	0.05
< 30 YRS	266	AGE	0.05
> 30 YRS	352	AGE	0.03

TABLE 36			
RESULTS FROM A STEPWISE REGRESSION TO PREDICT THE STANDARDISED PIFR OF NON-SMOKERS IN THE THREE ETHNIC GROUPS BY MEANS OF HEIGHT, MASS AND AGE			
SAMPLE SIZE		VARIABLES	R2
NON-SMOKING CAUCASIAN MALES:			
GROUP	112	HEIGHT	0.05
< 30 YRS	33	HEIGHT	0.15
> 30 YRS	78	NONE	-
NON-SMOKING MALES OF MIXED GROUP:			
GROUP	67	NONE	-
< 30 YRS	34	NONE	-
> 30 YRS	33	HEIGHT	0.24
NON-SMOKING BLACK MALES:			
GROUP	619	HEIGHT,AGE	0.05
< 30 YRS	266	HEIGHT	0.02
> 30 YRS	353	HEIGHT	0.04

This method of evaluating the standardisation formulae of Schoenberg *et al* would not detect a constant difference between the Schoenberg standardisation and the 'raw' lung function values.

5.3.1.5 *Prediction of unstandardised or 'raw' lung function measurements*

In an attempt to improve on the formulae of Schoenberg *et al*, the predictions of the unstandardised or raw lung functions were investigated for the three major ethnic groups contained in our sample. Each ethnic group was again further divided into two subgroups by an arbitrary division according to age, namely subjects below and above 30 years. This was done largely because of a change in the spread and the relations between the predicting variables and age. To establish prediction formulae for the various lung functions, the technique of stepwise regression was used. The statistical technique makes it possible to select the 'best' predicting (explanatory) variables to predict a single variable e.g. a certain lung function. The regression analysis was usually performed by means of two regression routines: SAS (1985) and a regression package called RECPAC (1981).

Forward selection of variables was used in selecting the variables in the regression equations and on each application the same conventions were applied. The sample was inspected for severe outliers (referring to values grossly out of keeping with the regression) because their presence could seriously influence the parametric method of multiple regression used. The result of the omission of some outlier values was that the number of values that were used to set up various regression equations did not remain constant.

The various regression equations predicted some important lung functions in the three major ethnic groups as well as in the two age categories. The comparison of these predicting equations was slightly hampered by the stepwise variables (height, weight, and age). The comparison was further influenced by the fact that the coefficient of

each predicting variable in the equation depended on the other variables in the equation and on those omitted from the equation.

5.3.1.6 Prediction of FVC of non-smokers

In black men we found that the predictability of FVC by means of height, mass and age was low as measured by the R2 (0,26). When dividing the group into younger and older groups, the predictability did not change appreciably. The coefficients associated with height and age also did not change considerably when the entire group was compared with the older groups. Age, however, did not enter the prediction formula in the younger age group.

In men in the mixed group the predictability changes with age, comparing an R2 of 0,51 in the complete group of R2 of 0,64 in the younger group and an R2 of 0,22 in the older group. For this ethnic group it can be seen that within the two age categories the variables allowed into the regression equation differed considerably, as did the predictability as measured by the R2.

A study of the regression equations for FVC prediction in non-smoking white men shows that the younger and older age groups did not differ as much as the non-smoking men of the mixed group. The predictability was, however, poorer than with the men of the mixed group and slightly better than with the black men.

TABLE 37 COEFFICIENTS FROM A STEPWISE REGRESSION TO PREDICT THE FVC OF NON-SMOKERS IN THREE ETHNIC GROUPS BY MEANS OF HEIGHT, MASS AND AGE						
	INTERCEPT	HEIGHT	MASS	AGE	R2	N
NON-SMOKING BLACK MALES:						
GROUP	-2.79374	0.04062	-	-0.01846	0.26	617
< 30 YEARS	-3.19271	0.04002	-	-	0.23	265
> 30 YEARS	-2,56617	0.04091	-	0,02540	0.27	352
NON-SMOKING OF MIXED GROUP:						
GROUP	-5.25785	0.05800	-	-0.02505	0.51	67
< 30 YEARS	-8.21034	0.07145	-	-	0.64	34
> 30 YEARS	5.50437	-	-	-0.04246	0.22	33
NON-SMOKING CAUCASIAN MALES:						
GROUP	-5.21896	0.06123	-	-0.03101	0.36	112
< 30 YEARS	-9.35038	0.07957	-	-	0.42	34
> 30 YEARS	-3.18843	0.05104	-	-0.03575	0.30	78

5.3.1.7 Prediction of the FEV_1 of non-smokers

Table 38 shows that the prediction equation hardly varied for the non-smoking black men in the two age categories and was similar to the prediction equation for the group as a whole. In the non-smoking men of the mixed group, predictability in the younger group (R2 = 0,61) was far better than the predictability in the older group (R2 = 0,17). The structure of the two prediction equations also differed between the two groups. In the non-smoking Caucasian men there was a slight slope difference with respect to height between the two age groups. The general feature of our prediction of FEV_1 was that mass never entered in any of the prediction equations established for the three ethnic groups.

TABLE 38

COEFFICIENTS FROM A STEPWISE REGRESSION TO PREDICT THE FEV_1 OF NON-SMOKERS IN THREE ETHNIC GROUPS BY MEANS OF HEIGHT, MASS AND AGE

	INTERCEPT	HEIGHT	MASS	AGE	R2	N
NON-SMOKING BLACK MALES:						
GROUP	-1.64307	0.03147	-	-0.02179	0.25	618
< 30 YEARS	-1.76565	0.03235	-	-0.02354	0.20	265
> 30 YEARS	-1.43695	0.03084	-	-0.02410	0.23	353
NON-SMOKING OF MIXED GROUP:						
GROUP	-3.83225	0.04676	-	-0.02673	0.46	66
< 30 YEARS	-7.31701	0.06316	-	-	0.61	33
> 30 YEARS	4.51070	-	-	0.03252	0.17	33
NON-SMOKING CAUCASIAN MALES:						
GROUP	-2.27498	0.04037	-	-0.03494	0.41	112
< 30 YEARS	-5.42692	0.05272	-	-	0.32	34
> 30 YEARS	0.79854	0.03315	-	0.03918	0.36	78

5.3.1.8 Prediction of FEF_{50} of non-smokers

For the non-smoking black males, predictability of FEF_{50} by means of the three predicting variables was poor in the two age categories and in the group as a whole. The most important predicting variable was age. In the non-smoking men in the mixed group none of the predicting variables entered the regression equation. Lastly, in the non-smoking Caucasian males only age featured in predicting FEF_{50} but the correlation was poor.

TABLE 39 COEFFICIENTS FROM A STEPWISE REGRESSION TO PREDICT THE FEF_{50} OF NON-SMOKERS IN THREE ETHNIC GROUPS BY MEANS OF HEIGHT, MASS AND AGE						
	INTERCEPT	HEIGHT	MASS	AGE	R2	N
NON-SMOKING BLACK MALES:						
GROUP	1.87651	0.02261	-	-0.04257	0.27	618
< 30 YEARS	6.70520	-	-	-0.07780	0.02	266
> 30 YEARS	5.87726	-	-	-0.04341	0.05	352
NON-SMOKING OF MIXED GROUP:						
GROUP	4.62537	-	-	-	-	67
< 30 YEARS	4.70265	-	-	-	-	34
> 30 YEARS	4.54576	-	-	-	-	33
NON-SMOKING CAUCASIAN MALES:						
GROUP	6.07262	-	-	-0.05023	0.15	111
< 30 YEARS	4.69324	-	-	-	-	34
> 30 YEARS	6.46171	-	-	-0.05909	0.16	77

5.3.1.9 Prediction of FEF_{75} in non-smokers

In the non-smoking black males the prediction was fairly similar for the two age categories, but the predictability (or the fit) was fairly poor. In the non-smoking males of the mixed group, the two age categories differ remarkably in that one finds a R2 of 0.22 in the younger ages, but none of the three predicting variables feature in predicting FEF_{75} in the older group. Of interest is that in the non-smoking Caucasian males 'age' had a negative influence in the older group but did not influence the prediction in the younger group.

TABLE 40						
COEFFICIENTS FROM A STEPWISE REGRESSION TO PREDICT THE FEF_{75} OF NON-SMOKERS IN THREE ETHNIC GROUPS BY MEANS OF HEIGHT, MASS AND AGE						
	INTERCEPT	HEIGHT	MASS	AGE	R2	N
NON-SMOKING BLACK MALES:						
GROUP	0.48523	0.01244	-	-0.02913	0.17	614
< 30 YEARS	1.36662	0.01296	-	-0.06625	0.10	266
> 30 YEARS	0.41108	0.01135	-	0.02258	0.10	346
NON-SMOKING OF MIXED GROUP:						
GROUP	1.83622	-	-	-	-	65
< 30 YEARS	-6.49165	0.04968	-	-	0.22	34
> 30 YEARS	1.50222	-	-	-	-	27
NON-SMOKING CAUCASIAN MALES:						
GROUP	2.88754	-	-	-0.03416	0.30	111
< 30 YEARS	2.11059	-	-	-	-	34
> 30 YEARS	2.72765	-	-	-0.03074	0.26	78

5.3.1.9 Prediction of PEFR in non-smokers

In non-smoking black males both height and age added to a better prediction of PEFR in the two age groups, and the predictability did not change much between these two age groups. In the group as a whole the predicting variable mass also featured in the equation. In the younger non-smoking men of the mixed group (< 30 years) good prediction was found (R2 = 0.31), whereas in the older group (> 30 years) none of the three variables entered the prediction. This showed a considerable difference between the two age groups. That height was entered in the group as a whole can be explained by the fact that height and weight are related. The predictability in the Caucasian males were poorer in general, for example in the older group 8% of the

variation height. None of the three predicting variables entered the regression equation in the younger group.

TABLE 41

COEFFICIENTS FROM A STEPWISE REGRESSION TO PREDICT THE PEFR OF NON-SMOKERS IN THREE ETHNIC GROUPS BY MEANS OF HEIGHT, MASS AND AGE

	INTERCEPT	HEIGHT	MASS	AGE	R2	N
NON-SMOKING BLACK MALES:						
GROUP	-0.44235	0.05404	0.01315	-0.06145	0.14	619
< 30 YEARS	-3.65185	0.08124	-	-0.0133	0.14	266
> 30 YEARS	1.54296	0.05140	-	-0.07437	0.13	353
NON-SMOKING OF MIXED GROUP:						
GROUP	-7.87112	0.09565	-	-	0.16	67
< 30 YEARS	2.67874	-	-	-0.09195	0.31	34
> 30 YEARS	8.81437	-	-	-	-	32
NON-SMOKING CAUCASIAN MALES:						
GROUP	-2.77801	0.06551	-	-	0.07	112
< 30 YEARS	8.87697	-	-	-	-	33
> 30 YEARS	-4.80224	0.07658	-	-	0.08	78

5.3.1.10 Prediction of PIFR in non-smokers

The predictability of PIFR in non-smoking black males was relatively poor, but similar in the separate age groups. In the non-smoking males of the mixed group a reasonable R2 of 0.21 was obtained in the over-30-year group, but none of the variables played a part in the under 30-year group. In contrast to the two non-Caucasian groups, height played no part in the Caucasian group. However, mass was important in the Caucasian group.

TABLE 42 COEFFICIENTS FROM A STEPWISE REGRESSION TO PREDICT THE PIFR OF NON-SMOKERS IN THREE ETHNIC GROUPS BY MEANS OF HEIGHT, MASS AND AGE						
	INTERCEPT	HEIGHT	MASS	AGE	R2	N
NON-SMOKING BLACK MALES:						
GROUP	-1.28207	0.04681	0.01315	-0.03806	0.08	619
< 30 YEARS	-4.54918	0.05978	-	-	0.06	266
> 30 YEARS	0.25537	0.03809	-	-0.03801	0.06	353
NON-SMOKING MIXED GROUP:						
GROUP	-4.83122	0.07486	-	-0.05290	0.17	67
< 30 YEARS	6.75324	-	-	-	-	34
> 30 YEARS	-13.78817	0.11456	-	-	0.21	33
NON-SMOKING CAUCASIAN MALES:						
GROUP	5.24335	-	0.04180	-0.05562	0.15	112
< 30 YEARS	1.45742	-	0.07002	-	0.20	33
> 30 YEARS	5.99680	-	0.03328	-0.05647	0.12	78

5.3.1.11 Conclusion

The sample which was used to establish predicting equations for workers at the Rössing uranium mine and which was also used to evaluate the accuracy of the standardisation formulae of Schoenberg *et al* consisted of clinically healthy non-smoking subjects of the different ethnic groups employed by the mine. The prediction equations were developed for local (Namibian) ethnic groups and conditions. The number of blacks in this group was very much larger than the number of blacks in the study of Schoenberg *et al*. It must, however be emphasised that the present prediction formulae were only calculated for adults and did not include women because of the small number available. The deductions made from this learning sample will

firstly be valid for similar populations living under comparable conditions and it may be possible to extend or apply the newly developed predicting equations in a limited fashion to other populations. We believe that in a project aiming to detect early changes, prediction formulae for the specific population are essential.

The prediction equations suggested are mostly linear and this simplifies their application to a great extent. The transformations suggested by Schoenberg *et al* were investigated but did not offer a better fit. Separating the samples by age (30 years) provided another interesting insight into the data in terms of changes in spread and predictability. It must be stated again that the elimination of severe outliers also improved the fit of the regression equations described here.

No statistical inferential comparison of the three main explanatory values, height, weight, and age, was done because the lung functions were standardised for the different values of the explanatory variables by the prediction process. The significance is incorporated in the regression process.

To show the need for separate prediction formulae for the different ethnic groups further, a group of 62 non-smoking Caucasians with an average height of 177.7 cm, average age of 30.2 years and average weight of 76.3 kg and a comparable group of 125 non-smoking blacks with an average height of 179.4 cm, average age 30.2 years and average weight of 76.9 kg were selected and the measurements for the different lung functions compared by means of box plots (Figs 21-27); the differences were comparable with the calculated predicted values. The mean FVC, FEV_1 and PIFR were significantly higher in the Caucasians than in blacks (P , 0.0001 for the first two and P <

0.0002 for the last). The differences for FEF_{25}, FEF_{50} or PEFR were small and not significant (P . 0.05). The number in the mixed group is too small to be included in this comparison.

5.3.1.12 Comparison of the prediction formulae described in this paper with the formulae of Schoenberg et al.

To relate the present predictions to those of Schoenberg *et al* the percentages of the observed lung function measurements, as related to the predicted values that had been calculated by means of both the present regression formulae and their formulae, were computed for each member of the sample. To compare these two different percentages of the predicted, the difference between the two was calculated by subtracting the percentage based on the Schoenberg predictions from the percentage based on the present formulae. The prediction equations for the subgroups (< 30 years and > years) were used. A positive difference meant that the present prediction was smaller than the standardisation according to Schoenberg *et al* for a specific value and vice versa, and can be deduced from the following:

observed value = O; present prediction value = P; Schoenberg predicted value = S

(O/P x 100 - O/S x 100) > 0;

O x 100 (1/P - 1/S) > 0;

1/P - 1/S > 0;

(1/P > 1/S) x (P x S):

implies P < S or present predicted value, Schoenberg predicted value.

In comparing the two different predicting formulae a few factors must be considered. The present prediction tables were set up only for clinically normal non-smokers. The present black group consisted of about 620 non-smokers compared with 120 black adults studied by Schoenberg *et al*, which included 'healthy' smokers. In setting up their

standardisation formulae, they also considered transformations of the three variables height, weight and age. These transformations were considered but not found to add to the present prediction formulae. Prediction equations for the mixed group were established and for comparison with the Schoenberg formulae, their black standardisation formulae were used for the mixed group in the present sample.

The difference in the two percentages of the predicted for FVC was compared in the non-smoking and smoking groups for all three ethnic groups. Fig. 28 shows that in the non-smoking Caucasian group the median difference was about 7% and that the present prediction is smaller than the value obtained by the Schoenberg formulae. The inter-quartile area of the non-smoking Caucasians shows that the whole box lies above zero mark and that it is relatively small. From this it can be deduced that the present prediction method produced values that were consistently lower than the standardisation of Schoenberg *et al*. This was also true for the non-smoking black group although the difference between the two standardisation methods was smaller in this group. In the mixed group of non-smokers the differences had a wider spread and the median difference was less than zero (approximately -7.3). This indicates that for the mixed group, the present prediction is larger than that of Schoenberg *et al*. Similar deductions can be made for FVC in the group of smokers.

Comparison of the two prediction formulae for FEV_1 are shown in **Fig. 42** . The pattern was the same as for the FVC and as in the case of the FVC the distribution of the differences of the FEV_1 in both the mixed groups differed more than in the other two ethnic groups.

Fig. 30 shows that the present prediction for PEFR was larger than the prediction of Schoenberg *et al* in all six subgroups. Here again the

inter-quartile distance of the mixed group was larger than in the other two groups.

The present predictions for the lung function measurement PIFR (**Fig. 31)** are generally smaller than those of Schoenberg *et al*. Again the inter-quartile distance of the mixed group was larger than those of the other two ethnic groups in both non-smokers and smokers.

The present predictions were similar to those of Schoenberg *et al* for the FEF_{50} (Fig. 32) for the black group (mean difference near to zero). They were, however, smaller in the Caucasians and larger for the mixed group.

The present predictions compared well for the FEF_{75} (Fig. 33) in the mixed and black groups but were smaller than the Schoenberg *et al* predictions in the Caucasians.

It could be argued that the smaller volumes found in the samples of workers at the Rössing Uranium Mine were due to the possible exposure to dust, causing restrictive lung disease. All the subjects were, however, clinically and radiographically normal and reports indicate that early changes caused by dust inhalation tend to be those of bronchitis and not those of restriction.

It must be emphasised that when comparing two sets of prediction tables, it does not necessarily mean that the one is 'better' than the other .

The most probable reason for any differences may be that different population groups were used. The formulae of Schoenberg *et al* may well be more applicable in other circumstances and each laboratory

testing large numbers of individuals should do its own prediction formulae and/or standards.

Table 43 - Comparison of predicted formulae with that of Schoenberg *et al*

FVC		FEV_1	
Blacks	18% < Caucasians	Blacks	15% < Caucasians
Blacks	9% < mixed group	Blacks	8% < mixed group
Mixed group	10% < Caucasians	Mixed group	7% Caucasians
FEF_{50}		FEF_{75}	
Blacks	1.5% < Caucasians	Blacks	3.6% < Caucasians
Blacks	2.2% < mixed group	Blacks	9% < mixed group
Mixed group	0.8% < Caucasians	Mixed group	12% Caucasians
PEFR		PIFR	
Blacks	6% < Caucasians	Blacks	12% < Caucasians
Blacks	9% mixed group	Blacks	9% < mixed group
Mixed group	3% < Caucasians	Mixed group	37% Caucasians

5.3.1.13 Abnormal lung function measurements indicating early airway impairment

As discussed, lung function measurements are influenced by many variables (including age, height, weight and ethnic group) and the identification of impaired lung function is determined by the size by which the predicted value differs from the observed value. Whenever a value falls below an agreed cut-off point, it is classified as impaired. The complexity of the determination of these cut-off points has been discussed in a previous chapter.

For the determination of a cut-off point to identify impaired values with no clusters, a method of cut-off points based on percentiles is recommended. When this procedure is followed it is not necessary to

transform the data to a Gaussian distribution in the case of skew or long-tailed distribution. As an illustration, the cut-off points determined by means of distributional assumptions like normality (Gaussian) (cut-off points recommended by Schoenberg *et al*) are applied to the present data set.

In **Table 44** the percentage of abnormal values for FVC, FEV_1, PEFR, FEF_{50} and FEF_{75} are given in the different ethnic groups separating the non-smokers from the smokers and also for the group as a whole. Although there appear to be more abnormal values in the smokers when compared with the non-smokers, it is only of significance in the FEF_{50} in the mixed group. The difference between non-smokers and smokers may become significant with larger numbers and/or when the total group becomes older, as we are now dealing with a predominantly young group of individuals (mean + standard deviation = 32.75 + 8.45 years).

TABLE 44								
PERCENTAGE ABNORMAL VALUES IN THREE ETHNIC GROUPS ACCORDING TO THE FORMULAE OF SCHOENBERG *ET AL.*								
NS	S	TOTAL	NS	S	TOTAL	NS	S	TOTAL
CAUCASIAN MALES								
FVC			FEV_1			PEFR		
15%	19%	18%	13%	21%	19%	2%	5%	4%
FEF_{50}			FEF75					
12%	16%	15%	5%	10%	9%			
MIXED GROUP MALES								
FVC			FEV_1			PEFR		
2%	3%	2%	3%	5%	4%	2%	0%	0.44 %
FEF_{50}			FEF75					
2%	10%	7%	2%	1%	1%			
BLACK MALES								
FVC			FEV_1			PEFR		
9%	9%	9%	10%	11%	10%	1%	0.4%	1%
FEF_{50}			FEF75					
8%	9%	8%	2%	4%	2%			
There was only a statistically significant difference between the number of abnormal values of the non-smokers and the smokers in the mixed group males for FEF_{50} (0.03). NS = non-smokers; S = smokers								

5.3.2 Results of the Analytical Cross-Sectional Study of X-rays and Lung Functions to Study Significant Differences from Predicted Measurements among a Workforce with more than 10 years Exposure in Uranium Mining and Milling.

The analytical cross-sectional study was used utilising existing records about the health status of the workers with respect to the conditions of interest. It described the individuals in the population in terms of their personal attributes and their history of exposure to the suspected causal agents. The data was examined in relation to the prevalence or absence of abnormalities under investigation with a view to developing or testing a specific hypothesis.

Occupational studies are subject to bias from the healthy worker survivor effect[314,315] (workers who are least healthy are not employed

or likely to leave work first). To minimise the healthy worker effect 200 employees were randomly selected from the ex-employee category and included as part of the population studied. Healthy worker effect is unlikely in cancer studies and is reduced with the use of internal comparison groups (as is the case in this study). The healthy worker effect is also greatly reduced if a latency of ten years is allowed, which is the case in this study. Furthermore, those who were employed for more than 15 years and who were not subjected to strict selection criteria were likewise included. Lastly it must be pointed out that the effect of the retrenchment was absorbed by the policy of "first in - last out".

5.3.2.1 Study population

The subjects for this study (834) have been selected from the total population of the workforce of 981. Excluded from the study were women (36) and those whose lung function and x-rays did not meet the prescribed technical requirements, those whose additional information i.e. unknown age and date of employment were suspect (111). A representative sample of 200 male ex-employees from an at-risk population of 799 male ex-employees with more than ten years of service were included as an additional study group, referred to as the terminated group. Twenty-six workers whose services were terminated due to ill health were included in this group. The study was designed to include men with respiratory abnormalities. In order to determine the mean effect of mining, smokers were excluded in the final statistical analysis. This was done because of the effects of smoking on the spirometric indices.

The environmental grading committee consisting of an environmentalist, a production engineer, a worker and the occupational health physician identified three groups. The groups were identified as a **Control group** (N=262) consisting of administrative personnel, office workers etc. A **Study group** (N=572) consisting of workers other than mentioned above and who were employed in the operational areas. The **Terminated group** (N=200) were randomly selected from ex-employees.

5.3.2.2 Exposure Groups

The **Study group** was further sub-divided into sub-groups of high and medium exposure:

High: Where exposure according to environmental surveys and time spent in area of work was considered to be "high" by the committee, who has an intimate knowledge of the workforce and their working environs. Usually exposure for this category was high for radiation, dust and/or gases. Areas included as high risk areas were open pit workers (excluding cabin workers), workers in crushers, acid plant, metallurgical plant, tailings dam and recovery area as well as workers which operate in all areas of the mine (surveyors, boilermakers, welders, rubberliners and environmental control personnel). (N=398)

Medium: Where exposure according to environmental surveys and time spent in area of work was considered to be "medium" by the committee, which has an intimate knowledge of the workforce and their working environs. Usually exposure for

this category was medium for radiation, dust and/or gases. Areas included as medium risk areas were workers in workshops, cabin workers and condition monitoring personnel. (N=174)

The **Control group's** (N=262) exposure was low according to environmental surveys and time spent in area of work was considered to be "low" by the committee, which has an intimate knowledge of the workforce and their working environs. Usually exposure for this category was low for radiation and dust and/or gases. Areas included as low risk areas were offices, laboratories and other low-exposed areas. It is accepted that this is not an ideal control group but other alternatives were not available. Often intra-population comparison groups provide much more detailed and precise information about the etiology of occupational diseases.

5.3.2.3 Smoking profile

Evaluation of the entire data set – smokers and non-smokers – reveal that the majority of workers are non-smokers. Non-smokers included those who have never smoked as well as those who stopped smoking for more than two years. Smokers are current smokers as well as those who have stopped for less than two years. Caucasians tend to smoke more than the other ethnic groups. The mixed group exhibits the same trend whilst the black group smokes the least. The percentage of smokers has diminished significantly since the previous study. The number of Caucasian smokers dropped from 63% to 42%, black smokers from 29% to 15% and the smokers from the mixed race group from 70% to 40%.

Table 45 CONTROL GROUP – Smoking by Ethnic Group				
	Ethnic Group			
	Black	Caucasian	Mixed Race	Total
Non-Smokers	135	40	23	198
Smokers	22	29	12	63
Total	157	69	35	261

Table 46 STUDY GROUP – Smoking by Ethnic Group				
	Ethnic Group			
	Black	Caucasian	Mixed Race	Total
Non-Smokers	341	52	42	435
Smokers	63	39	35	137
Total	404	91	77	572

Table 47 TERMINATED GROUP – Smoking by Ethnic Group				
	Ethnic Group			
	Black	Caucasian	Mixed Race	Total
Non-Smokers	88	19	26	133
Smokers	23	20	20	63
Total	111	39	46	196

5.3.2.4 Allergic Profile

History and skin prick test (SPT) determined allergy.

Table 48 Allergy by Ethnic Group in Control, Study and Terminated Groups				
Allergy by Group	**Ethnic Group**			
	Black	**Caucasian**	**Mixed Race**	**Total**
CONTROL GROUP				
Allergic	35	16	9	60
Non-Allergic	122	53	26	201
Total	157	69	35	261
STUDY GROUP				
Allergic	71	27	15	113
Non-Allergic	333	64	62	459
Total	404	91	77	572
TERMINATED GROUP				
Allergic	11	6	12	29
Non-Allergic	100	33	34	167
Total	111	39	46	196

5.3.2.5 Analysis of demographic data

The average age of this group (compared with the results of the previous cross-sectional study) is considerably higher (average age was 32 and is now 42.4). The Caucasians were the tallest and weighed the most with an average height of 178cm and an average weight of 85kg; the average height of the black participants was 172cm and weighed 74kg, whilst the mixed race members were on average also 172cm tall and weighed 78kg.

Table 49 Summary of Demographic Data per Exposure Group High & Medium						
	Ethnicity					
Study Group n=572	**Exposure High – n=398**			**Exposure Medium – n=174**		
	Black	Caucasian	Mixed	Black	Caucasian	Mixed
Count of Ethnic	277	71	50	127	20	27
Average Years of Service	16.65	16.03	16.96	16.65	14.50	16.44
Mean Age	42.66	47.14	42.34	44.37	41.50	40.30
Mean Height	172.67	178.15	172.84	173.05	178.60	172.78
Mean Weight	74.96	86.99	78.54	73.84	83.80	77.22

Table 50 Summary of Demographic Data per Exposure Group = Low			
Control Group	**Ethnicity**		
N=261	**Black**	**Caucasian**	**Mixed Race**
Count of Ethnic	157	69	35
Average Years of Service	16.27	15.93	16.4
Mean Age	44.13	48.55	41.37
Mean Height	172.83	178.00	171.34
Mean Weight	76.90	86.57	79.63

Table 51 Summary of Demographic Data Terminated Group Exposure –Intermediate			
Terminated Group	**Ethnicity**		
N=196	**Black**	**Caucasian**	**Mixed Race**
Count of Ethnic	111	39	46
Average Years of Service	>10	>10	>10
Mean Age	42.9	48.30	41.76
Mean Height	172.3	177.56	172.13
Mean Weight	72.84	80.82	77.32

Box plots for age, height and weight for ethnic groups in the various exposure groups were created.

FIGURE 37 Box Plots of AGE for Exposure Groups

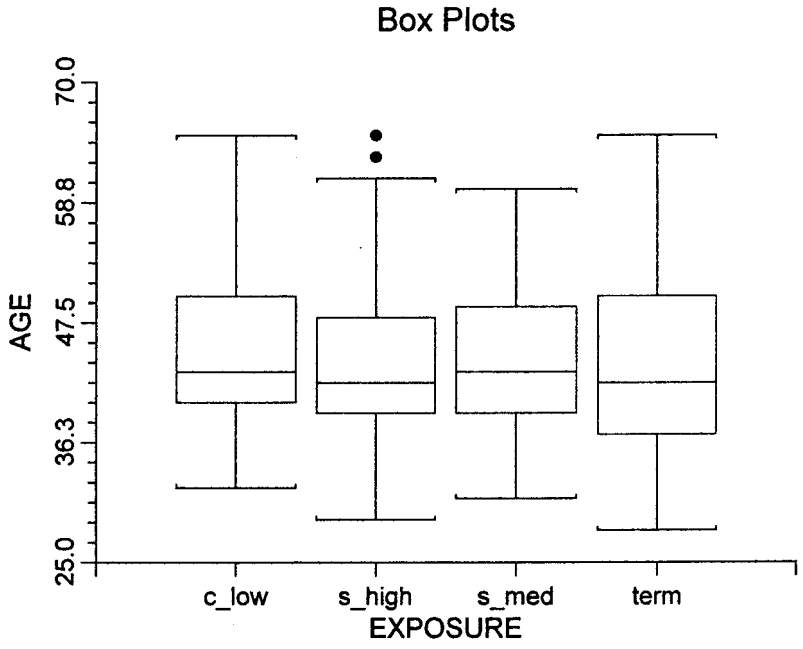


TABLE 52 Descriptive statistics of AGE for EXPOSURE groups

Exposure groups	S_High	C_Low	S_Medium	Terminated
N	302	198	133	133
Mean	43.53	45.37	44.20	43.78
Median	42	43	43	42
std. Dev.	6.85	8.02	7.21	8.72
Range	36	33	29	37

FIGURE 38 Box Plots of HEIGHT for Exposure Groups

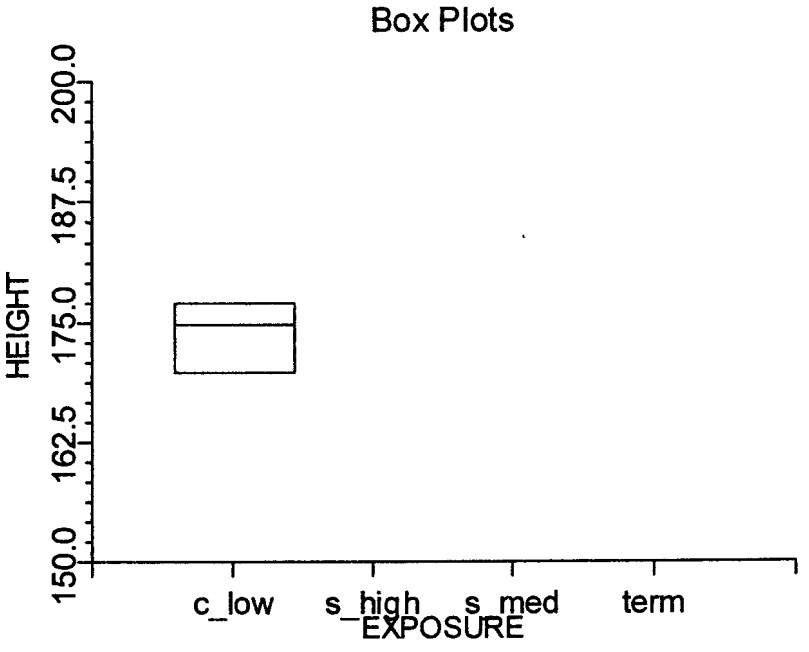


TABLE 53 Descriptive statistics of HEIGHT for EXPOSURE groups

Exposure groups	S_High	C_Low	S_Medium	Terminated
N	302	198	133	133
Mean	172.99	173.92	173.24	172.59
Median	173	175	173	175
std. dev.	6.78	6.61	6.45	5.97
Range	42	33	34	31

FIGURE 39 Box Plots of WEIGHT for Exposure Groups

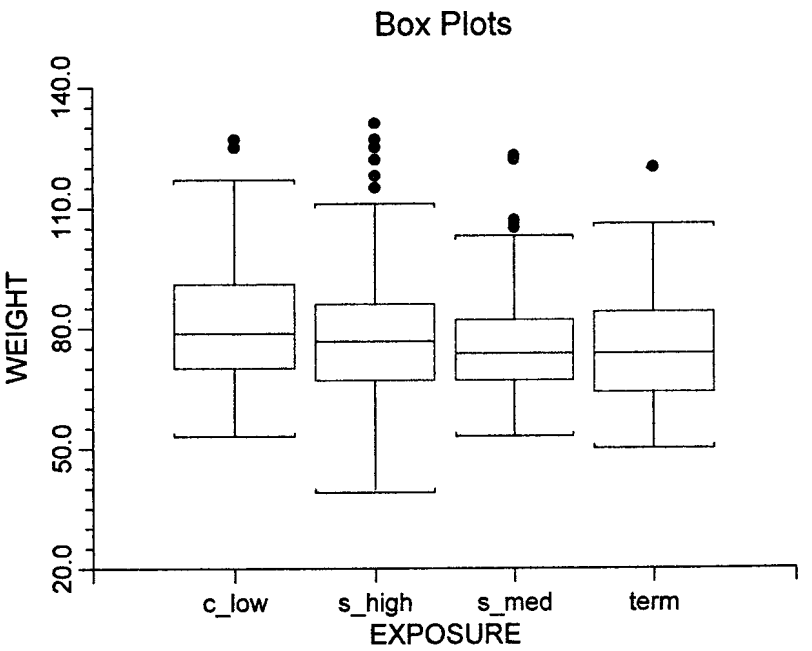


TABLE 54 Descriptive statistics of WEIGHT for EXPOSURE groups

Exposure groups	S_High	C_Low	S_Medium	Terminated
N	302	198	133	133
Mean	77.42	80.96	76.33	75.98
Median	77	79	74	74
std. dev.	14.30	14.41	13.08	13.70
Range	92	74	70	70

Significant differences between the mean values of age, height and weight were tested by means of two-tailed T-tests, and P-values were determined.

Two independent groups (group 1 vs group 2) by means of T-tests (only the significant differences are listed)

AGE

Group 1	Group 2	t-value	p-value
ctrl_b	ctrl_c	-3.5115	0.00057
ctrl_c	ctrl_m	2.4840	0.01576*
ctrl_c	stu_b	4.7580	0.000002
ctrl_c	stu_c	2.65810	0.00930
ctrl_c	stu_m	4.26740	0.000054
ctrl_c	t_b	3.8540	0.000184
ctrl_c	t_m	2.3650	0.021074*

HEIGHT

Group 1	Group 2	t-value	p-value
ctrl_b	ctrl_c	-5.1180	0.000001
ctrl_b	stu_c	-3.6932	0.000291
ctrl_b	t_c	-2.3719	0.018948*
ctrl_c	ctrl_m	5.1496	0.000003
ctrl_c	stu_b	5.8219	0.000000
ctrl_c	stu_m	4.0650	0.000112
ctrl_c	t_b	6.0972	0.000000
ctrl_c	t_m	4.4959	0.000030
ctrl_m	stu_c	-3.8536	0.000248
ctrl_m	t_c	-3.2998	0.002040
stu_b	stu_c	-4.4694	0.000008
stu_b	t_c	-2.7085	0.006759
stu_c	stu_m	2.9856	0.003626
stu_c	t_b	4.6684	0.000007
stu_c	t_m	3.1557	0.002295
stu_m	t_c	-2.0835	0.041545*
t_b	t_c	-3.2198	0.001707
t_c	t_m	2.6462	0.011325*

WEIGHT

Group 1	Group 2	t-value	p-value
stu_c	t-b	4.6541	0.000008
stu_c	t-m	2.2406	0.027973*
stu_m	t_b	2.0175	0.045736*

* These results will not be significant if all pairs are tested as the significance level will change due to multiple comparison testing.

Two independent groups (group 1 vs group 2) by means of T-tests (only the significant differences are listed)
Although all comparisons were tested the only significant difference for demographic variables were the following:

The subjects in the control group (exposure low) were significantly older than those in the study group (exposure high). **t-value = 2.75 p-value = 0.006**

The subjects in the control group, exposure low weighed significantly more than those in the high (**t-value = 2.70 p-value = 0.007**) and medium exposure groups. **(t-value = 2.97 p-value = 0.003)**

5.3.3 Analysis of Chest X-Ray Data

The cumulative exposure to respirable quartz dust and asbestos is the most important factor in the incidence of pneumoconiosis in minors. It is more evident in older and often retired workers. The chest x-ray and its interpretation are still the most valuable diagnostic tool in the diagnosis of lung cancer, silicosis, asbestos-related diseases and tuberculosis. The 1980 International Labour Organization (I.L.O.) International Classification of the Radiographs of Pneumoconiosis[317] provides a standardised system of reporting. All x-rays were retrospectively evaluated in line with the principles of the historical cohort. Because of relative low levels of dust

exposure combined with the relatively low silica content of the respirable fraction of the dust few abnormal x-rays were detected.

A simplified five point score system was used for this study. The grades were:

0: normal

1: pneumoconiosis (silicosis, asbestosis) as confirmed and classified according to the I.L.O > 0/1

2: cancer of the lung or mesothelioma confirmed

3: tuberculosis confirmed or strongly suspected

4: sarcoidosis

Table 55 – Summary of Chest X-Ray Results of Control, Study and Terminated Groups (>10 Years Employment)

		Black	Caucasian	Mixed	Total
Control Group (non-exposed)					
Grade 0	Normal	155	66	35	256
1	Pneumoconiosis	0	0	0	0
2	Lung Cancer/Mesothelioma	0	0	0	0
3	Tuberculosis	3	3	0	6
4	Sarcoidosis	0	0	0	0
Total		158	69	35	262
Study Group (exposed)					
Grade 0	Normal	397	89	76	562
1	Pneumoconiosis	0	1	0	1
2	Lung Cancer/Mesothelioma	0	0	0	0
3	Tuberculosis	8	1	1	10
4	Sarcoidosis	0	0	0	0
Total		405	91	77	573
Terminated Group (exposed)					
Grade 0	Normal	109	40	48	196
1	Pneumoconiosis	0	0	0	0
2	Lung Cancer/Mesothelioma	0	0	0	0
3	Tuberculosis	3	1	0	4
4	Sarcoidosis	0	0	0	0
Total		111	41	48	200

5.3.3.1 *Normal*

The vast majority of the x-rays were normal without any disagreement from the panel. The categories "non-specific fibrotic changes other than pleural changes" as well as " non-specific pleural changes" were initially used but since it is of little clinical value, it was decided to include them under the category "normal".

5.3.3.2 *Pneumoconiosis*

Two cases of radiologically diagnosed pneumoconiosis were detected. Both spent a considerable time in South African underground mines. When they joined Rössing the pre-employment screening system was not in place, yet they were detected as early as 1980. It was decided that their abnormalities could not be due to their employment at Rössing and were excluded from further statistical analysis.

5.3.3.3 *Lung cancer*

No cases of respiratory cancer were found among the population studied (study group, control group and terminated employees group). It is however possible that respiratory cancer was under-reported, especially among the terminated group, because only exit-medical examination data was used. This point will be discussed later.

5.3.3.4 *Tuberculosis confirmed or strongly suspected*

The cross-sectional survey revealed only two cases of pulmonary tuberculosis being investigated or being treated (March 1996 survey.) [prevalence]. Yet when the X-rays were retrospectively examined [historical cohort] a different picture emerged [incidence]. A total of 20

employees were diagnosed as either definite tuberculosis or strongly suspected (based on radiological appearance).

5.3.4 Analysis of lung function values

The main objective of this study was to investigate the mean independent effect of uranium mining on the lung function parameters of uranium miners at Rössing. Lung function measurements were investigated in four exposure groups.

Lung function measurements are influenced by many variables such as age, height, weight and ethnic group. The analysis of lung function values first examined the relationship between the various parameters (FVC, FEV_1, FEF_{50}, FEF_{75}, PEFR, PIFR) in the exposed and control groups. During the second phase the focus was on differences in the same exposure groups when lung function parameters were adjusted for predicted values. The next step was to separate the subjects in the various exposure groups into ethnic groups resulting in nine additional variables. Comparable tests between these variables produced masses of information. This, in turn, presented a problem in summarising significant relevant differences for predicted measurements and demographic variables. The significance of differences was tested by means of two-tailed T-tests and both T and P values are given of compared groups. The graphic method of "box- and –whisker" plots is used once again to display distributional information of a measurement taken on the members of the sample. The box-plots reflect indicated variables by exposure groups with descriptive statistics below each box plot. The "adjusted value" was calculated according to the values worked out in the previous chapter and then the predicted was calculated using:

PREDICTED FVC = ABSOLUTE FVC / ADJUSTED FVC

The following predicted results are used:

FVC%
FEV_1%
FEV_1/FVC%
FEF_{50}%
FEF_{75}%
PEFR%
PIFR%

The exposure groups are identified as s = study group; c = control group; t = terminated group. Exposures were classified as h = high; m = medium; l = low. Ethnic groups are identified b = black; c = caucasian (white); m = mixed races. Smoking habits are identified as s = smoker (currently smoking); ns = non-smokers (those who have never smoked and those who have stopped for more than two years). Allergies are identified as a = allergic; na = non-allergic.

Table 56 – Summary of Mean Lung Function Parameters in Various Exposure Groups

	Exposure Groups			
Lung Function Parameters (mean)	High	Med	Low	Terminated
FVC	3.75	3.72	3.86	3.79
FEV_1	3.10	3.11	3.18	3.13
FEV_1/FVC	82.92	83.4	82.15	82.23
FEF_{50}	4.05	4.19	4.07	4.19
FEF_{75}	1.50	1.53	1.56	1.55
PEFR	8.67	8.63	8.60	8.55
FIVC	3.82	3.81	3.94	3.86
PIFR	7.48	7.27	7.44	7.14
Lung Function Parameters Adjusted (mean)				
FVC	3.53	3.49	3.57	3.54
FEV_1	2.92	2.91	2.93	2.93
FEV_1%	106.03	106.95	108.29	105.59
FEV_1/FVC	83.03	83.31	82.30	83.15
FEF_{50}	4.02	4.00	3.94	4.07
FEF_{75}	1.39	1.39	1.35	1.40
PEFR	7.56	7.40	7.68	7.68
PIFR	5.40	5.44	5.35	5.44

Table 57 – Summary of Mean Lung Function Parameters % Predicted in Various Exposure Groups				
	Exposure Groups			
Lung Function Parameters (mean)	High	Med	Low	Terminated
FVC %	106.47	106.45	107.84	107.09
FEV_1%	106.03	106.95	108.29	105.59
FEV_1/FVC%	99.85	100.11	99.86	98.93
FEF_{50}%	101.21	105.21	103.98	103.45
FEF_{75}%	108.41	110.69	116.33	112.73
PEFR%	115.62	117.36	113.23	111.34
PIFR%	135.88	135.92	136.77	130.09

FVC

The **median** and **mean** values for FVC (whether adjusted or expressed as a percentage) were largest in the control group with low exposure. The smallest values were found in the study group with only medium exposure.

FEV_1

The largest **median** value for FEV_1 (adjusted and as a percentage) was in the terminated group. The largest **mean** FEV_1 value was in the control group and the lowest mean and median in the study group with high exposure. The lowest values for FEV_1 adjusted and FEV_1 was found in the study group with median exposure.

FEV_1/FVC%

The largest **mean** and **median** value was found in the study group with median exposure and the lowest value median value in the terminated group.

FEF_{50}

The lowest **median** value for FEF_{50} was in the terminated group and the lowest **mean** FEF_{50} in the study group with high exposure. When adjusted, the lowest values (**mean** and **median**) were found in the control group with the largest values found in the terminated group.

FEF_{75}

The lowest **mean** and **median** value for FEF_{75} was in the study group with high exposure. The adjusted FEF_{75}'s lowest values were found in the control group. The **mean** value of FEF_{75}% again points to the study group with high exposure. Highest values were found in different exposure groups depending on whether the measured, adjusted or percentage were used.

PEFR

The highest PEFR's were measured in the study group with medium exposure, if adjusted the highest values were obtained from the terminated group. The highest **mean** and **median** values were in and from the study group with medium exposure (when expressed as a percentage).

PIFR

The lowest values were again found in the terminated and study groups with medium exposure.

Box plots for lung function parameters were designed for lung functions in exposure groups.

FIGURE 40 Box Plots of FVC for Exposure Groups

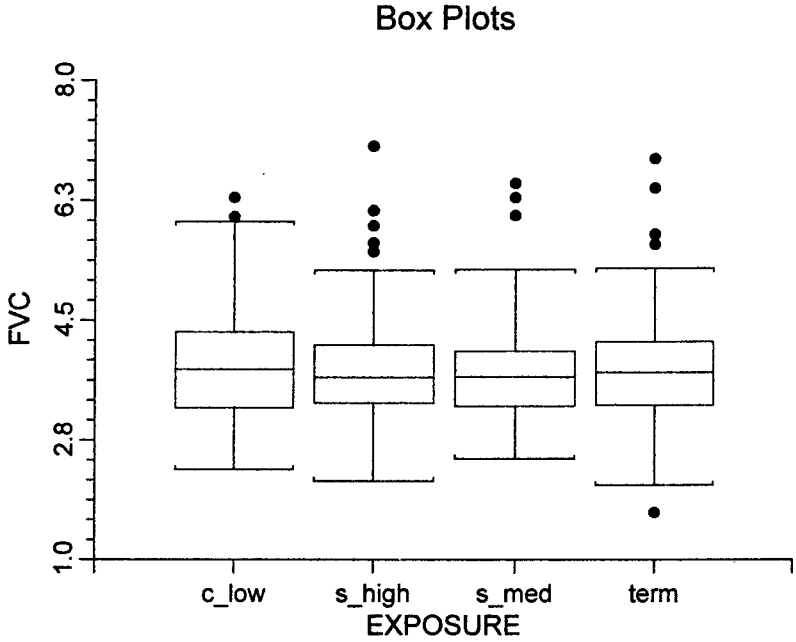


TABLE 58 Descriptive statistics of FVC for EXPOSURE groups

Exposure groups	S_High	C_Low	S_Medium	Terminated
N	302	198	132	133
Mean	3.75	3.86	3.72	3.79
Median	3.69	3.80	3.70	3.76
Std. Dev.	0.69	0.80	0.71	0.82
Range	4.89	3.79	4.02	5.17

FIGURE 41 Box Plots of FVC_ADJUSTED for Exposure Groups

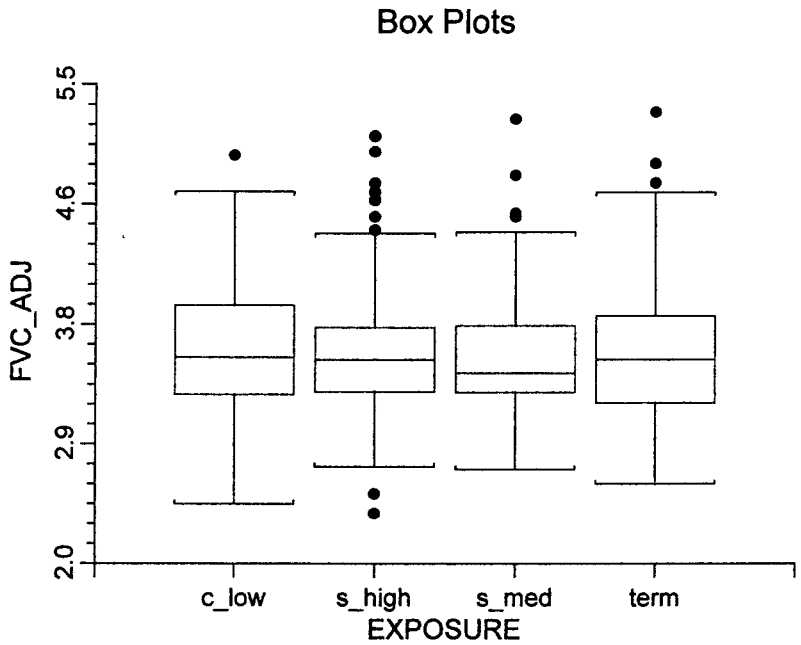


TABLE 59 Descriptive statistics of FVC_ADJUSTED for EXPOSURE groups

Exposure groups	S_High	C_Low	S_Medium	Terminated
N	302	198	133	133
Mean	3.53	3.57	3.49	3.54
Median	3.50	3.52	3.40	3.50
std. Dev.	0.42	0.47	0.42	0.48
Range	2.76	2.55	2.56	2.72

FIGURE 42 Box Plots of FVC% for Exposure Groups

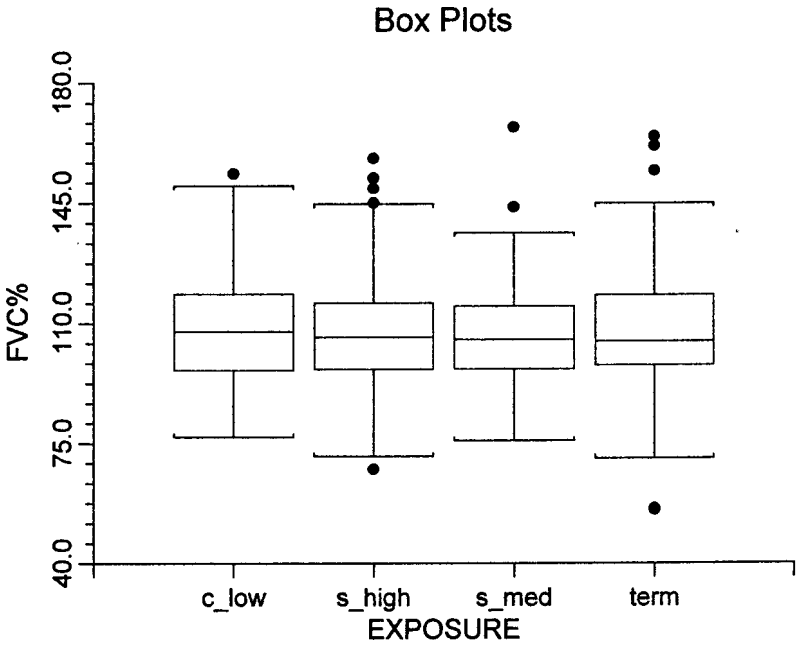


TABLE 60 Descriptive statistics of FVC% for EXPOSURE groups

Exposure groups	S_High	C_Low	S_Medium	Terminated
N	302	198	132	133
Mean	106.47	107.84	106.45	107.09
Median	106.41	108.03	105.71	105.15
std. Dev.	14.68	15.03	14.17	17.97
Range	90.49	76.68	91.34	108.78

FIGURE 43 Box Plots of FEV_1 for Exposure Groups

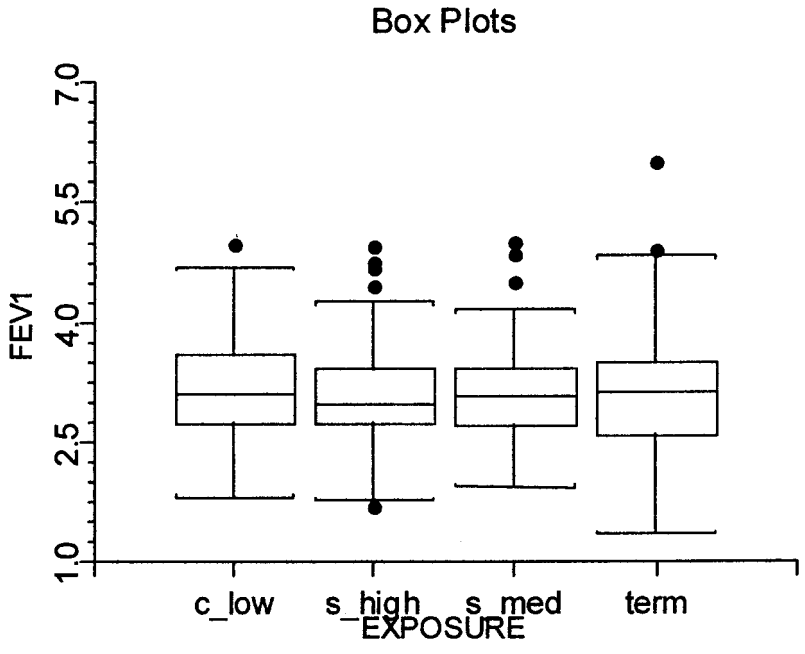


TABLE 61 Descriptive statistics of FEV_1 for EXPOSURE groups

Exposure groups	S_High	C_Low	S_Medium	Terminated
N	302	197	132	132
Mean	3.10	3.18	3.11	3.13
Median	3.03	3.13	3.12	3.16
std. Dev.	0.53	0.62	0.55	0.70
Range	3.26	3.16	3.05	4.65

FIGURE 44 Box Plots of FEV_1 ADJUSTED for Exposure Groups

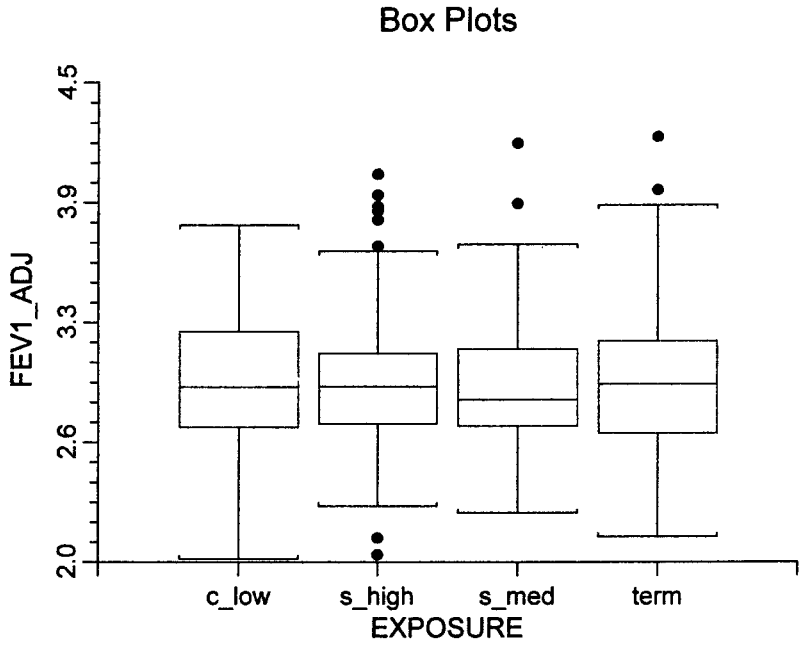


TABLE 62 Descriptive statistics of FEV_1 ADJUSTED for EXPOSURE groups

Exposure groups	S_High	C_Low	S_Medium	Terminated
N	302	198	133	133
Mean	2.92	2.93	2.91	2.93
Median	2.92	2.92	2.86	2.94
std. dev.	0.30	0.34	0.32	0.37
Range	1.98	1.74	1.93	2.09

FIGURE 45 Box Plots of FEV_1% for Exposure Groups

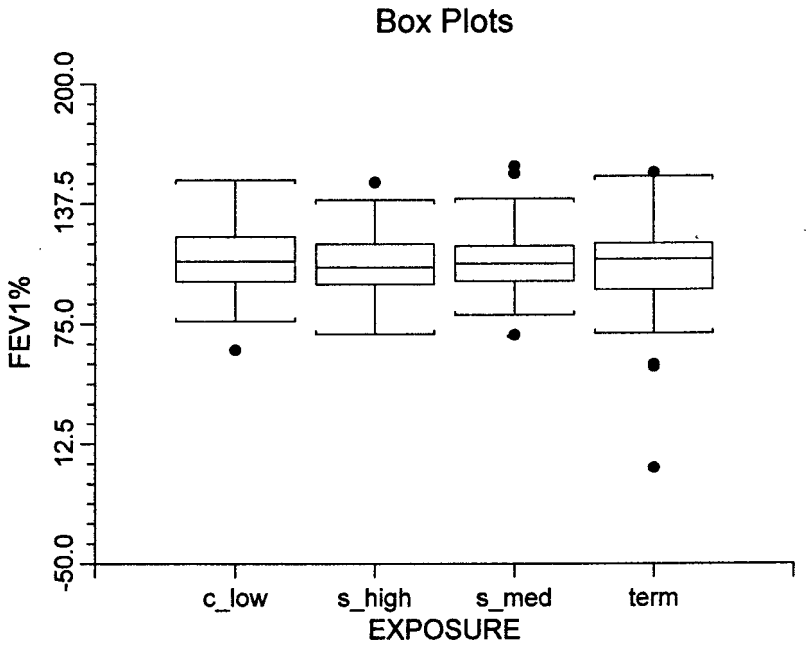


TABLE 63 Descriptive statistics of FEV_1% for EXPOSURE groups

Exposure groups	S_High	C_Low	S_Medium	Terminated
N	302	197	132	133
Mean	106.03	108.29	106.95	105.59
Median	105.08	108.29	106.98	109.32
Std. Dev.	14.72	16.43	14.18	20.89
0 Range	78.84	88.35	87.82	153.75

FIGURE 46 Box Plots of FEV_1/FVC for Exposure Groups

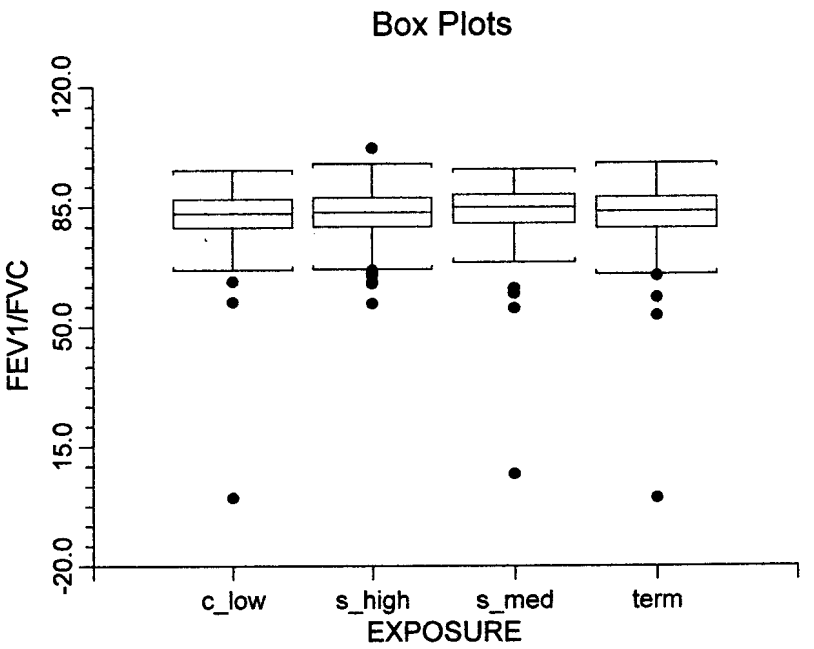


TABLE 64 Descriptive statistics of FEV_1/FVC for EXPOSURE groups

Exposure groups	S_High	C_Low	S_Medium	Terminated
N	302	198	133	133
Mean	82.92	82.15	83.34	82.23
Median	83.72	83.44	85.25	84.06
Std. Dev.	6.81	8.88	9.95	10.43
Range	45.34	95.72	96.12	97.85

FIGURE 47 Box Plots of FEV_1/FVC ADJUSTED for Exposure Groups

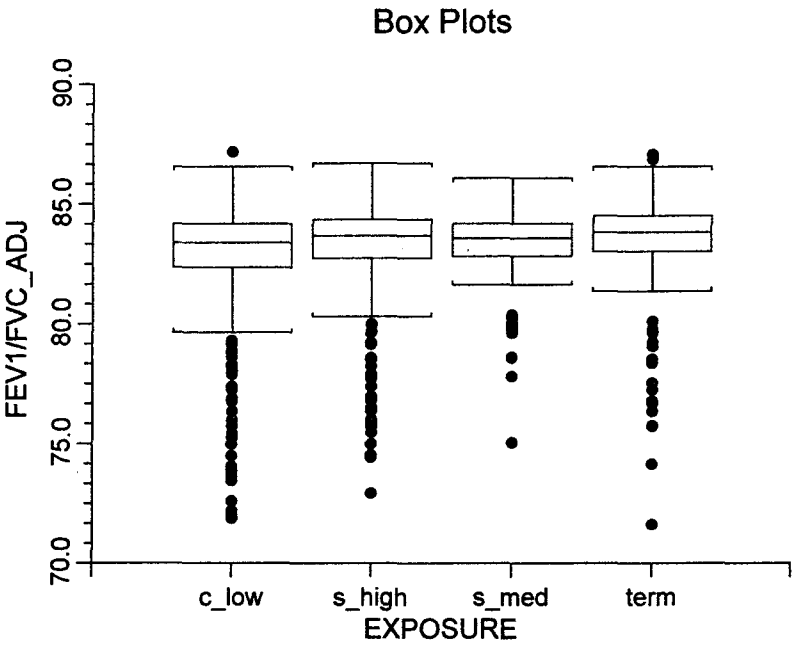


TABLE 65 Descriptive statistics of FEV_1/FVC_ADJUSTED for EXPOSURE groups

Exposure groups	S_High	C_Low	S_Medium	Terminated
N	302	198	133	133
Mean	83.03	82.30	83.31	83.15
Median	83.73	83.45	83.63	83.88
Std. dev.	2.45	3.27	1.58	2.61
Range	13.78	15.29	11.04	15.44

FIGURE 48 Box Plots of FEV_1/FVC% for Exposure Groups

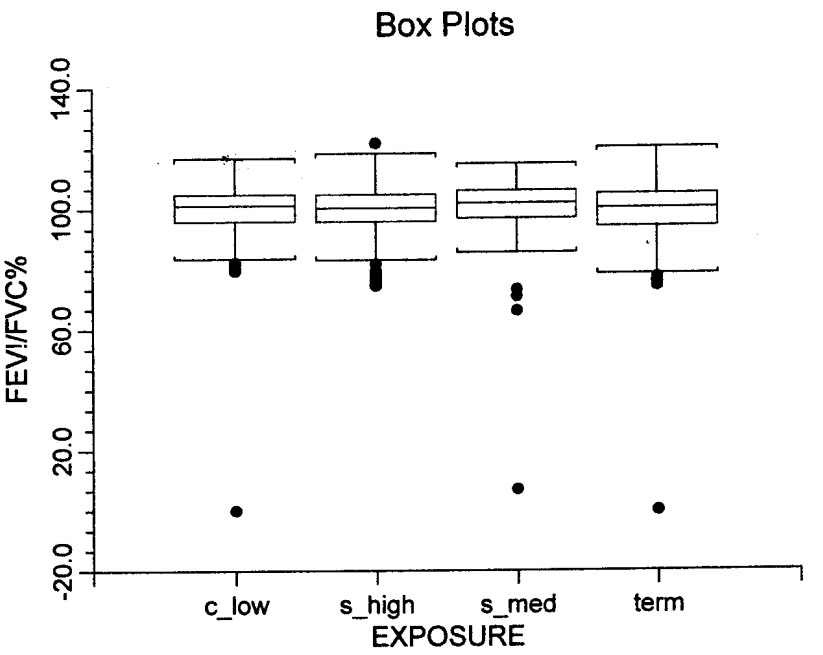


TABLE 66 Descriptive statistics of FEV_1/FVC% for EXPOSURE groups

Exposure groups	S_High	C_Low	S_Medium	Terminated
N	302	198	133	133
Mean	99.85	99.86	100.11	98.93
Median	100.72	101.66	102.34	100.66
Std. dev.	7.61	10.28	11.38	12.30
Range	47.30	116.93	108.09	120.27

FIGURE 49 Box Plots of FEF_{50} for Exposure Groups

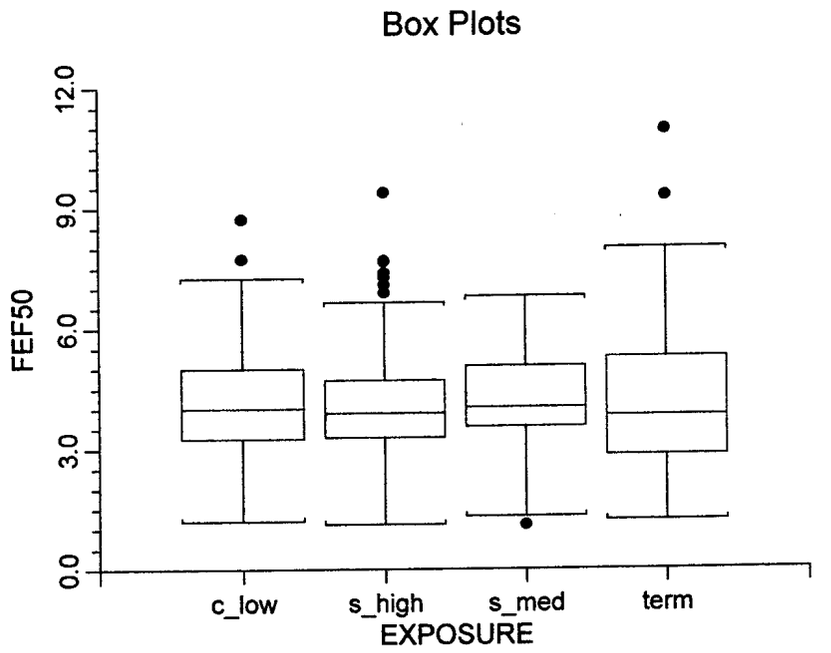


TABLE 67 Descriptive statistics of FEF_{50} for EXPOSURE groups

Exposure groups	S_High	C_Low	S_Medium	Terminated
N	302	198	132	133
Mean	4.05	4.07	4.19	4.19
Median	3.93	4.04	4.08	3.86
Std. Dev.	1.23	1.31	1.13	1.77
Range	8.26	7.53	5.69	9.71

FIGURE 50 Box Plots of FEF_{50} ADJUSTED for Exposure Groups

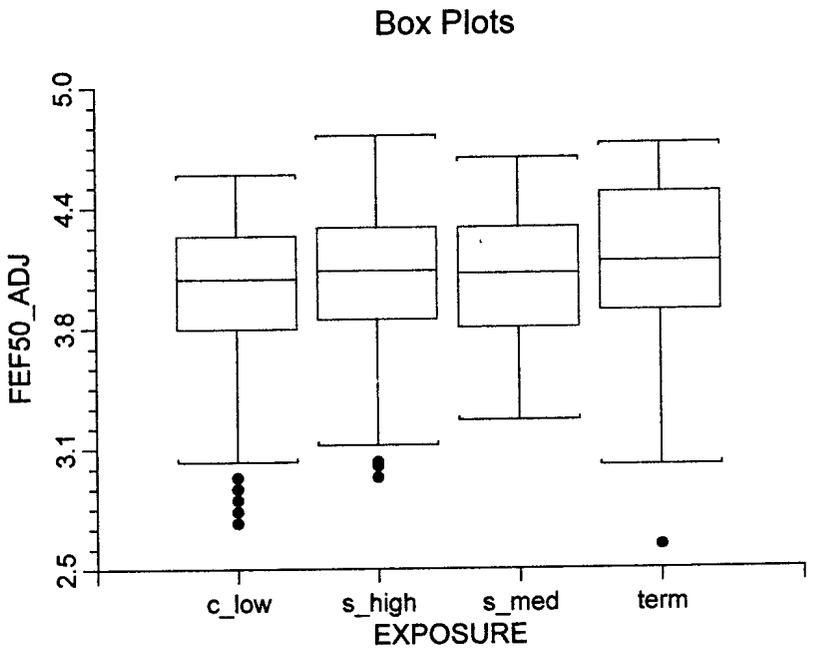


TABLE 68 Descriptive statistics of FEF_{50} ADJUSTED for EXPOSURE groups

Exposure groups	S_High	C_Low	S_Medium	Terminated
N	302	198	133	133
Mean	4.02	3.94	4.00	4.07
Median	4.05	4.01	4.04	4.10
Std. Dev.	0.36	0.44	0.36	0.43
Range	1.77	1.81	1.36	2.08

FIGURE 51 Box Plots of FEF_{50}% for Exposure Groups

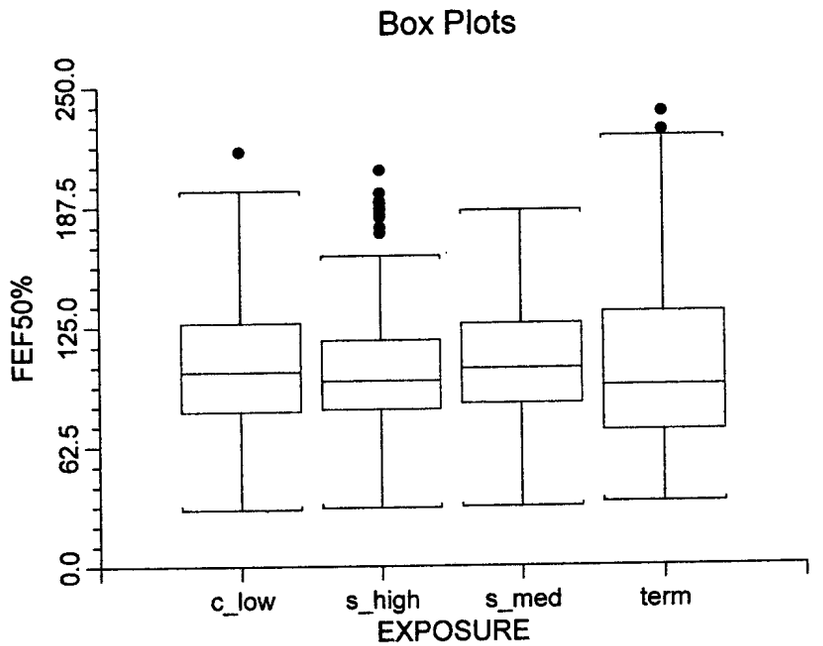


TABLE 69 Descriptive statistics of FEF_{50}% for EXPOSURE groups

Exposure groups	S_High	C_Low	S_Medium	Terminated
N	302	198	132	133
Mean	101.21	103.98	105.21	103.45
Median	97.41	102.09	103.82	94.69
Std. Dev.	30.48	33.23	29.23	43.64
Range	175.77	186.54	154.31	202.86

FIGURE 52 Box Plots of FEF_{75} for Exposure Groups

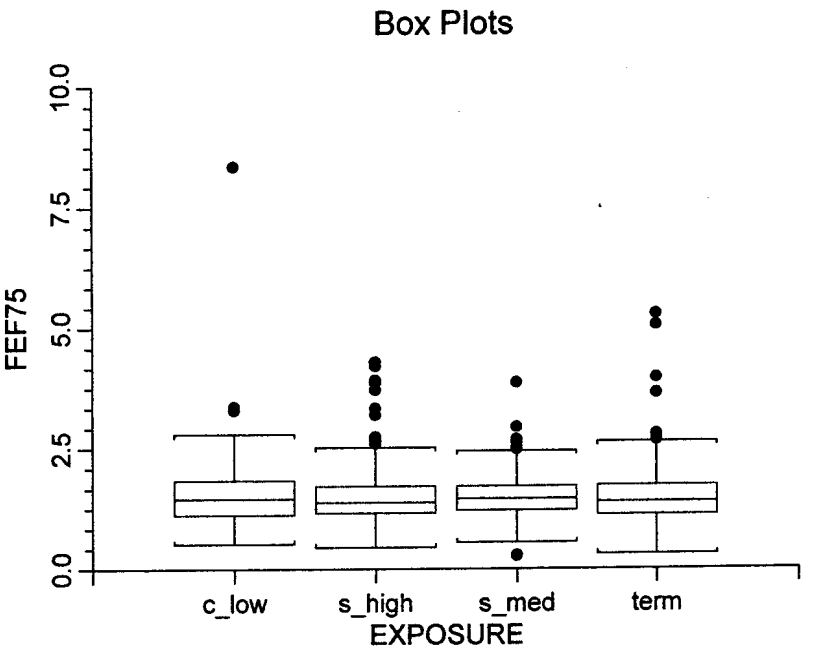


TABLE 70 Descriptive statistics of FEF_{75} for EXPOSURE groups

Exposure groups	S_High	C_Low	S_Medium	Terminated
N	302	198	132	132
Mean	1.50	1.56	1.53	1.55
Median	1.41	1.49	1.49	1.42
Std. Dev.	0.57	0.72	0.51	0.77
Range	3.85	7.83	3.6	4.98

FIGURE 53 Box Plots of FEF_{75} ADJUSTED for Exposure Groups

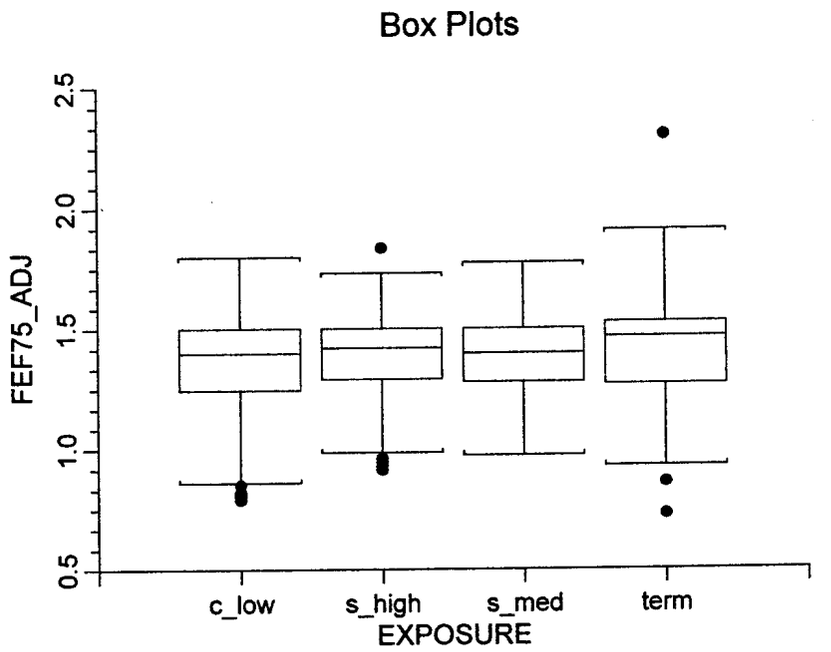


TABLE 71 Descriptive statistics of FEF_{75} ADJUSTED for EXPOSURE groups

Exposure groups	S_High	C_Low	S_Medium	Terminated
N	302	198	133	133
Mean	1.39	1.35	1.39	1.40
Median	1.43	1.40	1.40	1.47
Std. Dev.	0.17	0.22	0.18	0.22
Range	0.92	1.01	0.80	1.57

FIGURE 54 Box Plots of FEF_{75}% for Exposure Groups

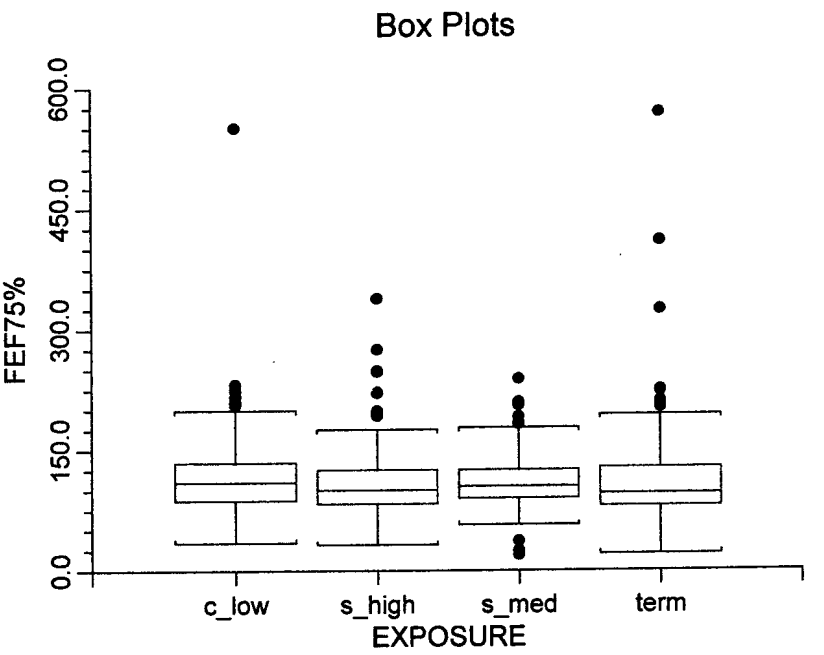


TABLE 72 Descriptive statistics of FEF_{75}% for EXPOSURE groups

Exposure groups	S_High	C_Low	S_Medium	Terminated
N	302	198	132	132
Mean	108.41	116.33	110.69	112.73
Median	102.41	111.66	106.92	97.97
Std. Dev.	39.27	49.70	35.41	65.66
Range	307.02	516.05	219.18	548.41

FIGURE 55 Box Plots of PEFR for Exposure Groups

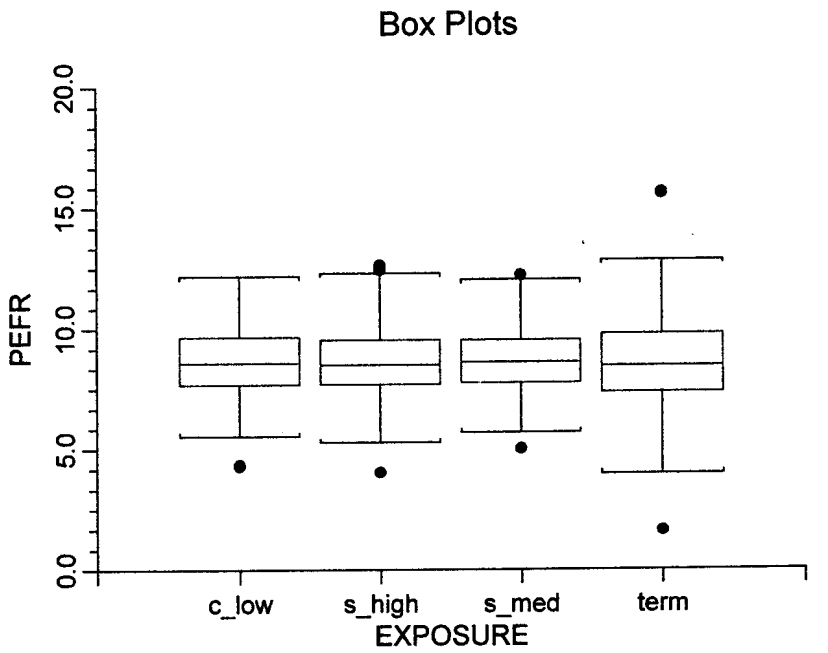


TABLE 73 Descriptive statistics of PEFR for EXPOSURE groups

Exposure groups	S_High	C_Low	S_Medium	Terminated
N	302	198	132	133
Mean	8.67	8.60	8.63	8.55
Median	8.56	8.64	8.67	8.50
Std. Dev.	1.39	1.48	1.32	2.10
Range	8.59	7.88	7.2	14.01

FIGURE 56 Box Plots of PEFR ADJUSTED for Exposure Groups

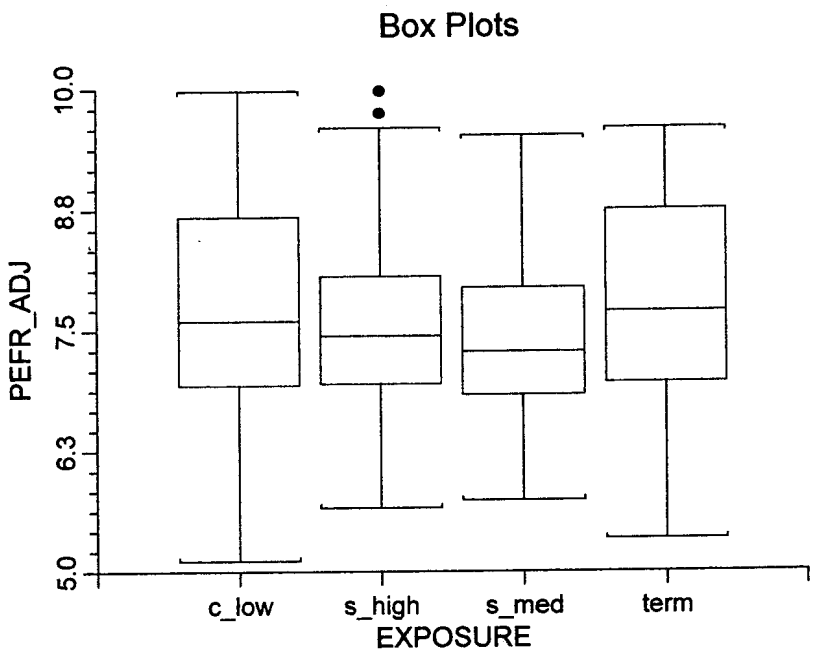


TABLE 74 Descriptive statistics of PEFR_ADJUSTED for EXPOSURE groups

Exposure groups	S_High	C_Low	S_Medium	Terminated
N	302	198	133	131
Mean	7.56	7.68	7.40	7.68
Median	7.46	7.61	7.29	7.71
Std. Dev.	0.86	1.02	0.86	0.98
Range	4.31	4.87	3.78	4.26

FIGURE 57 Box Plots of PEFR% for Exposure Groups

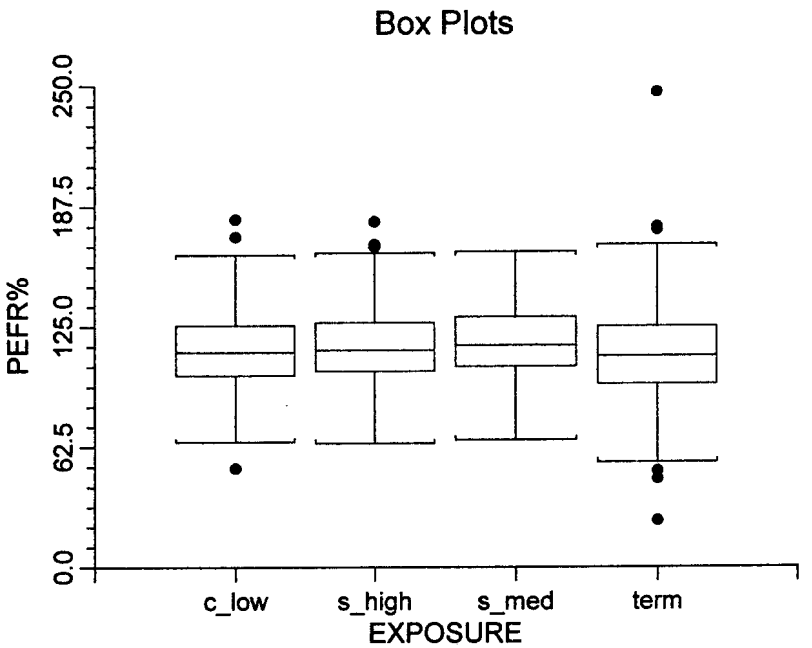


TABLE 75 Descriptive statistics of PEFR% for EXPOSURE groups

Exposure groups	S_High	C_Low	S_Medium	Terminated
N	302	198	132	131
Mean	115.62	113.23	117.36	111.34
Median	113.41	112.33	115.97	110.39
Std. Dev.	19.69	20.38	17.69	27.04
Range	115.26	129.59	97.77	222.21

FIGURE 58 Box Plots of FIVC for Exposure Groups

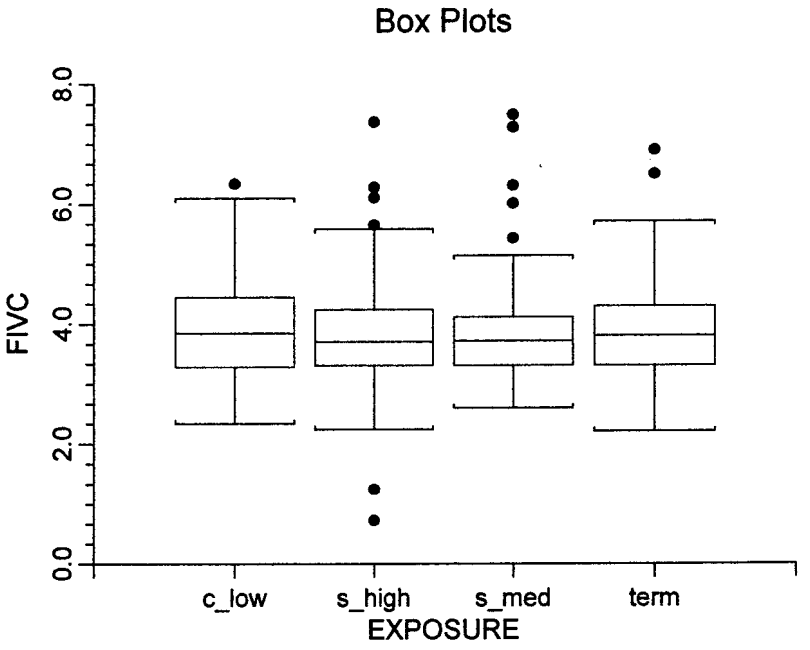


TABLE 76 Descriptive statistics of FIVC for EXPOSURE groups

Exposure groups	S_High	C_Low	S_Medium	Terminated
N	295	194	129	129
Mean	3.82	3.94	3.81	3.86
Median	3.73	3.87	3.74	3.83
Std. Dev.	0.75	0.83	0.83	0.81
Range	6.64	4	4.89	4.69

TEST FOR SIGNIFICANT DIFFERENCES

Two independent groups (group 1 vs group 2) were created and significant differences were tested by means of T-tests (only the significant differences are listed).

FVC%

Group 1	Group 2	t-value	p-value
Ctrl_b	ctrl_c	-2.5952	0.010265*
Ctrl_b	stu_m	-2.2220	0.027567*
Ctrl_b	t_c	-2.1183	0.035778*
Ctrl_c	stu_b	3.1493	0.001636
Ctrl_c	t_b	2.4840	0.014303*
Stu_b	stu_m	-2.8313	0.004635
Stu_b	t-c	-2.4394	0.014710*
Stu_m	t_b	2.1415	0.034130*
t_b	t_c	-2.0194	0.045999*

FEV_1%

Group 1	Group 2	t-value	p-value
Ctrl_b	ctrl_c	-2.4765	0.014236*
Ctrl_b	stu_b	3.2360	0.001212
Ctrl_c	stu_c	2.1706	0.032597*
Ctrl_c	t_b	2.2656	0.025185*
Ctrl_c	t_m	2.5257	0.014032*
Stu_b	t_c	-1.9788	0.047836*
Stu_b	t_m	2.1268	0.033438*

FEV_1/FVC%

Group 1	Group 2	t-value	p-value
Ctrl_b	t_m	2.9117	0.004111
Ctrl_c	stu_m	2.3932	0.019043*
Ctrl_c	t_m	2.5838	0.012064*
Stu_b	stu_m	2.7159	0.006609
Stu_b	t_m	4.3230	0.000015
Stu_m	t_b	-2.9585	0.003683
t_b	t_m	3.5428	0.000578

FEF_{50}%

Group 1	Group 2	t-value	p-value
Ctrl_c	stu_m	2.5948	0.011256*
Ctrl_c	t_m	2.4940	0.015224*
Stu_b	stu_m	2.3370	0.019438*

Stu_b	t_m	2.4692	0.013540*
Stu_m	t_c	-2.0780	0.042070*

FEF_{75}%

Group 1	Group 2	t-value	p-value
ctrl_b	t_m	2.5770	0.010875
ctrl_c	stu_b	2.0333	0.042025
ctrl_c	stu_c	2.5666	0.011922
ctrl_c	stu_m	2.4356	0.017089
ctrl_c	t_m	3.8104	0.000314
stu_b	t_m	2.9888	0.002801
t_b	t_m	2.0309	0.044659
t_c	t_m	2.5078	0.016002

PEFR%

Group 1	Group 2	t-value	p-value
ctrl_b	ctrl_c	5.4903	0.000000
ctrl_b	ctrl_m	3.9016	0.000142
ctrl_b	stu_c	5.1496	0.000001
ctrl_b	stu_m	5.7084	0.000000
ctrl_b	t_c	2.8502	0.004976
ctrl_b	t_m	4.5071	0.000013
ctrl_c	stu_b	-6.6172	0.000000
ctrl_c	t_b	-3.2501	0.001480
ctrl_m	stu_b	-4.6000	0.000004
ctrl_m	t_b	-2.2179	0.028639*
stu_b	stu_c	6.3201	0.000000
stu_b	stu_m	6.7971	0.000000
stu_b	t_c	3.4729	0.000515
stu_b	t_m	5.3657	0.000000
stu_c	t_b	-2.9446	0.003796
stu_m	t_b	-3.3516	0.001057
t_b	t_m	2.6712	0.008705

PIFR%

Group 1	Group 2	t-value	p-value
ctrl_b	t_b	3.0070	0.002639
ctrl_c	stu_m	-2.0392	0.044773
stu_b	t_b	2.3490	0.018824
stu_c	t_b	2.4204	0.016835
stu_m	t_b	2.9498	0.003978
t_b	t_m	-2.4891	0.014319

* These results will not be significant if all pairs are tested as the significance level will change due to multiple comparison testing.

ALTHOUGH ALL COMPARISONS WERE TESTED THE ONLY SIGNIFICANT DIFFERENCES FOR PREDICTED MEASUREMENTS AND DEMOGRAPHIC VARIABLES WERE THE FOLLOWING:

FEF75%
EXPOSURE S_HIGH / EXPOSURE C_LOW t-value = -1.9828 p-value = 0.047

PEFR%

EXPOSURE S_MED / TERMINATED GROUP t-value = 2.1395 p-value = 0.032

5.4 PHASE IV – A CASE-CONTROLLED STUDY OF THE RESPIRATORY HEALTH OF URANIUM WORKERS (AFTER 23 YEARS OF EXPOSURE TO URANIUM/SILICA DUST)

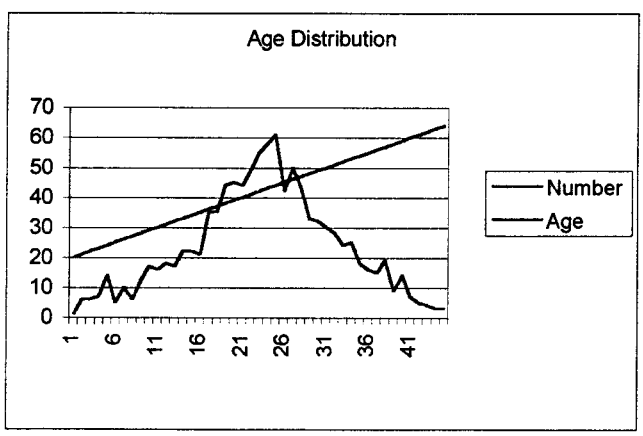
5.4.1 Introduction

Latency is defined as the time from the onset of exposure to measurable outcome. Latency effects are an important factor is assessing the occurrence of abnormalities in exposed workers. A possible reason for our non-detection of abnormalities in the previous study could be a function of latency. For this reason another study was designed to address the potential problem of latency.

5.4.2 Study population

Only a relatively small number of workers exceeded 23 years of service.

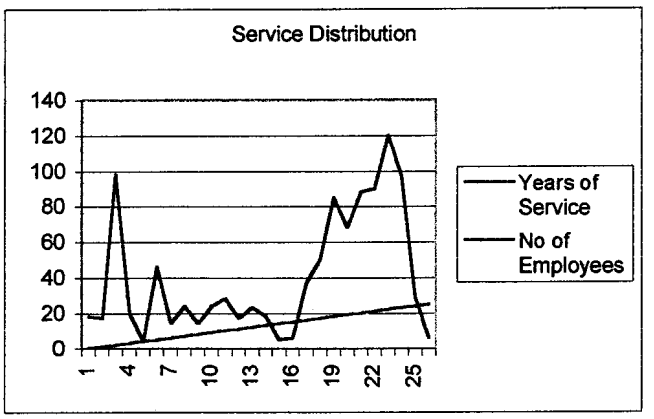
Graph 4 – Age Distribution



Only a total of 174 employees exceeded 23 years of service (these included 12 ex-employees). Six were women who were excluded from further statistical analysis. Only men were chosen and they were subdivided into exposed and unexposed groups. From 168 male employees a sample of 146 were selected. Six records were incomplete or the data was of an unacceptable standard. Inclusion criteria for the cohort can be summarised as follows:

- Person-years at risk > 23
- males
- personnel and employment records and they wished to participate
- lung function and chest x-ray were of an acceptable standard

Graph 5 – Service Distribution



The study population was sub-divided into an exposed group (N=96=68,6%) and an unexposed group (N=44=31,4%). There were 96 blacks (68,6%), 21 of mixed race (15%) and 23 Caucasians (16.4%). The average age of the group was 48,9 years with the minimum of 39 and a maximum of 65 years. Fifty-five workers (39,3%) were older than 50 years of age and 85 (60,7%) under fifty years of age. The average height was 174cm, (range 154-194cm) with an average weight of 79,77kg (range 40-107kg). Compared with the previous study population, this group was older and weighed on average more.

TABLE 77 – CHARACTERISTICS OF STUDY POPULATION					
Variable	Obs	Mean	Std. Dev	Min	Max
Age	140	48.9	5.881687	39	65
Height	140	174.1	7.133163	154	194
Weight	140	79.77143	16.48123	40	127

5.4.3 Smoking Status

Smoking status was given as: non-smokers = never smokers; ex-smokers = those who stopped for at least one year; current smokers = those who are currently smoking or who stopped for less than one year. The following tables describe the smoking status of the study population in terms of ethnic distribution, exposure, pack years and leucocyte count. The profile of the smokers is also given in terms of height and weight. The number of never-smokers was significantly higher than the smokers and ex-smokers, and the majority of never-smokers were black. The mean peripheral leucocyte count was markedly higher in smokers than in never-smokers and ex-smokers.

TABLE 78 – SMOKING STATUS OF TOTAL POPULATION		
SMOKING	FREQUENCY	PERCENTAGE
Smoke	23	16.43
Ex-Smoke	28	20.00
Never Smoke	89	63.57

TABLE 79 – SMOKING STATUS BY RACE				
RACE	Black	Caucasian	Mixed	Total
Smoke	10	7	6	23
Ex-smoke	8	10	10	28
Never sm	78	6	5	89
Total	96	23	21	140

TABLE 80 – SMOKING STATUS BY EXPOSURE			
SMOKING	Not exposed	Exposed	Total
Smoke	8	15	23
Ex-Smoke	7	21	28
Never Smoked	29	60	89
Total	44	96	140

In order to quantify smoking, pack years were calculated by multiplying the number of cigarettes smoked per day by the number of years smoked and the total was then divided by 20.

TABLE 81 – SUMMARY OF PACK YEARS			
Smoking	Mean	Std Dev	Freq
Smoke	18.652174	7.7495378	23
Ex-Smoke	10.428571	7.9741646	28
Never-Smoke	0.02247191	0.21199958	89
Total	5.1642857	8.6312222	140

TABLE 82 – PERIPHERAL LEUCOCYTE COUNT PER SMOKING CATEGORY			
Smoking	Mean	Std Dev	Freq
Smoke	6.5608696	2.0431124	23
Ex-Smoke	6.3928572	1.9970216	28
Never Smoked	5.5779776	1.6348918	89
Total	5.9024286	1.8207457	140

The mean age, height and weight were determined for the various smoking categories and it was noted that the ex-smokers were both taller and heavier than the smokers and never-smokers. The study population

thus included a majority of non-smoking black workers who did not differ much from the smokers in terms of age, height and weight.

TABLE 83 – SMOKING CATEGORIES BY AGE		
Smoking	Mean	Std Dev
Smoke	49	4.7290207
Ex-Smoke	49.642857	6.6623002
Never-Smoked	48.640449	5.9318999
Total	48.9	5.8816872

TABLE 84 – SMOKING CATEGORIES BY HEIGHT		
Smoking	Mean	Std Dev
Smoke	172.86957	7.4912333
Ex-Smoke	177.89286	6.5111829
Never-Smoked	173.22472	6.8982093
Total	174.1	7.133163

TABLE 85 – SMOKING CATEGORIES BY WEIGHT		
Smoking	Mean	Std Dev
Smoke	76.347826	19.163433
Ex-Smoke	90.607143	15.251811
Never-Smoked	77.247191	14.798864
Total	79.771429	16.481227

5.4.4 Allergy Status

Allergy status was determined by history, skin prick test or a combination of the two. The number of allergic workers (N=40; 28.57%) compares favourably with the figures obtained from family practice surveys done among the general population of Swakopmund and Arandis (residential areas). Six (4.32%) of the study population were asthmatics. Both the mine clinic and family practice files were investigated to confirm this figure. Forty-four percent of the atopes were under 50 years of age and 34% were over 50.

TABLE 86 – ALLERGY STATUS OF THE STUDY POPULATION		
Allergy	Freq	Percent
Not allergic	100	71.43
Allergic	40	28.57
Total	140	100

TABLE 87– ALLERGY STATUS BY AGE			
Allergy	Under 50	Over 50	Total
Not allergic	59	41	100
Allergic	26	14	40
Total	85	55	140

TABLE 88 – ASTHMA BY ALLERGY		
Asthma	Freq	Percent
No asthma	134	95.68
Asthma	6	4.32
Total	140	100

TABLE 89 – ASTHMA BY AGE			
Asthma	Under 50	Over 50	Total
No asthma	81	52	133
Asthma	4	2	6
Total	85	54	139

Fifty-three percent of smokers, 21% of the ex-smokers and 43% of the never-smokers were allergic. Smoking is associated with sensitisation and this could be the reason why such a high percentage of smokers were allergic. It is difficult to explain the 43% of atopes in the never-smoking category. It could be a function of exposure (63% non-smokers were exposed) and because allergic individuals tend to refrain from smoking.

TABLE 90 – ALLERGY BY SMOKING				
	Smoking			
Allergy	Smoke	Ex-Smoke	Never-Smoke	Total
Not allergic	15	23	62	100
Allergic	8	5	27	40
Total	23	28	89	140

TABLE 91 – ASTHMA BY SMOKING				
	Smoking			
Asthma	Smoke	Ex-Smoke	Never-Smoke	Total
No asthma	23	26	84	133
Asthma	0	1	5	6
Total	23	27	89	139

None of the asthmatics smoked whilst 3.8% of the ex-smokers were asthmatics and 5.95% of the never-smokers were asthmatics. Reasons for these differences remain speculative but could be explained on the basis that asthmatics usually do not smoke. (For obvious reasons.)

5.4.5 Results of Chest Radiographs

One hundred and twenty four (88.6%) of the chest radiographs were within normal limits. One case of pneumoconiosis (silicosis 1/1) (0.71%) was confirmed by the MBOD. One case of lung cancer was found in an ex-employee who was a smoker with more than 23 years of service. Thirteen cases with radiological features of pulmonary tuberculosis (9.29%) were found and confirmed. Surprisingly two cases of sarcoidosis were identified (1.43%). Both these cases were found in smokers or ex-smokers.

TABLE 92 – RESULTS OF X-RAY ANALYSIS		
Chest X-Ray	Frequency	Percentage
Normal	124	88.57
Pneumoconiosis	1	0.71
Cancer	1	0.71
Tuberculosis	13	9.29
Sarcoidosis	2	1.43
Total	141	100.00

TABLE 93 - RESULTS OF CHEST X-RAY ANALYSIS ACCORDING TO SMOKING CATEGORY					
SMOKING	normal	cancer	TB	sarcoidos	Total
Smoke	19	0	3	1	23
ex-smoke	26	0	1	1	28
never sm	79	1	9	0	89
Total	124	1	13	2	140

5.4.6 Results of lung function analysis

In this cross-sectional survey several lung function parameters (FVC, FEV_1, FEV_1/FVC, FEF_{50} and FEF75) and several outcome parameters (COPD, SAD, abnormality based on the observed lung function values) were studied in relation to: exposure time (less than 23 years of employment, employment of 23 years or longer) and: smoking history (never smoked, ex-smoker, current smoker). Categorical variables were summarised using frequencies and percentages while continuous variables (height, weight and lung functions) were summarised using descriptive statistics, eg mean and standard deviation and box plots. Measured values of lung function parameters were compared with predicted values of both Schoenberg *et al* and De Kock *et al*. The criteria for abnormal lung functions were:

FVC $\leq$ 75% of predicted

$FEV_1 \leq$ 75% of predicted

FVC $\leq$ 75% of predicted
$FEV_1 \leq$ 75% of predicted
FEV_1 ratio $\leq$ 0.75 (under 30 years of age)
$\leq$ 0.70 (between to and 59 years of age)
$\leq$ 0.65 (older than 60 years)
$FEF_{50} \leq$ 60% of predicted with a normal FVC
FEF75 $\leq$ 60% of predicted with a normal FVC

The criteria for chronic obstructive pulmonary disease (COPD) was an FEV_1 or FEV_1 ratio of less than 75% of predicted, and the criteria for small airways disease (SAD) was a FEF_{50} or FEF_{75} of less than 60% of predicted (Schoenberg *et al* and De Kock *et al*) in the presence of a normal FVC. Table 93 indicates the percentage abnormal lung functions found among the total study population. The trends of abnormality detected by using either of the two prediction formulae are similar. There is however a marked difference between the total percentages detected. A small number of abnormal FVC and FEV_1's were identified. The number of abnormal FEV_1 ratios, FEF_{50} and FEF_{75}'s were significantly higher. It could indicate that these parameters are more sensitive indicators of early lung abnormalities.

TABLE 94 - PERCENTAGE ABNORMAL LUNG FUNCTIONS OF TOTAL POPULATION USING SCHOENBERG *et al* AND DE KOCK *et al* PREDICTION FORMULAE

Lung Function Parameter	% Abnormal Schoenberg *et al*	% Abnormal De Kock *et al*
FVC	2.86%	0%
FEV_1	7.86%	4.29%
FEV_1%	18.57%	-
FEF_{50}	22.14%	19.29%
FEF_{75}	37.86%	35.00%

The study population was further subdivided according to smoking category. The percentage abnormalities were consistently and significantly higher in smokers than in ex- and never-smokers. The choice of reference value has a pronounced effect on the number of abnormal values. With the De Kock *et al* reference values a much lower percentage of abnormalities is found in smokers, ex-smokers and never-smokers. Although marked differences were found between the results of the two sets of reference values at FVC and FEV_1 level, a much closer correlation between FEF_{50} and FEF_{75} was found. No difference between FEV_1 values for either Schoenberg *et al* and De Kock *et al* were found in never-smokers. We believe that the de Kock *et al* reference values (for reasons discussed in previous chapters) are more appropriate for this specific study population. The high percentage of abnormal flows at 50% and 75% of vital capacity is consistent with previous findings and could prove to be a sensitive indicator of early lung function impairment.

TABLE 95 - ABNORMAL LUNG FUNCTION VALUES IN VARIOUS SMOKING CATEGORIES

	Smokers	Ex-Smokers	Never-Smokers
FVC (S)	13%	3.5%	0%
FVC (D)	0%	0%	0%
FEV_1 (S)	26%	14.28%	1.12%
FEV_1 (D)	1.3%	7.14%	1.12%
FEV_1%	47.8%	25%	8.9%
FEF_{50} (S)	47.8%	32.1%	12.3%
FEF_{50} (D)	39.1%	28.5%	11.2%
FEF_{75} (S)	69.6%	50%	25.8%
FEF_{75} (D)	65.2%	46.4%	28.3%

There are marked differences between COPD and SAD in the various smoking categories. A significant number (23% to 26%) of SAD is evident among never-smokers which could indicate adverse effects of environmental exposure.

TABLE 96 - COPD AND SAD IN VARIOUS SMOKING CATEGORIES OF THE TOTAL POPULATION (PREDICTION EQUATIONS ACCORDING TO SCHOENBERG *ET AL* AND DE KOCK *ET AL*)				
Smoking Status	COPD Schoenberg *et al*	COPD De Kock *et al*	SAD Schoenberg *et al*	SAD De Kock *et al*
Smokers	30.43%	17.39%	68.42%	65.21%
Ex-Smokers	17.8%	7.14%	46.15%	50.0%
Never Smoke	1.12%	2.2%	26.1%	23.5%

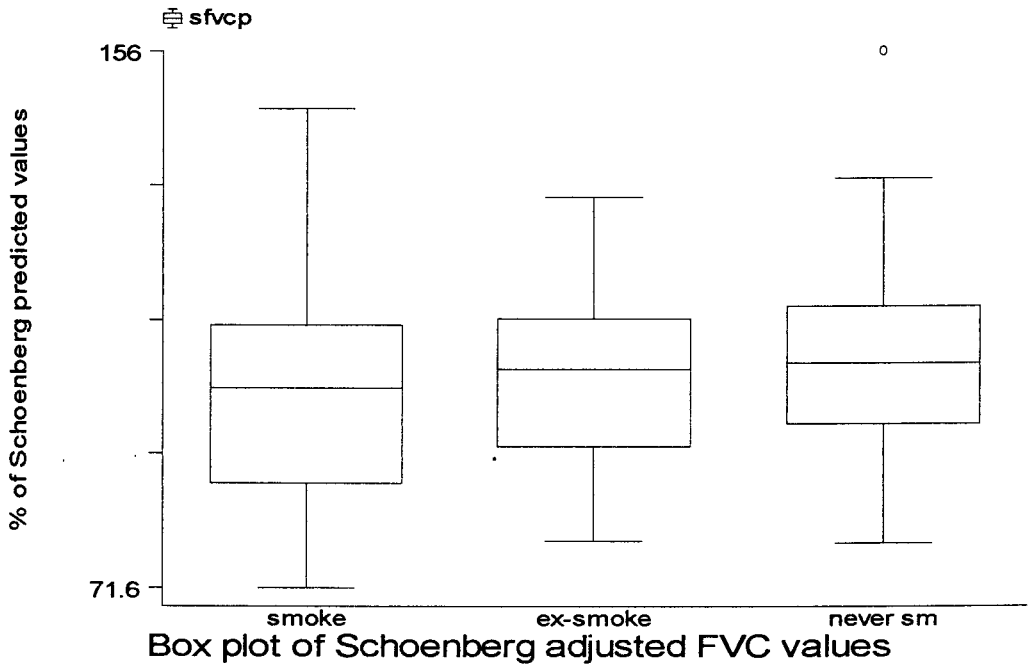
5.4.7 THE COMPARISON OF SMOKING CATEGORIES WITH LUNG FUNCTION VARIABLES

In the following tables the smoking history categories were compared with respect to the lung function parameters in a one-way analysis of variants. Particular differences between the smoking history categories were tested for employing the restricted student T and correcting for multiplicity according to the Bonferroni method. The P values on the right hand side of the columns indicate whether the smoking category differs from each other in relation to the lung function parameter measured (as a predicted percentage of the relevant predictive table used).

Significant smoker-response association was found for all parameters except FVC. It could indicate that cigarette smoking is causally related to the development of COPD and SAD. The prevalence of COPD was significantly higher in smokers and, to a lesser extent in ex-smokers than in non-smokers. There is also clear evidence that the lung function values of ex-smokers is significantly better than that of smokers. It could indicate that cigarette smoking is causally related to the development of COPD and SAD (in combination with dust exposure).

TABLE 97 - SUMMARY OF SCHOENBERG FVC PREDICTED					
SMOKING	Mean	Std. Dev.	Freq.	P Val	0.3729
Smoke	101.75652	19.54235	23	1.000	
ex-smoke	99.933572	23.921885	27	1.000	
never sm	106.38876	14.373456	89	0.603	
Total	104.33671	17.609681	139		

Figure 59



Box plot of Schoenberg adjusted FVC values

TABLE 98 - SUMMARY OF SCHOENBERG FEV_1 PREDICTED					
SMOKING	Mean	Std. Dev.	Freq.	P Val	0.0012
Smoke	90.413043	16.434673	23	0.660	
ex-smoke	95.439286	16.951988	28	0.96	
never sm	102.23933	13.086701	89	0.002	
Total	98.936428	15.115014	140		

Figure 60

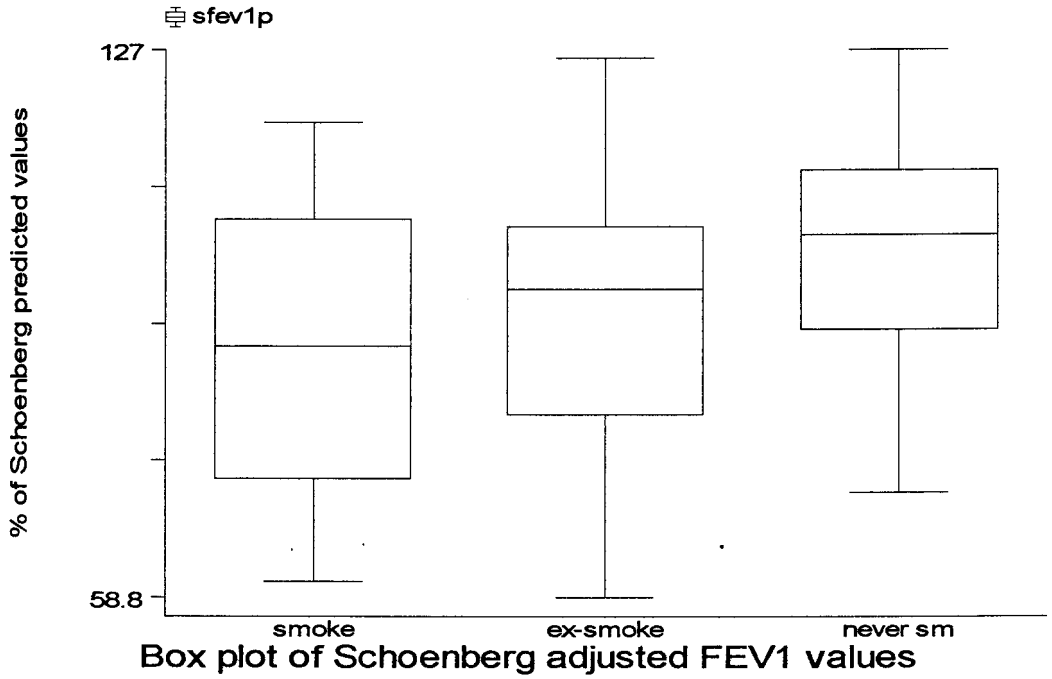
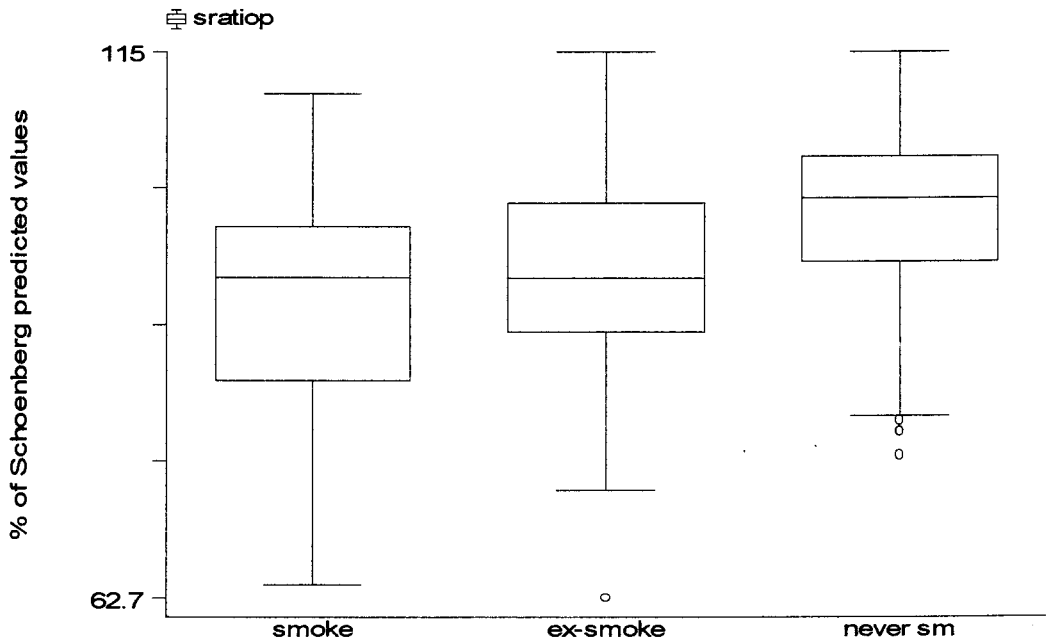


TABLE 99 - SUMMARY OF SCHOENBERG RATIO PREDICTED					
SMOKING	Mean	Std. Dev.	Freq.	P Val	0.0002
Smoke	91.056522	10.961661	23	1.000	
ex-smoke	89.989286	20.171401	28	0.001	
never sm	99.274157	8.1181127	89	0.011	
Total	96.067143	12.568102	140		

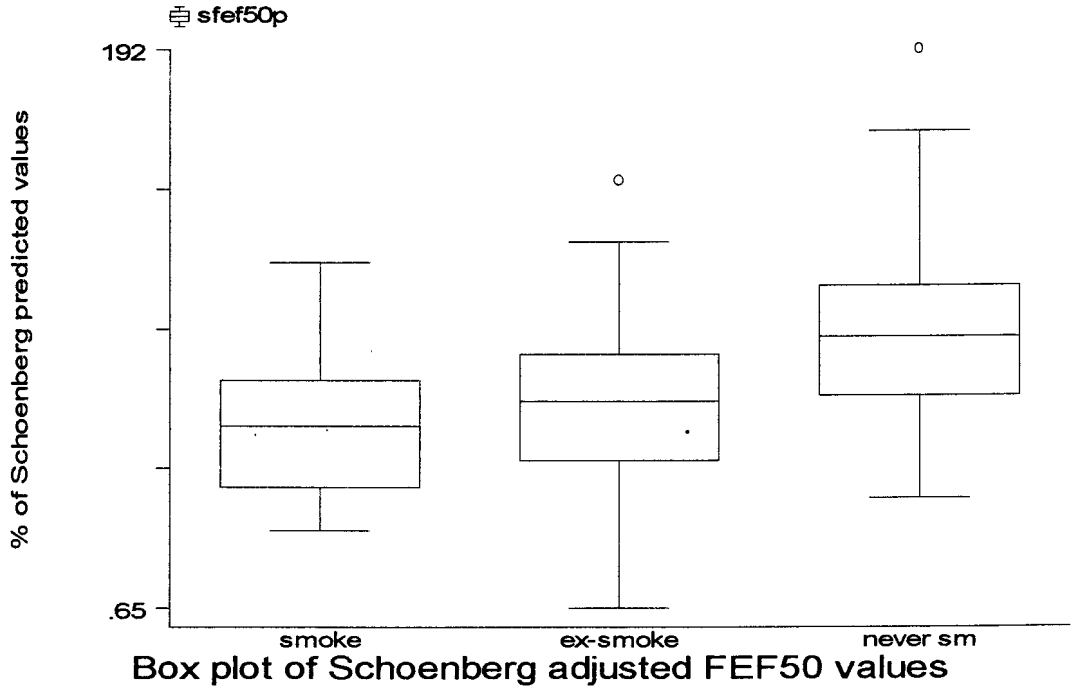
Figure 61



Box plot of Schoenberg adjusted FEV1/FVC values

TABLE 100 - SUMMARY OF SCHOENBERG FEF_{50} PREDICTED					
SMOKING	Mean	Std. Dev.	Freq.	P Val	<0.0001
Smoke	65.83913	26.963961	23	1.000	
ex-smoke	71.623214	30.946326	28	0.002	
never sm	93.503371	28.52472	89	0.000	
Total	84.5825	30.969922	140		

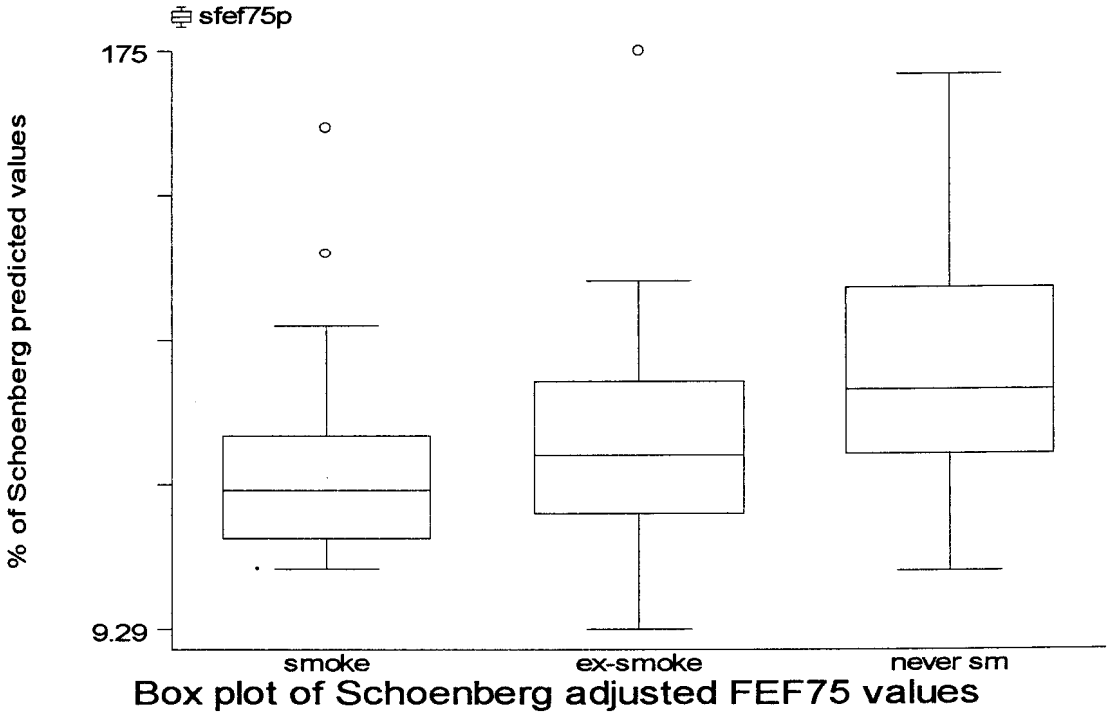
Figure 62



Box plot of Schoenberg adjusted FEF50 values

TABLE 101 - SUMMARY OF SCHOENBERG FEF_{75} PREDICTED					
SMOKING	Mean	Std. Dev.	Freq.	P Val	0.002
Smoke	58.734783	30.832459	23	1.00	
ex-smoke	64.5425	31.852829	28	.009	
never sm	84.844944	30.759537	89	.001	
Total	76.494929	32.74378	140		

Figure 63



Box plot of Schoenberg adjusted FEF75 values

TABLE 102 - SUMMARY OF DE KOCK FVC PREDICTED					
SMOKING	Mean	Std. Dev.	Freq.	P Val	0.4248
smoke	110.19547	21.675968	23	0.951	
ex-smoke	115.0229	18.94357	28	1.000	
never sm	115.37965	15.046152	89	0.590	
Total	114.45661	17.058994	140		

Figure 64

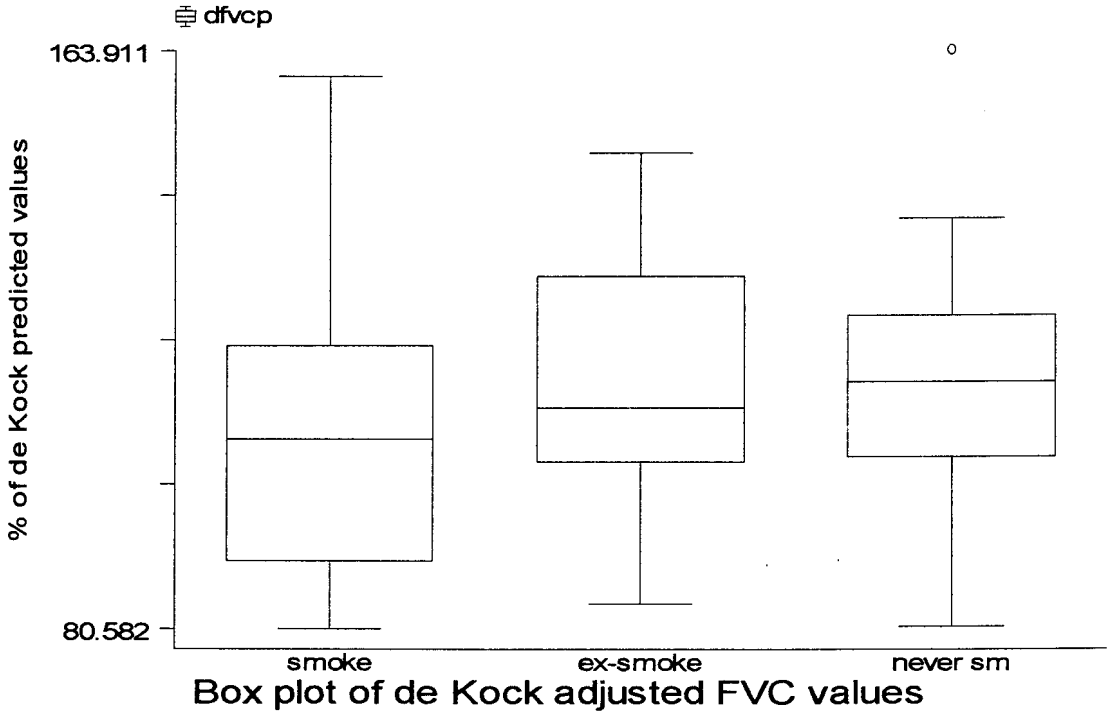
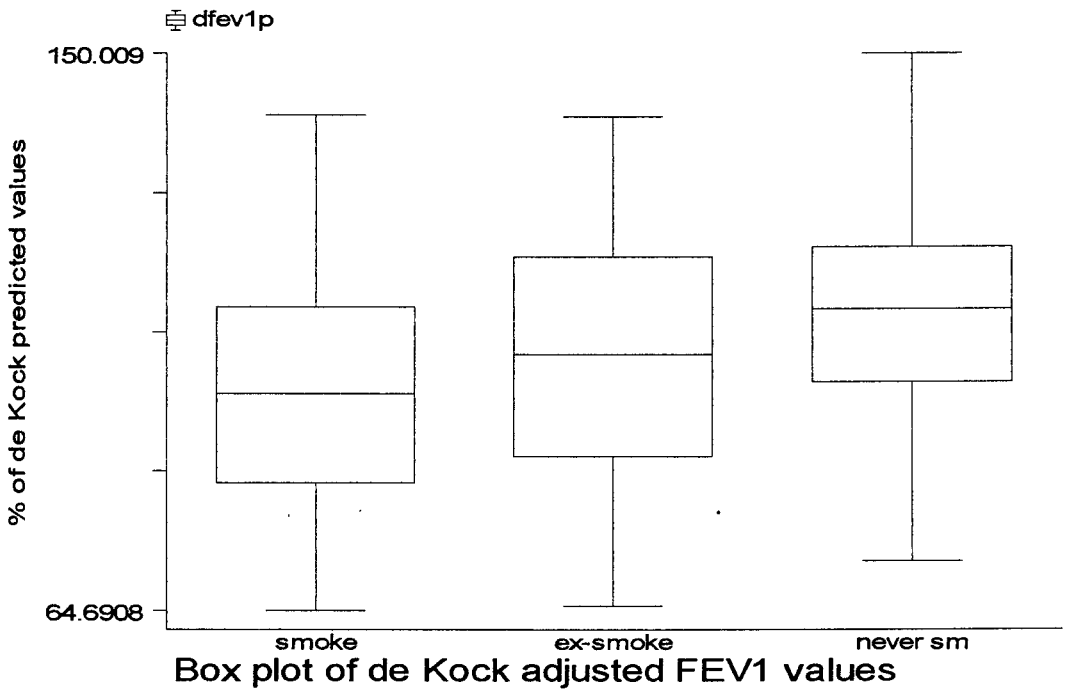


TABLE 103 - SUMMARY OF DE KOCK FEV_1 PREDICTED					
SMOKING	Mean	Std. Dev.	Freq.	P Val	0.0025
Smoke	96.403833	18.400659	23	0.359	
ex-smoke	103.81108	19.946783	28	0.304	
never sm	109.82116	15.275491	89	0.003	
Total	106.41487	17.434976	140		

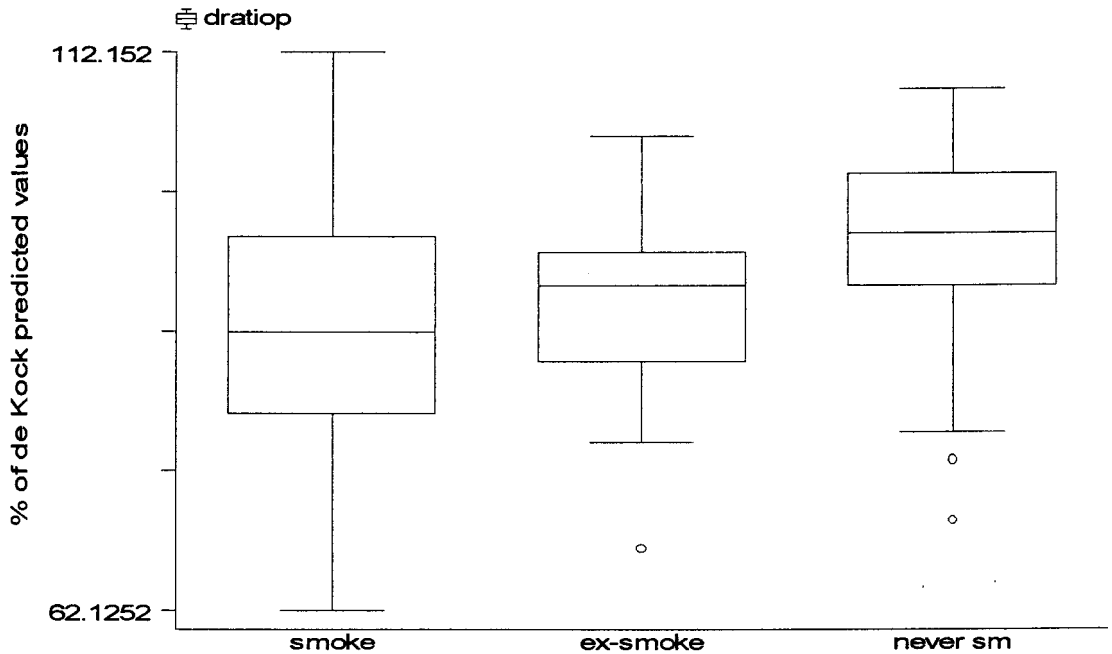
Figure 65



Box plot of de Kock adjusted FEV1 values

TABLE 104 - SUMMARY OF DE KOCK RATIO PREDICTED					
SMOKING	Mean	Std. Dev.	Freq.	P Val	0.0001
Smoke	88.164035	11.125681	23	1.000	
ex-smoke	89.982488	8.07577	28	0.008	
never sm	95.475328	7.4683897	89	0.001	
Total	93.175619	8.7845005	140		

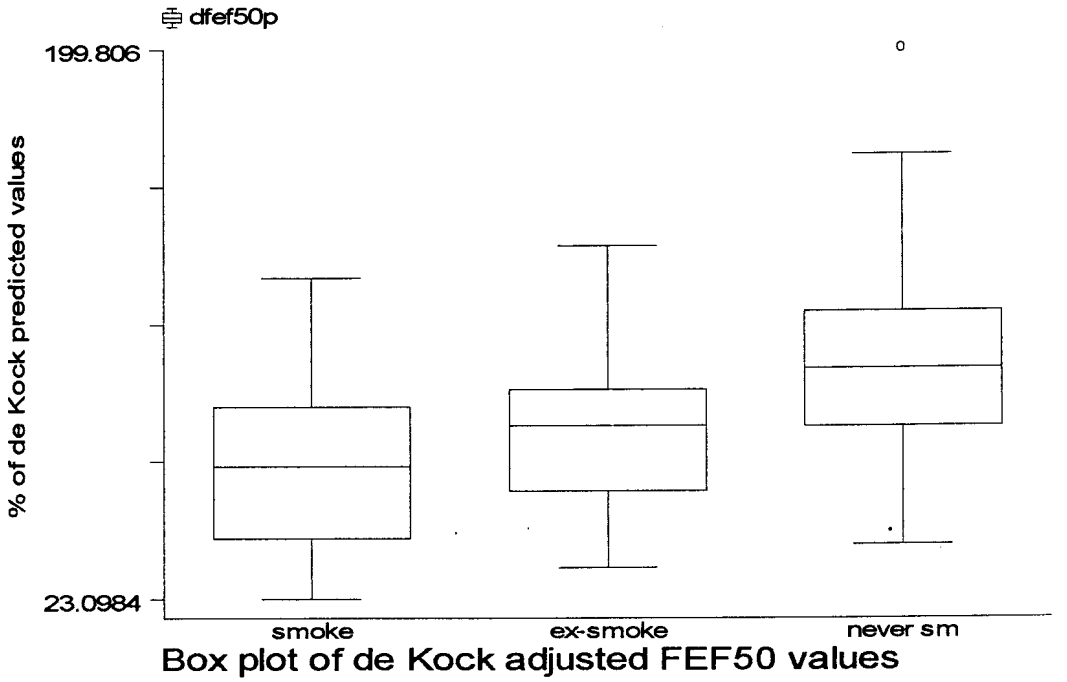
Figure 66



Box plot of de Kock adjusted FEV1/FVC values

TABLE 105 -SUMMARY OF DE KOCK FEF_{50} PREDICTED					
SMOKING	Mean	Std. Dev.	Freq.	P Val	<0.0001
Smoke	67.32048	28.042659	23	0.717	
ex-smoke	76.94382	26.370279	28	0.005	
never sm	97.189661	29.85886	89	0.001	
Total	88.233413	31.199012	140		

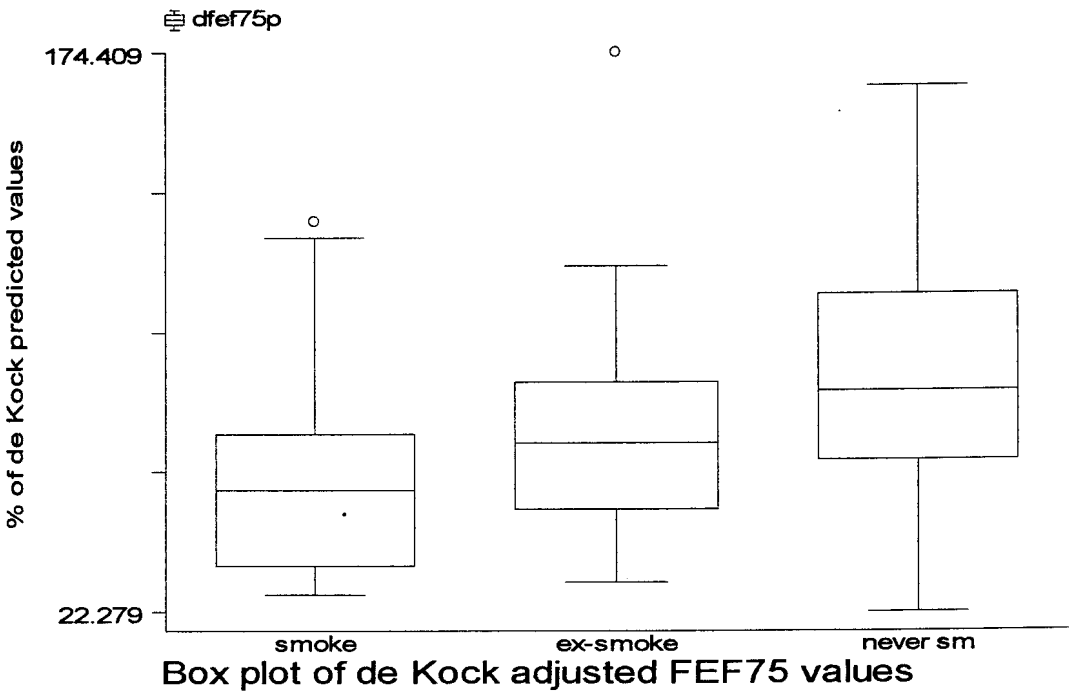
Figure 67



Box plot of de Kock adjusted FEF50 values

TABLE 106 - SUMMARY OF DE KOCK FEF_{75} PREDICTED					
	Mean	Std. Dev.	Freq.	P Val	0.0002
SMOKING	59.104673	29.661998	23	0.541	
ex-smoke	70.787325	29.81401	28	0.048	
never sm	87.062886	31.402245	89	<0.0001	
Total	79.214639	32.509525	140		

Figure 68



Box plot of de Kock adjusted FEF75 values

5.4.7 THE RELATIONSHIP BETWEEN EXPOSURE AND OUTCOME VARIABLES

The risk of exposure (years of employment) on the outcome variables of interest were assessed by considering the odds ratio (risk of poor outcome when exposed to 23 years or more relative to the risk of poor outcome when exposed to less than 23 years in the workplace). When possible, 90% confidence intervals according to Cornfield's method, were calculated for the odds-ratios. Differences between the exposure categories with respect to the proportion of poor outcomes for the respective outcome variables were tested for using Fisher's exact test. The risk that an exposed worker will develop COPD is 2.7 times (Schoenberg *et al*) and 3.38 times (De Kock *et al*) higher than for non-exposed workers. Sixty percent of COPD cases can be directly related to exposure (cigarette smoking and dust), and 53,5% of these cases could have been prevented. An even higher chance for prevention is possible when the De Kock *et al* figures are applied (70% occurred because of exposure and 60% of cases could have been prevented). The diagnosis of COPD is based on the direct measurement of FEV_1, which is the best repeatable and reliable indicator of airflow obstruction. FEV_1 associated abnormalities therefore (as expected) reflect the same relationships with exposure as COPD. The risk that a worker will develop SAD when exposed (controlled for smoking), is surprisingly low (odds-ratio is = 0.9 – 0.95). This "anomaly" could be related to the fact that the diagnosis of SAD is based on a number of variables (FEF_{50} and FEF_{75} and on a normal FVC). Mean mid- and late-forced expiratory flows represent flows at low lung volumes, and small changes have a large effect on the value measured. If values are derived from expirations with a low FVC the value obtained will be falsely elevated. The value of flows at lower lung volumes (FEF_{50} and FEF_{75}) in the presence of an abnormal FEV_1 (COPD) is also of limited value.

Odds-ratios for FEV1 shows a definite relationship with exposure while the other lung parameters measured (FEF50 and FEF75) shows a small but definite increased risk associated with exposure.

TABLE 107 – RELATIONSHIP BETWEEN EXPOSURE GROUPS & OUTCOME VARIABLES FOR THE TOTAL POPULATION ACCORDING TO THE PREDICTED EQUATIONS OF SCHOENBERG ET AL & DE KOCK ET AL (ODDS RATIOS)

COPD S	Exposed	Unexposed	Total	Odds Ratio	90% C I	AttrFrac Ex	Attr Frac Pop
Cases	11	2	13	2.7	.79-9.26	.632	.534
Controls	85	42	127				
COPD D							
Cases	7	1	8	3.4	.66-4.95	.704	.61
Controls	89	43	132				
SAD S							
Cases	32	16	48	.93	.49-1.74	.069	.47
Controls	58	27	85				
SAD D							
Cases	34	16	50	.96	.52-1.78	.040	.027
Controls	62	28	90				

Lung Function Parameter	Exposed	Unexposed	Total	Odds Ratio	90% C I	Attr Frac Ex	Attr Frac Pop
FVC (S)				1.38	.24	.27	.21
Cases	3	1	4				
Controls	93	44	136				
FEV1 (S)				2.17	.62 - 7.50	.53	.44
Cases	9	2	11				
Controls	87	42	129				
FEV1 (D)				2.36	.452	.57	.48
Cases	5	1	6				
Controls	91	42	134				
FEV1 %				1.3	.59 - 2.85	.23	.17
Cases	19	7	26				
Controls	77	37	114				
FEF50 (S)				1.41	.67 - 2.97	.29	.21
Cases	23	8	31				
Controls	73	36	109				
FEF50 (D)				1.77	.78 - 3.99	.44	.34
Cases	21	6	27				
Controls	75	38	113				
FEF75 (S)				1.09	.59 - 2.03	.08	.06
Cases	37	16	53				
Controls	59	28	87				
FEF75 (D)				.96	.49 - 1.7	.08	.06
Cases	33	16	49				
Controls	63	28	91				

Odds ratios for non-smokers were then calculated to evaluate the risk of dust exposure alone. The numbers investigated were small and in some categories no cases were found (which complicated statistical analysis and interpretation). An increased risk for COPD could not be established but there is a 1.16 times greater chance for SAD in exposed groups with a 14% chance that these cases could have been prevented. Once again, the risk to develop abnormal values for FEV_1, FEV ratio, FEF_{50} and FEF_{75} is higher in the exposed group (after controlling for smoking). Results indicate that the level of dust exposure at Rössing, without a confounding for tobacco smoking, is associated with a statistically significant impairment of lung function. Our findings support the literature that has estimated that the effect of dust relative to that of smoking is of smaller magnitude.

TABLE 108 – RALATIONSHIP BETWEEN EXPOSURE GROUPS & OUTCOME VARIABLES FOR NON-SMOKERS ACCORDING TO THE PREDICTED EQUATIONS OF SCHOENBERG ET AL AND DE KOCK ET AL (ODDS RATIOS)

Lung Function	Exposed	Unexposed	Total	Odds Ratio	90% C I	Attr Frac Ex	Attr Frac Pop
SAD (S)				1.16	.50 - 2.52	.14	0.1
Cases	16	7	23				
Controls	43	22	65				
SAD (D)				0.95	.40 - 2.25	.04	.02
Cases	14	7	21				
Controls	46	22	68				

Lung Function Parameters	Exposed	Unexposed	Total	Odds Ratio	90% C I	Attr Frac Ex	Attr Frac Pop
FEV_1%							
Cases	**7**	**1**	**8**	**3.69**	**.71**	**.729**	**.638**
Controls	**53**	**28**	**81**				
FEF_{50} S							
Cases	8	3	11	1.33	.0426-.412	.25	.181
Controls	52	26	78				
FEF_{50} D							
Cases	7	3	10	1.14	.36-3.6	.126	.088
Controls	53	26	79				
FEF_{75} S							
Cases	16	7	23	1.142	.89	.125	.0869
Controls	44	22	66				
FEF_{75} D							
Cases	14	7	21	.95	.04-2.253	.0434	.0294
Controls	46	12	68				

CHAPTER SIX

DISCUSSION

6.1 GENERAL COMMENTS

Occupational health is a complex and multifaceted concept which is difficult to measure. In the context of occupational lung disease no single measurement would do justice to the concept and therefore a number of components are measured. The best measure of occupational linked changes in lung function still results from controlled comparisons across groups with different levels of measured environmental exposure, and within individuals across time.[353]

Although all types of survey designs are used in developing countries, the commonest and most appropriate is the cross-sectional survey design.[353] One reason is that it is often extremely difficult to retain contact with any cohort while the influence of AIDS (prevalence > 27%) on the members of cohorts cannot be underestimated. Most mining operations have a very high labour turnover rate, especially when labour is recruited from other countries and regions. It is therefore debatable whether longitudinal studies would be more effective than a cross-sectional study. Aside from their value in planning, the descriptive cross-sectional study gives information on the prevalence of existing occupational diseases and provides a first step in elucidating the causes of disease by identifying groups with high and low rates of disease.[353,354]

The **initial studies** were **exploratory** in nature and for this purpose **descriptive cross-sectional studies** were used. Patients were selected irrespective of their exposure or disease. Data obtained was used to generate or support hypotheses of etiology and to justify further studies. The strength of these studies was the accuracy of the data obtained and the large sample-size studied. Weaknesses were the lack of detail of individual cumulative lifetime exposure and the fact that the study population was selected on the basis of the quality of lung function. Cross-sectional study designs are useful to assess whether associations exist between exposure and disease, but they do not establish the temporal sequence of events necessary for drawing causal inferences.[354,355]

The **analytical studies** were designed to examine the effects of low-level environmental exposure at Rössing on the lung function in various ethnic groups (making use of the predicted values generated for these populations). Generally only extensive longitudinal studies satisfy the requirements for determining

exposure response curves, and it is well accepted that the possibilities of etiological research in cross-sectional studies are limited **except** where the effects of long-term exposure is studied. If the intensity and duration of exposure is reliably recorded and, if main confounders are controlled for (matching, stratification), analytical cross-sectional studies may permit assessment of quantitative exposure relationships.[355] **An analytical cross-sectional study design** was chosen for the **16 years of exposure** study because it was cost-effective, identified abnormalities, had an exploratory character and assisted with the verification of the working hypothesis. There are also other factors which strengthen the cross-sectional survey design. Exposed and non-exposed groups were readily available and easy to identify. Internal control groups were also relatively homogenous with respect to most factors other than exposure. Another strength was the fact that exposure categorization as qualitative (yes/no), semi-quantitative (high/medium/low/no) and quantitative variables were available.[353] The data could also be treated as data from a cohort or case-controlled study (i.e., disease rates can be compared between exposed and non-exposed groups, or exposure percentages can be compared between diseased and non-diseased groups). Because the independent effects of the environment was investigated only non-smokers were examined. Once again the strength of the study lay in the large populations studied and the fact that the accurate. The populations chosen received estimated exposures and differences between lung function values (measured and predicted) in three ethnic groups were evaluated by means of significance testing. (Two tailed T-tests). The results of the first analytical study did not show significant differences between exposed and non-exposed groups (even when subdivided into ethnic groups). A case can be made for linear regression analysis of lung function as a continuous variable (% predicted) with exposure (also as a continuous variable) **if** significant differences existed.

For the **23 years of exposure study** both **cohort** and **case-control study designs** were considered to obtain a comparison of the occurrence of disease in exposed and non-exposed individuals. Occupational health hazards are usually evaluated through cohort studies. These studies are cumbersome, expensive and it is often extremely difficult to retain contact with the cohort. Large populations are required to obtain significant differences in incidence in various exposure groups. There is thus a tendency towards case-control designs which offer efficient and valid alternatives demanding fewer resources. Results can be obtained relatively quickly because the investigation does not have to wait for the

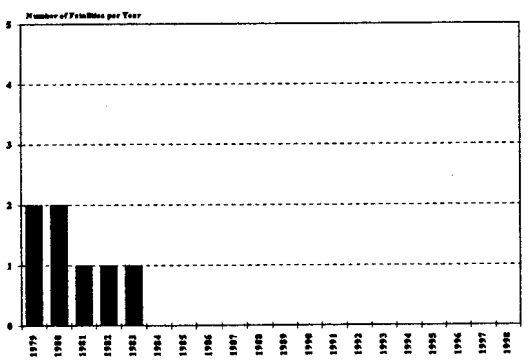
disease to develop as it does in cohort studies. The number of subjects may be small since the study is initiated by the identification of cases which is compared with controls. It is especially important for the etiology of rare diseases and may be the only feasible way to accumulate cases.[354]

Since only a small number of workers exceeded 23 years of employment (and few abnormalities were expected), a case-control study design was chosen. The referents were selected by means of a cross-sectional sample of individuals out of the populations, irrespective of whether or not they were healthy or whether they were exposed or not. The study showed clear evidence that exposure to uranium/silica dust is associated with a small mean deficit in lung function even in the absence of pneumoconiosis, and independent from the effects of smoking. The main weakness of case-control study design was the fact that it was difficult to be sure whether the demonstrable correlation was causal or not. More studies are necessary and must include employees who had left the mine.

6.2 EXPOSURE

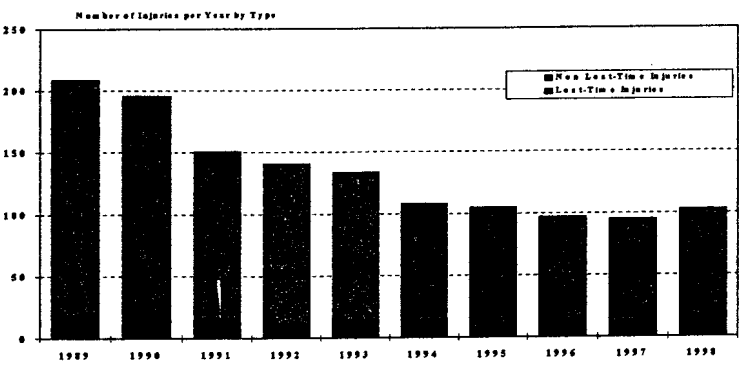
The Rössing mine, by any standards, is a safe mine with an excellent safety record. The following graphs support this statement.

Graph 6



Fatalities 1979 - 1998

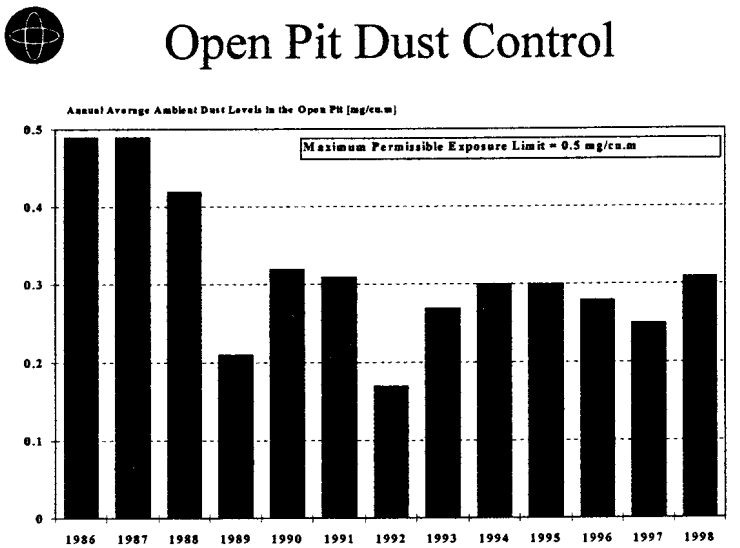
Graph 7



Total Injuries

Exposure to **dust**, especially respirable dust, has been a concern, particularly at crushers and in the plant where the average annual respiratory dust levels sometimes exceed the maximum permissible exposure level (MPEL) of 0,5mg/m^3. The crystalline silica content of the respirable fraction varies between 14% and 34% with an average of about 20%.

Graph 8

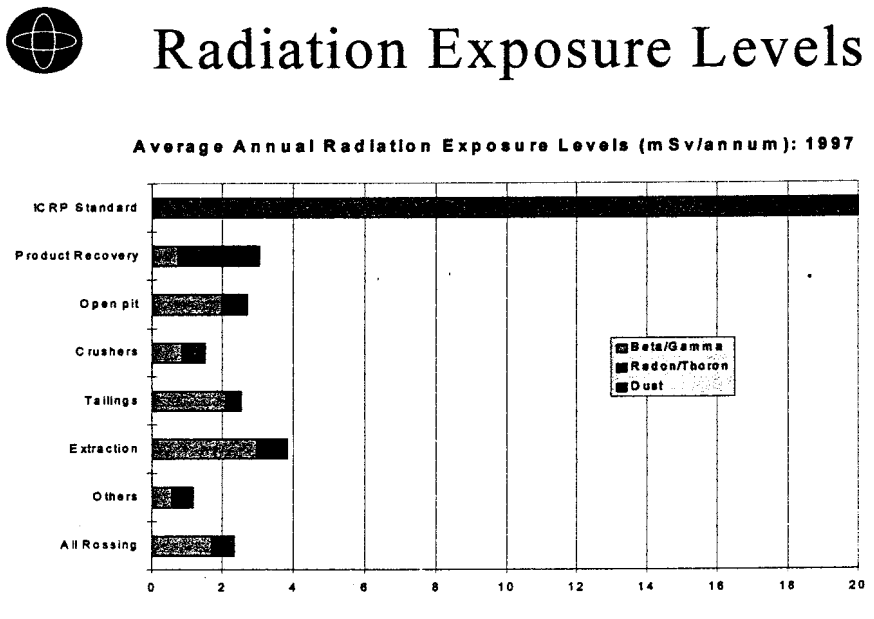


The average occupational **radiation** exposure amounts to 1,8 to 2,3mSv per annum with the maximum exposure for workers in the region of 5,94mSv per annum. Radon levels in the operating areas give an average annual exposure of 0,37 working level months (WLM) with a maximum of 1,2 WLM. Exposure in the non-operational levels averages an annual value of 0,036 WLM with a maximum of 0,072 WLM. The risk of low-dose radiation exposure has been widely discussed. Potential increases of cancer rates remain hidden under the statistical fluctuation of normal rates, but for the purpose of radiation protection, risk coefficients are

based on the extrapolation of observations obtained at moderate or high doses.[316]

Radiation protection is a multifaceted discipline. One of the new ways to assist with the management of high-risk groups is to determine the maximum permissible lung burden of uranium retained in the chests of exposed workers. Though none of the workers counted exceeded the MPLB of 25,6mg uranium, we have definitely shown that there existed lung burdens of at least up to 50% of the MPLB. It also appeared that it is primarily the workers at the final recovery plant that are at risk. We suggest that a repeat count be performed on the persons with the higher burdens.[325,326,327,328,329]

Graph 9



From an occupational health point of view (based on exposure levels x exposure time) one would thus expect to find a small but definite increased risk for COPD, silicosis and lung cancer among the workers of

the Rössing workforce.[13,25,27,28,64,82,84,158,217,223] Tremendous difficulties are however encountered when the independent effect of uranium mining is to be demonstrated. Research is complicated by factors such as unreliable smoking histories, cryptogenic asthma, airway hyper-responsiveness, increasing body weight, survivor bias and viral infections. For these reasons, smokers were excluded in the determination of reference values, and in the subsequent measurement of health outcomes.[20,27,62,92,144]

6.3 CHRONIC OBSTRUCTIVE PULMONARY DISEASE (COPD), ASTHMA AND CHRONIC NON SPECIFIC LUNG DISEASE (CNSLD)

Loss of lung function is often associated with exposure to silica dust, criteria pollutants, smoking and alpha-1-antitrypsin deficiency.[141] The most important effect of inhaled pollutants is chronic obstruction of the airways as evidenced by impaired spirometry. Age adjusted prevalence rates for COPD have increased over the last decade with the prevalence of 110 per 1000. Those with COPD invariably have a significant smoking history and differences between smokers are in direct proportion to the number of cigarettes smoked. Although COPD results predominantly from cigarette smoking, only a relatively small percent (15% to 20%) of smokers develop COPD[187,193,195,200]. Smoking has both a dependent and synergistic effect (smoking and environment).[20,143,144,145]

There is evidence that smokers weigh less than non-smokers (also confirmed in our study). It is thought to be linked to altered lung function and energy metabolism and not the suppression of appetite (as generally believed.) **Tobacco smoking is identified as the single most important cause of preventable morbidity and premature mortality in all the reports produced by the U.S.A. Surgeon General since 1964.**[20,143,144,145]

COPD and asthma both cause airflow obstruction with the major difference between the two, the fact that asthma is variable and reversible.[153,154] In the European arena, and especially with general population prevalence studies, the term chronic non-specific lung disease (CNSLD)[193,194,195,196] is used. CNSLD refers to the same group of diseases included under the term COPD, but also includes asthma. It is often extremely difficult, if not impossible, to distinguish between COPD[220,212,213] with a degree of reversibility, and when asthma and industrial bronchitis coexist. In our 1999 study we evaluated every individual's personal and medical record. We identified asthmatics on the basis of clinical significance i.e. those who experienced (or are treated for) exercised induced bronchospasm, bronchospasm associated with exposure to irritants or infections. Only 6 cases of asthma were identified among the study group of 140 workers. This figure compares favorably with the generally accepted figure of 3-5% found in the Erongo region of Namibia. The role of allergens is a critical issue concerning the pathogenesis of asthma. Many asthmatics have an atopic component with raised IgE levels. Both genetic and environmental factors may contribute to IgE production. Asthma can, however, be present in non-atopics in up to 30-4-% of cases. This raises the question of how a disease that is not mediated by mast cells, produces inflammatory changes in the lung. None of the asthmatics in our study were smokers and 40 (28.57%) of the 140 were identified as atopics (skin prick test and/or strong history).

Oxman *et al*[184] did a systematic review of all the published evidence in 1994 on occupational dust exposure and COPD. They concluded that exposure to occupational dust is an important cause of COPD. Hnizdo[212,213,223] claims COPD to be a more important cause of disability and mortality among South African underground workers than silicosis. She found that smoking was associated with COPD in 34% of cases. The association with the combined effect of smoking and dust exposure was

59%, and with dusts alone, 5%. In our studies we also found COPD to be associated with cigarette smoking and dust exposure.

6.4 SILICOSIS AND ASBESTOSIS

The respirable dust levels in South African mines contain up to 30% free silica whilst the silica content of the Rössing mine varies between 18% to 30%, with an average of 20%. Average mean annual exposure respirable dust levels fluctuate between 0.17-1.33 mg./m 3 depending on factors such as work area and climatic conditions. In contrast with the South African mines the Rössing mine is an open cast mine with excellent ventilation. It is therefore conceivable that the prevalence of lung function changes and silicosis could be higher among the uranium miners than among the general public (provided exposure time was long enough).

Loss of lung function has also been described in dusty environments in the absence of silicosis and smoking. Xiping *et al* , in a community based study, found that dust exposure is a significant predictor for abnormal lung function parameters such as FEV_1, FEVI% and FEF_{25} -FEF_{75}. Both current and ex-smokers appeared to be more susceptible to the effects of dust.[218,219]

Exposure to mineral dust containing silica can result in pathological changes in the lung parenchyma with measurable impairment of lung function. These pathological changes occur in the alveoli and the small airways. The American Thoracic Society (ATS) suggests that, in subjects at risk of developing COPD, pathological changes in the peripheral airways, precedes the development of emphysema. These changes, on their own, without emphysema, may be responsible for subtle abnormalities in pulmonary function tests that are not associated with physical impairment.

Oxman *et al*[184] is firmly of the opinion that exposure to dust is associated with COPD and that the risk appears to be greater for gold miners who are exposed to silica dust. Wiles *et al* could find no significant difference between the lung function of silicotic subjects and controls. Becklake[187], however, found significant differences between lung functions of miners with normal chest x-rays and those with radiological silicosis. Other researchers supported her finding. Cowie and Mabena,[210] in their cross-sectional survey of 1197 gold miners, with silicosis as an independent variable, found a reduction in all indices of lung function (even when controlled for the intensity of exposure and smoking). Cowie's final conclusion is that simple silicosis is associated with significant pulmonary dysfunction. Hnizdo, Sluis-Cremer and Abramovich[213] found that tobacco-smoking potentiates the effects of silica. The duration of exposure was found to be associated with significant reductions in FEV_1% comparable and, to an extent, equivalent to that produced by cigarette smoking in the same population.

In our 1996 survey 2 cases of silicosis were found. Both spent considerable time in South African gold mines and their radiological abnormalities were identified when they joined the company. It was decided that their abnormalities could not be due to their present employment and were therefore not included in this study.

In the 1999 study one case of pneumoconiosis (silicosis=1/1) was found in a black non-smoking man. He worked in a higher risk area (tailings dam) and the only logical explanation is that he is a susceptible individual whose working environment contributed towards his impairment. No asbestosis was identified.

6.5 LUNG CANCER

A number of conditions such as COPD, tuberculosis, silicosis, asbestosis, radon and cigarette smoking have been associated with an increased risk of lung cancer.[221,222,223] Tobacco smoking[144,145] is the most important cause of lung cancer in most studies and it is unlikely that confounding from tobacco smoke completely explains the excess of lung cancer found among uranium workers. After adjusting for smoking, ethnic and socio-economic factors there remains a high risk of lung cancer from exposure to uranium, radon and its daughter products. Dose and time from exposure modify the risk of lung cancer, associated with radon. To stop smoking can substantially decrease the risk. The risk for lung cancer may also be influenced by concomitant exposure to silica, diesel and blasting fumes that cause injury to cells, and potentiate the carcinogenic effect of radon. All of these suggest that the cause of lung cancer in uranium workers may be a multi-factorial etiological process with individual genetically determined susceptibility.[222,223,224]

The focus of most studies is on the increased risk of lung cancer associated with the joint exposure to radon and tobacco smoke. The sum of the risks associated with each factor individually is smaller than the combined risk of joint exposure. Apart from smoking and radon, the relationship between the age of occupational exposure to ionising radiation and cancer was investigated.[12,13,14,15,28,30,52,53,54] It was found that people who are approaching the end of their lifespan are more sensitive to the effects of radiation in the induction of cancer than younger workers. The question that begs answering is whether early retirement for workers should not be considered as part of a health strategy.

There are no reliable or readily available figures for cancer rates in Namibia. Records from state laboratories are not available for the pre-

1978 era and cancers recorded since 1987 do not reflect ethnic status. Furthermore, the diagnosis of cancer based on pathology is regarded as a poor source of information in a developing county such as Namibia. *Sitas et al*[352] established a database on cancer in Namibia. He made use of proportional cancer methods based on incident histologically diagnosed cancers. All persons diagnosed with cancer (excluding basal and squamous cell skin cancers) were recorded. Based on rates developed for Namibia, and taking into account the number of working person-years, a crude incidence rate cancer of about 140 per 100,000 cancer in 20-64 years group for males of all races were estimated. About 75-80 cancers can be expected from current and ex-employees, rather than the 60 found (all ethnic groups). The indigenous peoples (predominantly black) of Namibia do not appear to be at a greater risk for occupational cancer. A South African study found a higher incidence of lung cancer at younger ages than among whites. The burning of firewood indoors was identified as a contributory factor.[242,243,244,245,246] Rössing workers live in houses with electricity. The role of genetic predisposition in cancer is most evident in familial transmission of cancers such as the inherited mutated gene (P53 tumour suppressor gene)[245] – the most commonly mutated gene found in cancer. Published literature, however, does not contribute much towards a better understanding of the complex relationship between occupational cancer and race.

Cytological abnormalities found in high-risk groups have a strong positive predictive value for cancer (sensitive and specific).[334,335,336,337,338,339] One of the newer diagnostic tests for the early identification of lung cancer, exfoliative sputum cytology, was investigated as a definitive diagnostic test. Worldwide the results were disappointing because the early diagnosis of lung cancer does not reduce the mortality rate of the disease and cytology screening for lung cancer is therefore not specifically recommended.

Recently there has been a resurgence of interest in sputum cytology as a preventative tool. Much attention was focused on exfoliated cell micronuclei assays (a relative cytogenic technique). Micronuclei are small cytoplasmatic bodies that contain deoxyribonucleic acid (DNA). During cell division small parts of chromosomes are left outside the nucleus. The frequency of micronuclei is an indication of increased frequency of structural and/or numerical chromosome aberrations.

Studies done by Stich *et al* in 1984, and Sarto *et al* in 1987, positively correlated the increased frequency of micronuclei with increased exposure to cigarette smoking and ionising radiation. A study done in 1990 by Loomus, Saccamanno *et al* [343] failed to demonstrate the same effect. In our 1996 study we found no cases of lung cancer but during the 1999 survey one case of pulmonary cancer in an ex-employee, with more than 23 years of service, was diagnosed. He was a smoker and over 50 years of age. Reasons for our low detection rate remains speculative, but is most probably a function of the age of workers examined, and because current data of ex-employees was not available (only exit-medical data were used). The latency is probably insufficient and therefore has a high probability of under-estimating the true risk, because the cancers among current and retired employees only manifest after a long genesis period.

In a not yet finalised study done by Sitas *et al*,[352] a number of cases of respiratory cancers were found among current and ex-Rössing employees (± 55 000 working persons-year of exposure). The majority of respiratory cancers were found in smokers and highlights the fact that ex-employees must be examined.

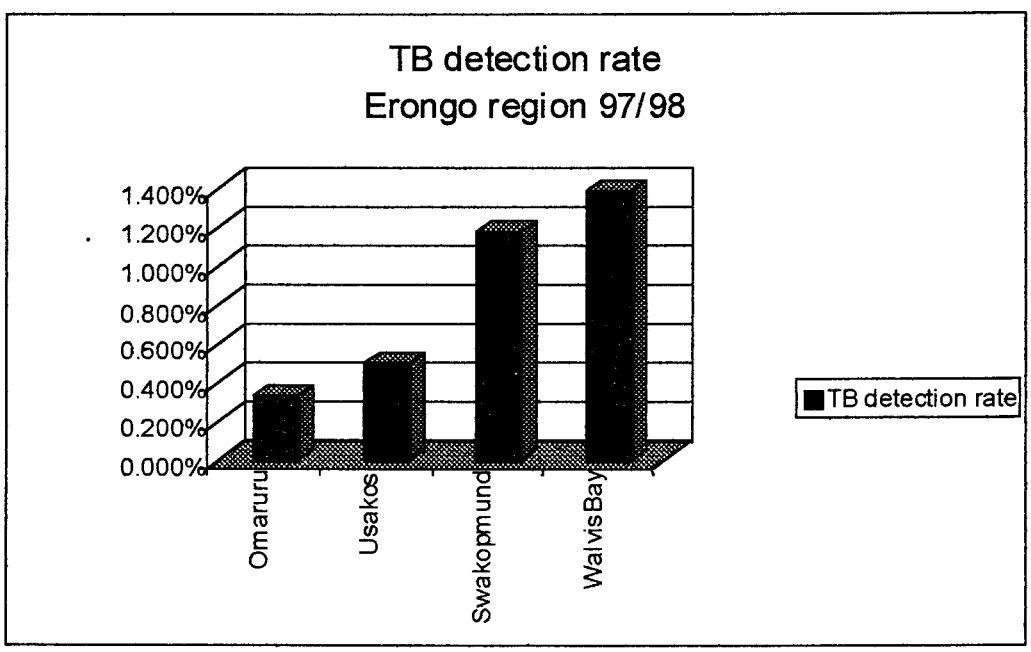
Stewart and Kneale [86] points out that the sensitivity to carcinogenic effects of radiation increases progressively with age (provided the dose is small). This must be borne in mind by Rössing's strategic planners.

6.6 TUBERCULOSIS

The World Health Organization (W.H.O.) declared tuberculosis a global public health emergency. The AIDS pandemic compounds the problem, and in some African countries the case rates have doubled. In Central Africa up to 70% of tuberculosis patients are HIV-positive.

Tuberculosis continues to increase in Namibia (and Southern Africa) in spite of chemotherapeutic interventions.[225,226,227,228] The notification rate of 200 per 100 000 is thought to be lower than the true incidence of the disease. (The rate indicates the size of the problem and expresses the frequency per 100 000 persons in the population.) Incidence rates are highest in the mixed race communities of the Western Cape (700 per 100 000). The same scenario is found in the mixed race/black population of the residential areas of Rössing employees. Figures in excess of that of the Western Cape are reported in the harbour town of Walvis Bay (30 kilometres from Swakopmund).

Graph 10



The risk for contracting tuberculosis is calculated at 0.1% for Caucasians and 2.2% for blacks (South African figures).[226,227,228] The discrepancy is based on the higher incidence of poverty, overcrowding, malnutrition, AIDS and alcoholism among mixed race and black communities. The reported incidence for tuberculosis in the Erongo region is estimated at 1.16% - 1.3%

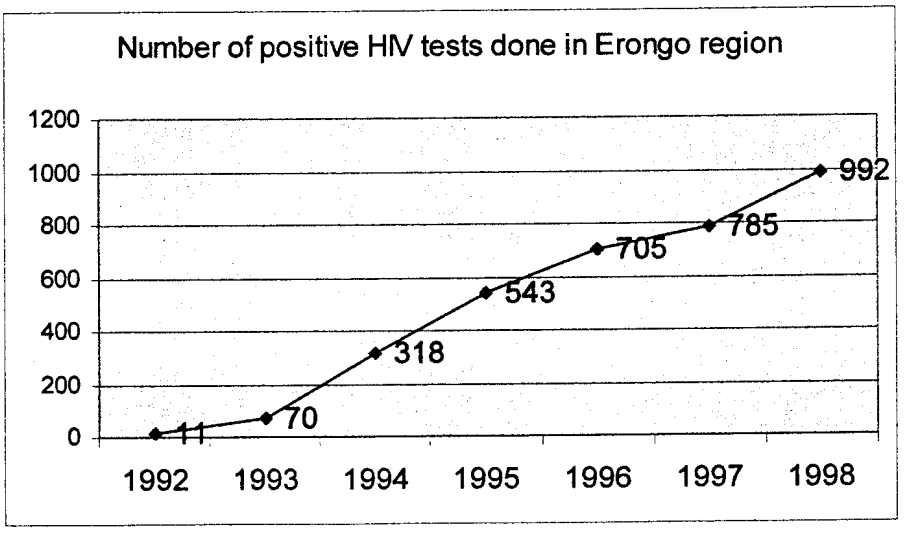
In the 1996 study the cross-sectional survey only revealed two cases of pulmonary tuberculosis being investigated or treated. When the x-rays were retrospectively studied (historical cohorts) a different picture emerged. A total of twenty employees were diagnosed as having definite tuberculosis or strongly suspected of having it (based on radiological appearance).

The incidence of tuberculosis among Rössing employees was not higher (200 per 100 000) than the average for the region. In the 1999 study a relatively higher number (13 cases) of radiological apparent tuberculosis was identified (9,3% of the workforce). This must be seen in its the proper context and there are several explanations. The first reason is the high yield rate of the historical cohort and the other centres around the "diagnosis" of tuberculosis. There are two different stages in the diagnosis of pulmonary tuberculosis; namely to consider the **possibility** based on the radiological features and secondly to **establish** the diagnosis[226,227] (x-rays, sputum, microscopy, culture, clinical picture and a tuberculin test). The method used in this survey combines both of the above and thus overstates the problem, as it is based on too little evidence. The incidence of tuberculosis increases with age and is higher in men, and the level of surveillance among the workers in the study is very high. An interesting find was the high number of cases (6/44) in the 1999 survey in the "non-exposed" group versus those (7/96) in the "exposed" group. The reason is obvious: those with tuberculosis were transferred to "non-exposed" areas.

The question whether a worker who has been treated for tuberculosis should be returned to his previous employment in a dusty area is open for discussion. Often a transfer from an operational to a non-operational area is associated with a reduction in income, status and more stress. Dr Robert Cowie from of the Ernst Oppenheimer Hospital in South Africa, is of the opinion (personal communiqué) that every case should be evaluated on individual merit. It is most probably better for the worker to be treated, followed up and returned to his previous employment; with the proviso that the environmental health and protection of the individual should be investigated and improved.[226]

The ever increasing HIV seroprevalence (34% for Namibia and 28% for the region) advocates a change in the way that tuberculosis is viewed and managed. Tuberculosis treatment is simple and cost-effective. The short course (6 months') treatment regime will cure most cases. The principle of D.O.T. (direct observed therapy) is innovative and effective. Mines (with their in-house medical apartments) offer an ideal site for organized and effective D.O.T. This system has been in place at Rössing since the early 1980's.

Graph 11



An association between tuberculosis and silicosis has been known for centuries. It was investigated by numerous researchers and confirmed by many epidemiological studies.[225,226,227,228,229,230,231,232,233,234] It is also true that the response to tuberculosis treatment in silicotic patients is often less effective. Silica does not impair the delayed hypersensitivity response, but appears to be cytotoxic to the body's first line of defense, the macrophage. The inability to effectively combat mycobacterium is associated with the individual lung silica load. J Balmes[225] of the San Francisco General Hospital in California recently addressed the question whether silica-exposed individuals (without the classical radiological features of silicosis) are at an increased risk to contract tuberculosis. Sherson and Lander's study in Denmark strongly suggests that silica exposure confer an increased risk of tuberculosis. Robert Cowie of the Ernest Oppenheimer Hospital in South Africa also confirmed this.[232] Surveillance programmes for these workers at risk are thus mandatory.[344]

The argument that chest x-rays increase the total radiation exposure is valid, but should be seen in the Rössing context where the average occupational radiation exposure is 1.8 - 2.3 mSv per annum, and the maximum annual exposure among the workforce is 5.94 mSv per annum. The acceptance of risk comes from placing it into perspective. The justification principle states that any practice involving additional radiation exposure should produce a significant benefit and must be weighed up against the optimising principle that governs the norm "as low as reasonably achievable" (A.L.A.R.A).[70]

6.7 SARCOIDOSIS

The etiology of the disease is unknown but the pathological process is well described. It is a benign phenomenon mediated by an intensive cellular response. The condition is often symptomless and often incidentally discovered.

The relationship between silica, autoimmune diseases and sarcoidosis has been investigated but it is still unsure whether such a link exists.[346,347] Further studies are required. Some evidence about an association with silica is slowly emerging but more research is needed.

Sarcoidosis is found worldwide and tuberculosis has been considered as a possible causative agent because mycobacterium or mycobacterium-like organisms can be cultured from sarcoid tissues. Parallel changes in prevalence of tuberculosis and sarcoid have been observed in communities.[345,346,347] The prevalence varies from 10 to 100 per 100 000 population. Two cases of sarcoidosis were found in the 1999 study, and could be associated with silica dust exposure and possibly with tuberculosis. Information on the association remains uncertain and no official figures on the incidence of sarcoidosis is available for Namibia.

6.8 LUNG FUNCTION EVALUATION OF URANIUM WORKERS.

We believe that in the industrial setting the flow volume curve affords the best test to detect airflow limitation.[286,287,288] Lung function measurements are influenced by many variables including age, height, weight and race.[290,291,292,293,294] The identification of impaired lung functions is determined by the magnitude by which the observed value differs from the predicted value.[293,294]

The importance of studying the changes in lung function in workers in the mining industry, is more than just to show that lung changes do occur and/or to determine the prevalence or incidence of these changes. Early detection and follow-up are essential to prevent the development of symptomatic disease. An attempt should also be made to identify predisposing factors that may be associated with a higher risk of developing irreversible lung changes in the individual.

One of the major problems encountered in the recognition of early changes is the choice of relevant and accurate prediction formulae.[289,290] Universal predictive formulae are not available and are affected by a number of factors such as race,[292-313] and the methodology used to determine these formulae. Myers[306] proposed a universal standard based on middle-class subjects in an adequate working and living environment. In his study he only studied a population of South African blacks without including Caucasians or other ethnic groups. We agree with Davies and Becklake[309] that the problem of reference values and possible socio-economic factors, as highlighted by Myers[306,308] and others,[310,313] are important and that further studies are indicated.

Values for lung function differ from laboratory to laboratory. It is therefore essential that members of all ethnic groups should be included in the same study if comparisons were to be made.

A number of respiratory health surveys have been done in Southern Africa and prediction formulae for normal values were developed. Prediction equations[303,306,311] are derived from multiple linear regression, taking into account age and height. The effect of gender and race are taken into account through stratification.[313] All the studies showed a clear difference in some lung function values between different ethnic groups. Correlating height, sitting height, torso height and arm span did not contribute towards a universal formula. Predicted normal values such as for " FVC predicted" for a person aged 35 with a height 170cm varied between 4.46 to 5.0 whilst "FEV_1 predicted" for such a person fluctuated between 2.94 to 3.77.[311]

A number of formulae were evaluated before the formulae of Schoenberg *et al* were applied to the Rössing workers. Most studies give prediction

equations only for the mean values of the spirometric indices. Although a standard deviation is given it is of limited value in predicting the lower levels of normal which is of clinical importance. These indices tend to have a non-normal distribution skewed towards high values. If the population is assymmetrically distributed about the mean, too low an estimate of the lower limit of normal values is given if 1.65 SD is subtracted from the predicted mean. Schoenberg *et al* has addressed this problem and has provided estimates of the lower limit of normal values in addition to the predicted values. Furthermore, only Schoenberg *et al* provides non-linear regression equations and the most satisfactory predictions with the most satisfactory predictions for the mean and low limit of normal for FVC, FEV_1, FEV_1 ratio, FEF_{50} and FEF_{75}.[273,274,278] One of the problems encountered with the Schoenberg *et al* formulae was that it did not make specific allowance for subjects falling into the mixed ethnic group.[292] Even if ethnic differences are taken into account it appears that, where practical, specific prediction formulae should be computed, as was found necessary for the workers at the Rössing mine. In an attempt to improve on the formulae of Schoenberg *et al* predictions of unstandardised lung function data were investigated in three ethnic groups. Stepwise multiple regressions were used to develop site-specific prediction formulae for normal values based on data collected on 1407 Caucasian, black and mixed race workers at the Rössing mine in Namibia. In our study we found definite ethnic differences for FVC, FEV_1 PEFR, and PIFR and to a lesser degree for FEF_{50} and FEF_{75}. The actual values of FEF_{50} and FEF_{75} did not differ much between the Caucasians and non-Caucasians, possibly being slightly higher in the non-Caucasians. It is also of interest to note that the FEV_1/FVC ratios of the Caucasian non-smoking group were significantly lower than those of the non-Caucasian group ($P < 0.001$). Significance levels were adapted for multiple comparisons using the Bonferroni method. These findings indicate that the non-Caucasians may have mechanically more efficient lungs, no other

evidence of restrictive disease being present. This is supported by the ratios of FEF_{25}/PEFR, FEF_{50}/PEFR, and FEF_{75}/PEFR, which are higher in blacks than in Caucasians with significance levels of ($P < 0.001$) in all three instances. The relatively higher flow rates at lower lung volumes together with normal slope of stage IV and a normal closing volume, as determined with the single-breath oxygen-nitrogen wash-out curve, indicate that the smaller lung volumes in the non-Caucasians are not associated with any small-airways disease.[34,278-287]

In 1996 lung function values were obtained from 1034 miners in both exposed and non-exposed areas. The data was controlled for age, height, weight, exposure and non-exposure. The prediction equations calculated specifically for the workforce at Rössing were used to determine departures from normal. The data from different exposure groups were investigated for associations and to estimate the mean independent effect of mining on lung functions.

The data obtained in the 1996 study suggests that low-level long-term (more than 10 years) exposure to the environmental pollutants at Rössing does not necessarily cause major respiratory dysfunction. There was no corresponding significant effect on the traditional indicators of lung function abnormalities (FVC, FEV_1 and FEV_1/FVC ratio). These indicators, however, often under-estimate the true prevalence of small airways disease (SAD)[281,282,283,284,285] among non-smoking mine workers. Analysis of the data did not yield major abnormalities among the cohorts of the workers studied. However, the PEFR and FEF_{75} proved to be the most significant difference between the study group's high-exposure sub-group and the low-exposure control group.

Peak expiratory flow (PEFR): (t=2.1395 p=0,032) is one of the most commonly measured flow rates is the PEFR. PEFR is highly sensitive to

effort and may vary considerably within the same subject. It reflects the conductance of the large upper airways and is associated with the size of the person's larger airways, rather than the small airways, and as such is insensitive to low levels of airway obstruction and does not exclude significant lung disease. PEFR is influenced by the respiratory muscles, the elastic recoil of the thoracic cage and the airflow resistance of the larger airways. This statistical finding has little clinical significance because PEFR[273,274,287] exhibits too great inter-subject variability, is effort dependent, and provides little or no information about the smaller airways.

FEF_{75} (t=1.9828 p = 0.047) The most commonly reported FEF, is the FEF_{75}. Flow rates at lower lung volumes are often surprisingly repeatable and effort-independent in spite of variations in initial effort. This phenomenon has prompted the description of the descending portion of the curve as effort-independent. When flow is plotted against volume instantaneous flow can be noted at any specified lung volume. Instantaneous flow at low lung volumes (near or below functional residual capacity) is useful in the detection of small airway disease as well as having a role in epidemiological studies and in following the natural history of disease.[273,274,275,276,277,287]

The measurement of maximal flow at 50 and 75% of expired forced vital capacity is relatively accurate provided that attention is paid to the continuation of expiration down to residual volume. Under these circumstances the variables described reflect changes in the small airways. This measurement is especially indicative of early disease when it yields abnormal results in the presence of a normal FEV_1, peak flow rate and flow at 25% of forced expiratory vital capacity.[286,287,288,289,290] Under the above mentioned conditions the FEF_{75} could be, and is, a good measurement for small airways involvement as an indicator of pre-clinical lung disease. This study thus provides further evidence of a small, but clear effect of uranium

mining on the lung functions of miners with no evidence of pneumoconiosis, and with traditionally "normal" lung functions.

This finding correlates with that of JR Joubert *et al*'s[349,350] study done in 1996 at the Rössing Uranium Mine when they evaluated the influence of environmental factors on the lung health of the workers. In their study 114 mine workers were followed up for a period of 16 years. The 114 workers included 36 terminees who were followed up for a mean period of 11.3 years. No evidence of a mean effect of mining on lung function values, bronchial carcinoma or silicosis was found. It also correlated with the finding of a study done by Maree *et al* [351] who investigated the longitudinal decline of lung functions in fume exposed workers at Rössing. They concluded that welding and fume exposure as practiced under rigid health control did not impact negatively on the lung functions of workers. Within the major groups an effect of smoking and allergy was noted, but not in the control group.

In the 1999 study a sub-set (N=140) of older (average age of 48,9 years) workers with long (>23 years)employment were investigated. Both lung function and other outcome parameters (COPD, SAD) were studied in terms of exposure. Measured lung function values were compared with predicted values of Schoenberg *et al* and de Kock *et al*. The percentage abnormal lung function values identified differed (as expected) according to the prediction formulae used. The percentage abnormal lung function values found in the total study population was high. The population was then further sub-divided into smoking categories. The percentage lung function abnormalities found in smokers (and to a lesser extent in ex-smokers) was significantly higher than in non-smokers, which clearly illustrates the effect of smoking on lung function. As expected, the prevalence of COPD (S=9.29%; D=5.71%) was high in the total population. The prevalence of SAD was much higher (S=36.09%; D=35.1%). Likewise

the prevalence of COPD in smokers was very high (S=30.43%; D=17.39%) but the prevalence of SAD in smokers was even higher (S=68.42%; D=65.21%). The percentage of SAD was also surprisingly high in never smokers (S=26.1%; D=23.5%). The risk for an exposed worker (without controlling for smoking) to develop COPD was 2.7 times higher than for those who are not exposed. For non-smokers the risk to develop COPD was insignificant but there was a 1.16 times risk to develop SAD. The impact of exposure on FEV_1%, FEF_{50} and FEF_{75} was significant.

6.9 CONCLUSION

This study attempted to describe the respiratory health status of miners exposed to the effects of low-level, long-term exposure in a high tonnage, opencast uranium mine. A specific feature of prolonged exposure to low levels of environmental factors is that the distribution between specific and non-specific effects are blurred, and that it is difficult to detect marginally increased risks. It is also extremely difficult to disentangle the effects of bias and uncontrolled confounding. The published literature however supports the hypothesis that low level long-term exposure (over time) of environmental agents is associated with the clinical expression of occupational lung diseases.[11,26,144,172,210,230,245] There is no doubt that workers in the uranium and mining industry[9,10,11,12,13,14,15,16,32,34,51,52,53,54] run a risk of contracting respiratory diseases depending on the level of exposure and exposure time.

Silicosis and exposure to radon progeny is a major problem in most opencast mines.[69,86,145,215,216] Respiratory cancer is strongly associated with exposure to radon progeny and tobacco smoking and a loss of lung function; an increase in the incidence of pulmonary cancer and tuberculosis are also associated with exposure to silica.[8,223,224] Tuberculosis remains, together with AIDS, our number one public health

emergency and mines are ideally placed to assist with the identification and treatment of these diseases.[226,227,228,230,231,232] Of special concern is the fact that an increased risk of pulmonary silicosis, tuberculosis and pulmonary cancer **exists after** exposure to silica dust and radon progeny ends.[344]

The results of the 1996 study suggests that the level of exposure in this study group (without the confounding effect of cigarette smoking) is **not** associated with a statistically significant impairment of lung function, increased prevalence of silicosis, or respiratory cancer after an average exposure time of 16 years. This could be a function of a combination of factors such as low levels of exposure, efficient environmental control measures, and low smoking levels combined with active smoking cessation programs. Investigation of the actively employed group may be biased by the" healthy worker" effect, and the time allowed for latency might have been insufficient. Latency for these diseases to develop is usually in excess of fifteen years, but once established they are irreversible.

In order to address the perceived problem of latency, and to evaluate the combined effect of dust exposure and smoking, a case-control study was done in 1999 on those who had more than 23 years of employment. The data from this study supports the hypothesis that there is a significant exposure-response between prolonged exposure to low levels of silica dust and lung function abnormalities. This effect is evident in the absence of radiologically diagnosed silicosis. The results also indicate that the levels of silica dust to which the miners were exposed, without a confounding from tobacco smoking, is associated with a small but statistically significant impairment of lung function. The prevalence of COPD and SAD was significantly higher in exposed workers and the risk of developing COPD was 2.7 times higher for exposed workers. The risk

for non-smokers was small but significant. Our studies support the literature that has shown that the estimated effect of silica dust relative to that of smoking is of smaller magnitude. The incidence of tuberculosis and cancer was not higher than expected. It appears that Rössing had a young, healthy workforce until the average age of 40 was reached. After that signs of smoking and exposure related diseases emerged, which could lead to premature respiratory disabilities.

The findings of this study help to refocus our attention to identify relatively accessible risk groups and to launch cost effective intervention strategies and the need for health surveillance programmes to include exposed ex-employees. The practical importance of being able to detect disease early is that the patient can be advised on prevention of further damage to his lungs.

When accurately performed and properly reported, x-rays and lung functions are still considered the best basic instruments to detect respiratory abnormalities. Every population is unique, and formulae predicting normal values for measured lung function must be computed for every population group studied. Quality control of lung functions is paramount and enables the clinician to identify accurately those who are at risk.

Conclusive assessment must await sufficient latency and early indicators of risk must be obtained. This study also has a high probability of underestimating the **true** risk of advanced CNSLD, silicosis, tuberculosis and pulmonary cancer because **ex-employees** were not fully investigated. Longitudinal studies that include miners who have left the industry are necessary to establish the true magnitude and distribution of the effects of siliceous and uranium dust on the health of workers. The mine

management should devote energy and resources to address this and evaluate updated intervention strategies.

Legislation often requires environmental impact assessments (E.I.A) before a project is approved. Future mining, and other industrial endeavors, must consider the potential health outcomes of workers in the design phase. Well-planned, and properly carried out epidemiological studies, will identify depressions in functions measured, expose changes in morbidity patterns and eventually help to establish causal relationships. Unfortunately, health impact assessments (H.I.A.) are often not considered on a scientific basis.

To see the future – page the old books - Emperor Augustus