

RESPIRATORY HEALTH STATUS IN RELATION TO OCCUPATIONAL EXPOSURE IN URANIUM MINING AND RECOVERY

BY

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Dedicated to my friend and mentor,

Professor M A (Attie) de Kock

Our real problem is in the hearts and minds of men.
It is not a problem of physics, but of ethics.
Man's skills have outstripped his morals.

His engineering - has leaped ahead of his wisdom.
We cannot cancel or call back his scientific advances,
but we can, and must, if the world is to survive,
help man to catch up.

In God's name, if we still believe in God.
Take him seriously, and somehow get control,
of what science has given to the world,
or else we shall likewise perish.

A. Einstein

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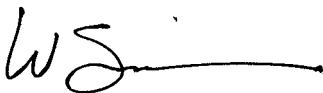
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DECLARATION

I, the undersigned, declare that the work contained in this thesis (dissertation) is my own original work and it has not been submitted in any form for similar purposes to any University for a degree.

Signed: 

Date: 20 October 1999



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ABBREVIATIONS AND DEFINITIONS

<u>AEC:</u>	Atomic Energy Corporation (R.S.A.)
<u>Alpha decay:</u>	Radioactive disintegration resulting in emission of α -particle. Also alpha disintegration.
<u>Alpha Particle:</u>	Nucleus of helium atom of mass number four, consisting of two neutrons and two protons and so double positively charged. Emitted from natural or radioactive isotopes. Often written α -particle
<u>ATC:</u>	American Thoracic Society
<u>Atomic number (Z):</u>	Number of protons
<u>BEIR IV</u>	U.S. Academy of Science Committee on Biological Effects of Ionizing Radiation.
<u>Best practical means</u>	Term with statutory force since 1863, and the basis for control of atmospheric pollution in the UK. Defined as the best practicable means with regard to local conditions, financial implications and current technical knowledge, and includes the provision, maintenance and correct use of plant. Abbreviated BPM.
<u>Beta decay:</u>	Radioactive disintegration with the emission of an electron or positron accompanied by an uncharged antineutrino or neutrino. The mass number of the nucleus remains unchanged but the atomic number is increased by one or decreased by one depending on whether an electron or positron is emitted.
<u>Beta particle:</u>	An electron or positron emitted in beta decay from a radioactive isotope.
<u>Bq:</u>	Symbol for becquerel, the SI unit of radioactivity.
<u>CNSLD</u>	Chronic Non Specific Lung Disease
<u>COPD</u>	Chronic Obstructive Pulmonary Disease
<u>Daughter Product</u>	A nuclide that originates from the radioactive disintegration of a parent nuclide. Also decay product.
<u>Decay:</u>	The process of spontaneous transformation of a radionuclide. Radioactive Decay: Disintegration of the nucleus of an unstable nuclide by spontaneous emission of charged particle, photons, or both.
<u>Dose equivalent:</u>	The quantity obtained by multiplying the absorbed dose by a factor to allow for the different effectiveness of the various ionizing radiations in causing harm to tissues.
<u>Dose:</u>	General term for quantity of radiation.
<u>ECCS</u>	European Community for Coal and Steel
<u>Element :</u>	Material whose atoms all have the same number of protons.
<u>EPA:</u>	Environmental Protection Agency
<u>ERS:</u>	European Respiratory Society

<u>Worker's Daily Exposure:</u>	The average work shift concentration of radon progeny for each work area shall be used to calculate each miner's daily exposure. If no monitoring has been conducted in a work area on a particular day, the daily average work shift concentration for that area shall be determined by averaging the results obtained on the last day of the monitoring with the results from the next day that monitoring is conducted.
<u>FEF₂₅</u>	The forced expiratory flow after a quarter (25%) of the FVC has been exhaled.
<u>FEF₅₀</u>	The forced expiratory flow after half (50%) of the FVC has been exhaled.
<u>FEF₇₅</u>	The forced expiratory flow after three-quarters (75%) of the FVC has been exhaled.
<u>FEV₁</u>	The FEV ₁ is the volume of air forcefully expired over the first 1 second of the FVC maneuver.
<u>FEV₁%</u>	The FEV ₁ % is the ratio of the FEV ₁ and FVC expressed as a percent (i.e. $FEV_1/FVC \times 100$)
<u>FEV₁/FVC%</u>	The forced expiratory volume (over 1 second) divided by the forced inspiratory vital capacity expressed as a percentage.
<u>FIVC</u>	FIVC is the volume of gas that can be forcefully inspired from RV to TLC.
<u>Follow-up Period</u>	The length of time between a person entering an epidemiological study cohort and the present report (or the end of the study).
<u>FRC</u>	Functional residual capacity - the amount of air that remains in the lungs after a normal resting expiration.
<u>FVC</u>	The FVC is the volume of air that can be expired as forcefully and rapidly as possibly from TLC to RV.
<u>FVC/FIVC</u>	The forced vital capacity (FVC) divided by the forced inspiratory vital capacity (FIVC) expressed as a ratio.
<u>Gamma Radiation</u>	Electromagnetic radiation of high quantum energy emitted after nuclear reactions or by radioactive atoms when the nucleus is left in an excited state after emission of alpha or beta particles. Also gamma rays.
<u>Half-Life:</u>	The time required for a radioactive substance to decay to one half of its initial activity.
<u>ICRP:</u>	International Commission on Radiological Protection.
<u>Ion:</u>	Strictly, any atom or molecule that has resultant electric charge due to loss or gain of valency electrons. Free electrons are sometimes loosely classified as negative ions.
<u>Ionisation:</u>	Formation of ions by separating atoms, molecules or radicals, or by adding or subtracting electrons from atoms by strong electric fields in gas, or by weakening the electric attractions in a liquid, particularly water.



<u>Ionising energy:</u>	The energy required to produce an ion pair in a gas under specified conditions. Measured in eV. Air is about 32 eV.
<u>Ionising radiation</u>	Any electromagnetic or particulate radiation capable of producing ions, directly or indirectly, in its passage through matter
<u>Isotope :</u>	One of several nuclides with the same atomic number i.e. one of a set of chemically identical species of atoms which have the same atomic number but different mass numbers. A few elements have only one natural isotope.
<u>Linear Hypothesis:</u>	The hypothesis that excess risk is proportional to dose.
<u>Mass number (A)</u>	Number of protons plus neutrons.
<u>MRC:</u>	Medical Research Council.
<u>MVV</u>	The maximum volume that can be breathed per minute by voluntary effort.
<u>NRPB</u>	National Radiological Protection Board (U.K.)
<u>Nuclear energy:</u>	In principle, the binding energy of a system of particles forming an atomic nucleus. More usually, the energy released during nuclear reactions involving regrouping of such particles (e.g. fission or fusion processes). The term atomic energy is deprecated as it implies rearrangement of atoms rather than of nuclear particles.
<u>Nuclide :</u>	An atomic nucleus as characterized by its atomic number, its mass number and nuclear energy state.
<u>PEFR</u>	The maximum flow rate attained during an FVC maneuver recorded in litres per second.
<u>Person Years (PY):</u>	A standard technique for handling variable follow-up periods; multiply the number of persons by the number of years of follow-up. Person-years at Risk (PYR): In a life table analysis, the number of PY at risk of dying from disease, usually calculated from the time the miner enters the cohort until death or the end of follow-up. Some authors adjust the PYR for an assumed 10-year latent period for lung cancer by subtracting PYR accumulated during the first 10 years after a miner starts to work underground [see above, (Lagging)].
<u>PIFR</u>	The maximum inspiratory flow rate attained during an FIVC maneuver recorded in liters per second.
<u>Radiation:</u>	The dissemination of energy from a source. The energy falls off as the inverse square of the distance from the source in the absence of absorption. The term is applied to electromagnetic waves (radio waves, infrared, light, x-rays, γ -rays etc) and to acoustic waves. It is also applied to emitted particle (α , β , protons, neutrons etc)
<u>Radon (Rn) or Radon and its progeny</u>	Specifically refers to the "parent" noble gas (Rn-222), and its short-lived alpha radiation emitting radioactive decay products ("progeny" or "daughters"). Radon is a gas, the radon progeny are radioactive solids.



<u>Rössing Worker</u>	Rössing workers include all mine personnel who are employed by Rössing Uranium (eg drilling, blasting, haulage, maintenance, laboratories, administrative personnel etc)
<u>RV</u>	Residual volume - the amount of air that is left in the lung after a maximal inspiration.
<u>Sievert (Sv):</u>	The SI unit for dose equivalent, measured in grays times a quality factor for the type of radiation and a weighting factor for the tissue irradiated. Numerically equivalent to gray for electrons and X-rays irradiating the whole body. Symbol Sv. Sievert = grays of QF x modifying factors. The QF for alpha particles from inhaled radon progeny is generally considered to be in the range of 10 to 20.
<u>Thoron</u>	A metallic radioactive element, dark-gray in colour. Symbol Th, At. No. 90, r.a.m. 232.0381, mp 1845°C, rel.d. 11.2. Its abundance in the Earth's crust is 8.1ppm and there are few independent thorium minerals. It has six isotopes: Thoron progeny are the solid, short-lived, alpha radiation emitting decay products (progeny or daughters) of thoron gas.
<u>TLC</u>	Total lung capacity is the maximum amount of air that can be held in the lung after deep inspiration.
<u>UNSCEAR</u>	United Nations Scientific Committee of the effects of Atomic Radiation (U.S.)
<u>Uranium</u>	A hard grey metal. Symbol U, at no 92, r.a.m. 238.03, mp 1150°C, rel.d. 18.68. It has seven isotopes. Because the half life of uranium -235 is very much less than that of uranium -238 the relative abundance of these two isotopes has varied over time with uranium -235 being about 3% 2 x 10 ⁹ years ago.
<u>VC</u>	Vital capacity - the volume of air from a maximal expiration to a maximum inspiration.
<u>WHO</u>	World Health Organisation
<u>Worker's Daily Exposure</u>	The average work shift concentration of radon progeny for each work area shall be used to calculate each miner's daily exposure. If no monitoring has been conducted in a work area on a particular day, the daily average work shift concentration for that area shall be determined by averaging the results obtained on the last day that monitoring is conducted.
<u>Working Level (WL):</u>	A standard measure of the alpha radiation in air. This energy can come from the radioactive decay of radon (Rn-222) and thoron (Rn-220) gases. The working level is defined as any combination of short-lived radon decay products per liter of air that will result in the emission of 1.3 x 10 ⁵ million electron volts (MeV) of alpha energy during decay to lead-210.



<u>Working Level Month (WLM):</u>	A working level month (WLM) is the product of the radon progeny concentration in WL and the exposure duration in months. For example, if a miner is exposed at a concentration of 0.083 WL for 1 month (170 hours [hr]),* then the cumulative exposure for the month is 0.083 WLM. If the cumulative exposure of the same miner is 0.083 WLM for each of 12 consecutive months (2,040 hr), then the cumulative exposure for the year is 1 WLM.



SUMMARY

OBJECTIVE

The objective of this study is to examine the exposure- response relationship between prolonged exposure to low levels of silica, uranium, radon progeny and criteria pollutants and the respiratory health of uranium workers.

METHOD

Initially two pilot studies were done on selected groups of high-risk workers to determine the prevalence of alpha-1-antitrypsin deficiency and the retained burden of uranium in the lungs of exposed workers. The value of sputum cytology was also evaluated. A cross-sectional study was conducted in 1984 to determine the prevalence of spirometric abnormalities among uranium miners. The data from non-smokers without symptoms was used to develop lung function reference values relevant for the present population. Follow up analytical cross-sectional and case control studies were done in 1996 and 1999 to determine the mean independent effect of uranium on the respiratory health of miners and to detect abnormalities in both smokers and non-smokers. Data was collected on employment history, smoking habits, pulmonary function and chest radiographs. To determine the independent mean effect of uranium mining on the respiratory health of workers, only data of non-smokers in exposed cohorts were compared with unexposed control cohorts.

RESULTS

The prevalence of alpha-1-antitrypsin appeared to be high in workers with abnormal spirometric indices. The lung burden of retained uranium in workers in the final product recovery area was within normal limits. The sputum cytology was abandoned because it was found worldwide that cytological screening had no impact on population survival rates. Lung function prediction equations derived from multiple linear regressions were calculated

for the study population which differed from Schoenberg *et al*/ prediction equations. The data from the analytical cross-sectional study in 1996 suggests that the level of exposure in this study group (without the confounding effect of cigarette smoking) is **not** associated with statistically significant impairment of lung function, increased prevalence of silicosis, tuberculosis and respiratory cancer. Only the FEF₇₅ was found to be an indicator of early lung abnormality.

Data from the 1999 study supports the hypothesis that there is a small but significant exposure-response relationship between prolonged exposure to low levels of silica dust, and lung function abnormalities (in the absence of radiologically diagnosed silicosis). The prevalence of chronic obstructive pulmonary disease (COPD) and small airways disease (SAD) was small but significantly higher in exposed workers. The risk of developing COPD was 2.7 times higher for exposed workers. The risk for non-smokers was small but significant. The incidence of tuberculosis and lung cancer was not higher than expected (probably because ex-employees were not fully investigated).

CONCLUSION

Calculation of location specific prediction equations for different ethnic groups is advocated to enable the earliest detection of lung function abnormalities. FEF₇₅ could be used as an early indicator of lung function impairment (provided strict quality control is maintained). Exposure to a combination of silica dust, radon progeny and smoking was associated with an increased risk of lung function abnormalities, but not with tuberculosis, silicosis and lung cancer. Conclusive assessment must await sufficient latency, and **ex-employees** must be investigated to establish the true magnitude and distribution of the effects of siliceous and uranium dust on the health of workers (which may continue after exposure cease).

OPSOMMING

DOELWIT

Die doelwit van hierdie studie was om die respiratoriese gesondheidstatus van uraanwerkers te bepaal wat langdurig blootgestel was aan lae vlakke van silika, uraanstof, omgewingsbesoedelingstowwe en radon.

METODE

Aanvanklik was twee loodsstudies van stapel gestuur om die voorkoms van alfa-1-antitrypsien te bepaal, en om die uraanlading in die longe van werkers vas te stel. Die waarde van sputum-sitologie was ook geëvalueer. 'n Kruissnit-studie was in 1994 geloods om longfunksie abnormaliteite in werkers te identifiseer. Die inligting is gebruik om normale verwysingswaardes vir longfunksies in die studie populasie te bepaal. Opvolg analitiese studies was gedoen in 1996 en 1999 om die onafhanklike effek van uraan sowel as die invloed van lugbesoedeling op die respiratoriese sisteem te bepaal in rokers en nie-rokers. Inligting rakende werk en rooksgeskiedenis, longfunksie en borskas x-strale is ingewin. Om die onafhanklike invloed van lugbesoedeling op die respiratoriese status te bepaal, is slegs inligting van blootgestelde, nie-rokers gebruik en vergelyk met nie blootgestelde, nie-rokers.

RESULTATE

Die voorkomssyfer van alfa-1-antitrypsien blyk hoog te wees in werkers met abnormale longfunksies. Die uraanlading in die longe was binne normale perke. Die sputum sitologie projek is laat vaar omdat wêreldwye resultate nie enige impak op die oorlewingsyfers van pasiënte met longkanker gehad het nie. Voorspelde normale waardes vir longfunksies was bereken vir dié studie populasie wat in sommige opsigte verskil het van die van Schoenberg *et al.* Inligting verkry tydens die 1996 kohort studie het geen onafhanklike effek van lugbesoedeling op die longfunksie van nie-rokers aangetoon nie. Die vloeï by 75% van vitale kapasiteit (nie algemeen aanvaarde maatstaf) was egter statisties beduidend abnormaal.

Die inlingting verkry in die 1999 kohort studie, staaf die hipotese dat langdurende, laegraadse blootstelling wél geassosieer word met longfunksie abnormaliteite in beide rokers en nie-rokers (in die afwesigheid van radiologies bewese silikose). Die insidensie van kroniese obstruktiwe lugwegsiekte was statisties beduidend verhoog in blootgestelde werkers. Die risiko vir nie-rokers was klein, maar statisties beduidend. Die voorkoms van tuberkulose en longkanker was nie hoër as verwag nie (waarskynlik omdat vorige werknemers nie volledig ondersoek is nie).

GEVOLGTREKKING

Om longfunksie abnormaliteite so vroeg as moontlik op te spoor, moet normale longfunksie verwysingswaardes vir verskillende etniese groepe bepaal word. Die vloei by 75% van vitale kapasiteit kan gebruik word as 'n indikator van vroeë longfunksie abnormaliteite (indien streng kwaliteitkontrole toegepas word). Blootstelling aan 'n kombinasie van lugbesoedelingstowwe en rook word geassosieer met 'n verhoogde voorkoms van longfunksie abnormaliteite en kroniese obstruktiwe lugweg siekte, maar nie met 'n verhoogde voorkoms van tuberkulose, silikose en longkanker nie. Finale gevolgtrekkings kan slegs gemaak word nadat voldoende voorsiening vir latentheid gemaak is. Vorige werknemers moet ondersoek word om die volledige impak en distribusie van abnormaliteite wat met uraanmynbou geassosieer word, te evalueer, (effekte wat vererger nadat blootstelling gestaak is).

CHAPTER ONE

1.1 INTRODUCTION

In May 1996 the World Health Organisation (WHO) assembly adopted a resolution; the WHO Global Strategy for Occupational Health for All (OHA). This was a significant decision for a health discipline that still does not feature prominently on the world's health policy agendas.¹

It is a well established fact that health and the environment are inextricably linked, yet "health" defined by the World Health Organisation (1948) as a *state of complete physical, mental and social well-being and not merely the absence of disease or infirmity*, is an Utopian ideal. Many view this as an unattainable and unrealistic goal², but it strengthened the need to re-examine the definitions of health and disease. In the occupational setting with its emphasis on prevention, the development of criteria to distinguish between "disease present", "disease absent" and between "normal" and "abnormal" calls for precise diagnostic criteria.^{2,3,4}

Considerable uncertainty exists regarding the risks to human health that can be caused by agents present in the environment. Environmental diseases are increasing and could pose a serious threat to mankind. The problem is compounded by the rapid pace of technological change and progress, and exposure to new and unknown substances that may seem to be innocuous at first, but may cause major problems in years to come^{2,3,4}.

The pathogenesis of environmental and occupational diseases is extremely complex and multi-factorial in etiology. The interplay between genetic predisposition and environmental conditions governs the manifestations of environmental diseases. The detrimental effect(s) often become apparent only after a long delay of many years (genesis time) and is only registered if the effect can be measured.^{2,3,4} Often the exposure-response relationship is hidden and obscured by non-occupational endeavours⁵, and complicated

by the fact that the variance in human population responses to environmental exposures will probably never accurately be defined. It is thus clear that diverse patterns of diseases manifest and are often complicated by the absence of comparable statistics. The best that we can do is to identify sources of difference, and their responses, in major sub-populations of human beings.

Occupational lung diseases are one of the most frequent occurring occupationally related problems and listed as a priority area in pulmonary health research. Pneumoconiosis is probably the best known, but more and more attention is being paid to problems such as occupational asthma and work related chronic obstructive airways disease. Whilst some have estimated that between 80% to 90% of cancers may be related to environmental influences, only a few cancers have been definitely attributed to exposure to specific agents.^{6,7,8}

Uranium mining operations in Central Europe, Canada, Australia and the United States of America in particular, have been the focus of considerable debate. A number of well documented health effects are associated with the mining and milling of uranium.^{9,10,11,12,13,14,15,16,17,18} The main effects unique to the mining of radioactive ores are those arising from the inhalation of radioactive gases and dust particles, and those arising from chronic external exposure to low levels of radiation. The bulk of the published data on the health effects of uranium mining and milling focused on radon as a causal agent for excess cancers.^{19,20,21,22,23,24,25,26,27,28,29,30,31} Uranium ore contains, apart from the metal itself, siliceous rock and the decay products of uranium; radium and radon. Workers in this industry are thus also exposed to a number of other environmental agents such as siliceous dust and gases.^{32,33}

A unique opportunity presented itself in 1978 when I was appointed as the first Chief Medical Officer of the new uranium mine, Rössing Uranium. The mine is situated in the Namib Desert, approximately 75 kilometers from the coastal town of Swakopmund. The Rössing Uranium Mine commissioned in

Namibia during the early 1970's, represented an ideal environment for research as it is situated in an unpolluted desert. The workforce is drawn from the similarly pollution-free areas of Owambo, Damara and Hereroland and from a variety of socio-economic backgrounds employed in a wide variety of jobs. The mine afforded work to approximately 3000 persons of various ethnic origin, and although the environment is well controlled and exposure is minimised, workers are exposed to a variety of risk factors. The exposure to silica and uranium dust, acid fumes and vapours associated with the welding of a number of different metals and other factors, naturally varies according to the specific work environment of the different persons involved; administrative work, open cast mining, work in the sulphuric acid preparation area, in the ore mills, recovery and final product concentration area.

The extrapolation from high to low doses and from animals to humans causes great problems for exact studies. Therefore much reliance is placed on well-designed epidemiological studies of people exposed to environmental hazards in real life situations. The exposure of Rössing Uranium workers to air pollutants and the health effects associated with this exposure could not be calculated solely from American and European data, and the effects can not be projected on grounds of mining in other continents. A unique set of circumstances prevails at Rössing Uranium. It also has the excellent environmental health infrastructure required for a research study. A further advantage is that the workers (until recently; 1994) were relatively free from HIV/AIDS that has since confounded observations on miners' respiratory illnesses.

This thesis deals with some of the research conducted and will serve as a source document for others to follow. The study of the miners was complicated by a number of unforeseen factors; high labour turnover (apparently a "normal" situation in the development phase of a mine); a fire which devastated a large portion of the mine; loss of computerised data (development phase of computing technology); the loss of the strategic value of uranium; changes in management and financial constraints and the

advent of HIV/AIDS which created a dimension never experienced before. At present, 34% of the Namibian population and 28% of the inhabitants of this region is infected with the AIDS virus.

The focus of this thesis is on the respiratory health status of a sub-population of Namibians employed in an open-cast uranium mine, exploring available methods and accurate measurements to detect abnormalities as early as possible.



1.2 OBJECTIVES

The main objective of this study is to broaden the information base on the respiratory health status of uranium workers and to use the information gathered to describe the relationship between respiratory health status and occupational exposure to uranium and siliceous dust in mining and recovery operations, whilst taking into account other relevant factors with a view to improving preventative policies and practices.

1.2.1 Specific objectives

- * To review current thought and knowledge pertaining to the health effects of uranium mining and milling.
- * To determine the prevalence of various Pi-phenotypes in the Rössing workforce in order to exclude high-risk individuals from high-risk work areas.
- * To determine the lung burden of uranium in the lungs of Rössing workers in order to assess their risk of lung cancer.
- * To re-evaluate the value and significance of sputum cytology as a predictor of early lung abnormalities.
- * To determine the prevalence of workers with abnormal pulmonary function parameters in relation to personal characteristics, age, height, sex and race.
- * To develop predictive equations for lung functions with reference to chronic obstructive pulmonary disease.
- * To examine the relative contribution and influence of exposure to other potential respiratory hazards (principally cigarette smoking) on the development of lung pathology.

- * To examine the relationship between the prevalence of lung abnormalities and exposure to environmental agents in uranium mining and milling as determined by both length of employment and environmental exposure.

CHAPTER TWO

2.1 LITERATURE REVIEW (REVIEW OF CURRENT EVIDENCE)

A detailed discussion on environmental health, pulmonary medicine, physics and biology is beyond the scope of this thesis, yet an overview of relevant published data is given to explain current thoughts on the behavior of inhaled particles and the forces which govern their deposition, retention and subsequent host responses. Published data pertaining to uranium and its health effects tend to concentrate on cancer risks,⁹⁻³¹ but virtually no information is available on investigations of risks in relation to variables such as silica dust, asbestos, uranium dust, criteria pollutants etc.^{32,33,34}

2.2 HISTORY OF URANIUM MINING

Uranium was handled and used long before it was identified. The oxides have been used in the glass and ceramics industry for centuries. Glass produced in Southern Italy in the first century AD was coloured by uranium, and the Bohemian glass and tile industry used uranium salts to produce various ceramic glazes.^{9,35}

Silver was originally discovered near Goslar in 965 and in the Erzgebirge in the 1100's and 1300's. (This mountain range is the natural border between Saxony and Bohemia). Mining became well established in Central Europe and was an important industry, providing work for many people for more than 300 years.^{35,36} They mined copper, silver, iron, cobalt, nickel and manganese, and the rock formations included granite, slate and mica.³⁵ The opening of the silver mines in the Schneeberge in 1410 and at Joachimstal (now called Jachymov, a town 20km north of Carlsbad in Czechoslovakia) in 1516 proved to be of special importance to occupational medicine. The silver was threaded through a hard black ore called pitchblend (because it resembled pitch). A silver coin called a Joachimsthaler was minted in the Bohemian town of Joachimstal in 1519. This was later

changed to "thaler" and "daller" and was eventually corrupted in about 1553 to coin the word "dollar".^{9,35}

Silver mining played an important role in the history of uranium and its health effects. Documents from the 15th century noted that a large proportion of the miners in the Erzgebirge region contracted and died from a respiratory tract disease called "Schneeberg Bergkrankheid" (Schneeberg Mountain Sickness). The cause of the disease was not known and subject to much speculation.^{36,37,38,39,40,41,42}

A number of medical practitioners feature prominently in the unraveling, and eventual identifying, of the health effects of environmental exposure to uranium, radon, dust and tuberculosis.

2.2.1 Agricola (1499 - 1555)

The plight of the miners was first accurately described by the physician Georg Bauer, known as Georgius Agricola. He was born in Saxony in 1499 at the time when Columbus discovered America, and three years before Vasco da Gama sailed around the Cape of Good Hope. He studied philosophy, natural sciences and medicine in Italy and he qualified as a physician.^{35,43}

In around 1526-1527 he was appointed as a physician in the mining town of Joachimstal. A year after his death in 1556 his 12 books, collectively known as "DE RE METALLICA"⁴³, were published. The separate volumes dealt with various aspects of mining and ventilation. In the last part of his 6th book Agricola describes the harmful effects of dust inhaled: "on the other hand some mines are so dry that they are entirely devoid of water and this dryness causes the workman even greater harm, for the dust, which is stirred and beaten up by digging, penetrates into the windpipe and lungs, and produces difficulty in breathing and the disease which the Greeks called Asthma. If the dust has corrosive qualities, it eats away the lungs and implants consumption in the body. In the mines of the

Carpathian mountains women are found who have married 7 husbands, all of whom this terrible consumption has carried off to a premature death". He also described the fatal respiratory disease known as "Schneeberg Bergkrankheid" but did not elaborate on its etiology.^{35,43}

2.2.2 Paracelsus (1493 - 1541)

Aureolus Theophrastus Bombastus von Hohenheim was born in Switzerland. He was known as Paracelsus and was a very controversial figure indeed.^{35,44}

He obtained his medical degree in 1515 and traveled throughout Europe enlisting in armies and working in mining and industry whilst associating himself with "barbers, gypsies, executioners and fortune tellers."³⁵ He was popular as a physician and original in his thoughts, but his independent spirit brought him into conflict with his colleagues. He was killed in a tavern brawl in 1541.^{35,44} Today Paracelsus is known for his accurate description of ailments and for being the first man to successfully use mercury in the treatment of syphilis. His book "Von Der Bergsucht und Anderen Bergkrankheiten" was published posthumously.^{35,44} He described how certain mines gave rise to dyspnoea, cough and cachexia and thought the symptoms were due to the climate or vapours of the mine. In the second and third books of "Von Der Bergsucht", Paracelsus describes the diseases of smelter workers and metallurgists, also mentioning most of the important symptoms of mercurism. The work of Paracelsus had a profound influence on the practice of medicine.

2.2.3 Ramazzini (1633 - 1714)

The physician Bernardino Ramazzini made the greatest contribution towards our understanding of occupational disease. He qualified as a medical doctor in 1659, held various academic positions at the Universities of Modena and Padua, and was well known throughout Europe. He had a capacity for exact observation and an ability to arrive at accurate

conclusions. His momentous work "DE MORBIS ARTIFICUM DIATRIBA"⁴⁵ established occupational medicine as a scientific, modern discipline (published in 1700). He studied the relationships of various occupations and diseases and introduced the vital question to the Hippocratic art: "When a doctor visits the working class home he should be content to sit on a three-legged stool if there isn't a gilded chair and he should take for his examination, and to the questions recommended by Hippocrates, he should add one more: What is your occupation?" Ramazzini made it his motto to think of the dangerous trades when examining a patient "medici munus plebeios curantis est interrogare quas artes exercent".^{35,45} (the doctor must enquire about the patient's occupation.)

This also highlights the tremendous social paradox that existed in the days of Ramazzini. Occupational diseases did not affect the privileged classes and prior to the days of Rousseau, Carlyle and Marx, the problems associated with mining, manual labour and the diseases peculiar to the working class, were given little attention. Although there was a gradual increase in awareness of occupational related diseases, legislation, enforcement and the general lack of knowledge prevailed well into the 1920's.^{35,45}

2.2.4 Unraveling Schneeberg Bergkrankheid

Saxony and Bohemia's "Schneeberg Bergkrankheid" features significantly in the history of uranium-associated occupational lung diseases and modern physics. Worked out mine dumps were widely found in Saxony and Bohemia and the material was piled around the mines, essentially useless, but it had a certain curiosity value because it glowed in the dark. Pieces of it were sold all around Europe and such a piece led Becquerel in 1896 to the discovery of radioactivity. It was from pitchblende, found in the Joachimstal area, that the German chemist Klaproth first isolated uranium in 1789. One hundred years later Marie and Pierre Curie separated the intensely radioactive element, radium.³⁵

In 1717, Dr Schlemer, a medical officer employed by the mines, accurately described signs and symptoms of a number of respiratory diseases. He associated them with exposure to sulphur fumes; arsenic and dust derived from the ores, cobalt and rocks in the area. He was critical of the attitudes of his colleagues towards the prevention and management of these diseases. They regarded miners as a low form of human life.³⁵

In 1878 Dr Hesse, a district physician in Bohemia, published an article recognising the disease previously described as Schneeberg Bergkrankheit to be a form of respiratory cancer. The next year Dr Hesse and Dr Harting (a medical officer employed by the mines) jointly published a three-part article in the "Quarterly Journal of Forensic Medicine and Public Health".^{36,38,39,40,41,42}

Part I dealt with the layout of mines as well as the frequency, clinical and pathological features of lung cancer. Part II described environmental conditions and environmental control whilst Part III dealt with the search for a causal agent and recommendations for improving general health. Their studies included information obtained from comparable mines in Sweden, Hungary, Bohemia and Tyrol. Their work was outstanding, and a landmark in investigative research. It is worthwhile noting that they were allowed to publish their findings although subsequent collateral information hinted at management interference, and a lack of support for future work. This assumption is supported by the fact that, in 1913, Arnstein wished to continue with Harting and Hesse's work, but was denied access to company records.^{38,39}

Dr Ühlig⁴⁰ (1921) knew the Schneeberg area well, and researched the mortality statistics for the miners in the period 1879 - 1913. She found an excessive number of lung cancers, concluding that the lung cancer hazard persisted, and also made a causative association between radioactivity and lung cancer. H E Müller, the director of the mine in Zwickauer (another mine in the Erz mountains) is, however, credited to be the first person to suggest that radioactivity played a role in miners' lung cancer. Dr Ühlig

enquired about the incidence of lung cancer in the Joachimstal area but the Imperial Counselor assured him that there was no such problem. An excessive number of cancers were diagnosed in Joachimstal with a positive association between cancer and ionising radiation, proving him wrong.^{40,41,42}

In 1920 a number of autopsies were performed on miners who died in this area. They found that most of them died from lung cancer, and the rest from silicosis, tuberculosis or a combination of these diseases. Since 1920, the radioactive gases associated with uranium were implicated as the causal agent for the excessive cancers of the uranium mine. The exposure effect relationship was initially uncertain because actual exposures were not well documented and because the latent or genesis period for the development of the lung cancers is lengthy (5 - 15 years). However since 1932 lung cancer among miners were compensatable in both Germany and Czechoslovakia.⁴²

William .C. Hueber emigrated from Germany to America and was a founder member of the environmental section of the National Cancer Institute of America. Hueber, in his classic review (1943) of occupational cancers, listed a number of publications between 1559 and 1869 and commented that a major problem was the general disagreement on nomenclature and the suspected etiology of diseases. He eliminated non-occupational causes and implicated radon in causing lung cancer⁴⁶.

2.3 URANIUM

2.3.1 Uranium Mining

In the 1940's uranium became a strategic mineral for the production of atomic bombs, and uranium mining increased. By 1948 the competition with the Soviet Union escalated, and many uranium mines opened all over the U.S.A. (Arizona, Utah, New Mexico and Colorado). Thousands were employed, many being Navajo Indians. Revival of the uranium industry also prompted the United States government to initiate a number of studies, one being the very important study regarding the health of the uranium miners on the Colorado plateau.^{11,13,47} Excessive cancers were found, and since then numerous studies indicated that cigarette smoking, an important synergistic agent, and small cell undifferentiated lung cancers (rare among the general population) have been clearly associated with radon exposure in uranium mines.^{47,48,49,50,51,52,53,54}

Since 1970 uranium mining in the USA has declined but continued in Canada, Australia, Southern Africa and Namibia. In March 1976, an open cast uranium mine (Rössing) was commissioned in the Namib Desert (approximately 72km northwest of Swakopmund on the Atlantic coast of Namibia). Rössing Mine is a subsidiary of the Rio Tinto Zinc Corporation (RTZ) which has a worldwide interest in uranium mining.⁵⁵ (A detailed summary of Rössing is appended.)

2.3.2 Uranium - The Metal

Uranium is a heavy, hard, silvery-white metal. It is the fourth element in the actinide series, with an atomic weight of 238,03 and an atomic number of 92. It has a specific gravity of 19, a boiling point of 3818°C, a melting point of 1132,2 ± 0,8°C and valency of 3, 4, 5 or 6. Uranium was first isolated in 1841 by Eugene Peligot, although uranium oxide had already been extracted from pitchblende by Martin Heinrich Klaproth in 1789. He named

uranium after the planet Uranus which was discovered in 1781 by Hirschel.^{56,57,58}

The radioactive properties of uranium were first discovered in 1896 by Henri Becquerel when he discovered that emissions from uranium salts blackened photographic plates. In 1934 Enrico Fermi and co-workers observed beta-activities associated with uranium, and in 1938 Hahn and Strassmann showed that uranium could break up into lighter elements with the release of energy. Various investigators pursued the research into the radioactivity of the heaviest element in the known periodic system (developed by Dmitri Ivanovich in 1869). On 2 December 1942 the first self-sustaining nuclear chain reaction was conducted at the University of Chicago whilst the first atomic bomb was detonated on 16 July 1945. The first atomic-powered submarine (the USS Nautilus) was launched in 1955, and the first nuclear power reactor commissioned on 2 December 1957.⁵⁶

2.3.3 Chemistry

Four stable oxides exist, namely UO_2 (uranium dioxide found in uranite), U_3O_8 (uranium oxide found in pitchblende), UO_3 (uranium trioxide) and UO_4 (uranium oxide). Uranium ore contains less than 0,1% of uranium oxide (U_3O_8). This is processed into a uranium concentrate known as yellow-cake which is 85 - 95% pure uranium oxide. Only 0,7% of this uranium is ^{235}U will sustain a chain reaction. To be used in a nuclear reactor, concentrations of ^{235}U must be 3% and for an atomic bomb ^{235}U must be enriched to more than 9% of ^{235}U .^{56,57,58}

2.3.4 Distribution of Uranium

Uranium is found widely in all kinds of ore, and is also measurable in the ocean. There are about three parts per million by weight in the earth's crust (about 3g per ton), and three parts in 10^9 in the sea giving a total mass in the ocean of 4 times 10^9 . It is as common as zinc and one thousand times

more abundant than gold. Despite this abundance it is rarely found in concentrations sufficiently high to mine.^{9,62} The main natural sources for uranium are the Precambrian Age pyritic conglomerate beds in Ontario, South Africa and Namibia, as well as those found as hydrothermal veins in Saxony, Zaire and Canada. Other deposits are found in sedimentary rocks in Colorado, Utah and New Mexico. The uranium is extracted from gold mine tailings in South Africa or produced as a by-product of the gold mining industry.

The grade of the uranium ore mined varies from 0,02% to sometimes as high as 10 - 15%. At the Rössing Uranium mine in Namibia the ore is of a low grade (0,02%) which means that the production of 115 tons of natural uranium would require about 750 000 tons of ore. This could be compared to approximately 4 million tons of coal for 1Gw/y.^{59,60}

2.3.5 Radioactivity

Uranium has 14 radioactive isotopes. Natural occurring uranium contains 99,28% ^{238}U , 0,71% ^{235}U and 0,0058% ^{234}U . ^{238}U has a half-life of $4,49 \times 10^9$ years, and emits alpha particles (energy 4,81MeV) and gamma rays (energy 48KeV). Uranium gives rise to decay chain products of which ^{238}U is the first member. The uranium series include radioactive elements such as ^{234}Th with a half-life of 24,1 days, ^{234}Pa with a half-life of 1,17 minutes, ^{234}U with a half-life of $2,48 \times 10^5$ years, ^{230}Th with a half-life of 1622 years and to the gas ^{222}Rn (Radon).

With a half-life of 3,82 days, ^{222}Rn rapidly gives rise to isotopes known as radon daughters (^{218}Po , ^{214}Po and ^{210}Po). The end product is the stable lead ^{206}Pb . Nine of the radionucleides emit alpha particles and six are beta-particle producers. Weak gamma radiation is also associated with the disintegration of some elements. It is important to note that thorium, fairly abundant in the earth's crust, is usually found in association with uranium and decays into thorium gas (radon-220) ^{216}Po , ^{212}Pb and ^{212}Bi .^{56,57,58,59,60}

2.3.6 Radon

Radon, a radioactive isotope that originates from the natural decay of uranium and thorium, is a noble gas with a half-life of 3,8 days. It emits alpha radiation whilst producing a series of short-lived alpha, beta and gamma-emitting daughter products. Alpha emitters include ^{218}Po and ^{214}Po whilst ^{214}P and ^{214}Bi emit beta and gamma rays.

Radon is usually trapped in rocks and in materials containing radium-226. ^{218}Po Radon diffuses continuously from rock, and when ore is crushed more surfaces are exposed and therefore radon escapes from the solid parts and diffuses through the pores to the surface. Radon is a mobile gas and concentrations are dependent on convective motion, ventilation and other meteorological conditions. In poorly ventilated closed places the concentrations of radon are high and it may also be carried into underground mines by water from elsewhere. The radiation hazard associated with radon is the effect that is produced by short-lived radon daughter products in the decay chain. These radioactive substances are found in the particle or gaseous form and are usually (90%) positively charged because of their alpha particle emission property. They tend to diffuse to and stick to any surface (plate out). Radon is continuously inhaled but not metabolised in the body.^{61,62,63,64,65,66,67,68,69,70}

2.3.7 Health Effects Associated with the Mining and Milling of Uranium

2.3.7.1 Toxic Effects

The main effects associated with the mining and milling of uranium are those arising from the inhalation of radioactive gases and dust (also containing silica); those arising from chronic external exposure to low levels of external radiation and those caused by the toxic compound uranium (and its chemical complexes).

Uranium and its compounds are toxic substances and uranyl ions form stable complexes with carbonate and phosphate ligands in biological fluids. The water soluble uranium bicarbonate complex is stable and only dissociates at low pH's (such as found in the skeletal bones). Both albumin and DNA binds with uranyl ions and the gastrointestinal absorption of soluble uranyl salts is about 10% whilst insolubles are poorly absorbed. Absorption of uranyl salts via the skin occurs, and uranium which reaches the lungs is either dusts of oxides and fluorides (which are hardly diffusible), or soluble uranyl salts.⁶² The insoluble dusts remain in the lung for longer periods and produce a radiation hazard (uranium tetrafluoride and uranium dioxide). The highly diffusible compounds such as uranium hexafluoride or uranyl nitrate are quickly cleared from the respiratory tract and for the larger part pass into the systemic circulation. Upon entering the bloodstream two complexes are formed, namely a non-diffusible uranyl albumin complex, and a diffusible ionic uranyl bicarbonate. The tetravalent (U^{4+}) is mainly deposited in the liver, the cortex of the kidney, and the epifascial portion of the bones.^{63,64,65,66} Faecal excretion is over 2 - 4 days and prominent whilst little is excreted via the kidney. The hexavalent uranyl compound is excreted via the kidney, and deposited in the bones. After glomerular filtration in the kidney the complexes dissociate at the level of the convoluted tubules, and bicarbonate ions are reabsorbed. 20% is reabsorbed in the epithelial cells of the convoluted tubules of which 60% is excreted over the next 24 hours. Uranium salts exhibit both chemical and radiological harmful effects. The solubility influences the toxicity, i.e. uranyl salts are more toxic chemically whilst insoluble salts pose a greater radiological hazard. Renal injury is the main pathological finding (at the tubular level) followed by hepatic impairment. Uranium-235 and uranium-238 are known radiocarcinogens and these findings are confirmed by various studies. The LD_{50} is 0,12mg per kg body weight for rats and 0,55mg per kg for rabbits.⁵⁷

2.3.7.2 *Radiation Effects*

The harmful effects of radiation were first recognized in occupationally exposed individuals. Daniel (1896) and Stevens (1896) described radiation injuries among exposed workers and both Pierre and Marie Curie as well as Antoine Henri Becquerel sustained radiation burns. As early as 1903 Albers-Schoenberg and von Frieden reported on the sterilising effects of radiation. Since then a wide spectrum of abnormalities have been associated with various levels of exposure to ionising radiation. It was soon obvious that a difference should be made between "exposure" and "absorbed dose". A major step forward was the introduction of a precise and quantitative system of dosimetry. A short review of substantiated effects is given.^{62,71,72}

2.3.7.3 *External Radiation*

The broad term **radiation** usually refers to "ionising radiation" (radiation which can cause charged particles {ions}), and includes alpha, beta and gamma radiation. Alpha particles are positively charged helium with two protons and neutrons. Alpha particles are large with great potential energy but with low penetration capabilities, whilst beta particles are electrons with less ionising potential but with slightly greater penetrating capacity. Because of their radiation properties it is clear that alpha and even beta radiation has only a local surface effect unless the radioactive material is present internally. Penetrating gamma rays, however, can irradiate the whole human body. Ionising radiation is usually penetrating and can therefore produce biological damage.

Exposure to ionising radiation can cause both immediate as well as delayed harm to health. Information about the effects on radiation is based on animal experiments and on observations in human beings exposed to various levels of radiation, i.e. survivors of atomic explosions, populations subjected to medical diagnosis and therapy, and populations incurring occupational exposure.^{9,62,75,76,78} Although the

ways in which radiation causes damage to the cells is not fully understood, it may involve changes to the DNA which controls the structure and function of the cell, and passes on copies of itself. DNA can be changed either by being ionised (direct chemical change) or indirectly through the formation of highly reactive free radicals (atoms or molecules which are electrically neutral but with an unpaired electron shell). These mechanisms may result in the prevention of cell division, and/or modify the cells which can be passed on to daughter cells. Damage to the genetic material of somatic cells does not only damage the DNA genus line (which can lead to the development of genetic abnormalities), but also plays an important role in the etiology of cancers. Early development of the foetus is very sensitive to genetic (chromosomal) abnormalities, and it is known that almost 20% of human conceptions abort spontaneously. Non-lethal changes can be reversible, and harmful biological effects have not been demonstrated at low doses of ionising radiation (below 10mSv), either to individual human beings or to human population groups.^{62,70,72}

It is customary to distinguish between two broad classes of effects, namely deterministic and stochastic effects. Deterministic effects are those that result from the killing of cells which, if the dose is large enough, cause sufficient cell loss to impair the function of the organ or tissue. The probability of causing such harm is effectively zero at small doses, but at some levels of dose (above the threshold) the severity of the effect is a function of the magnitude of the dose. Typical examples are the development of cataracts, skin erythema and interference with blood formation. Stochastic effects result from the modification, rather than the killing, of an irradiated cell. Such modified cells may, after a prolonged delay, develop into cancer. Whilst there are repair and defense mechanisms, the probability of cancer induction increases with increments of dose, probably without a threshold. The severity of the cancer itself is, however, not related to the level of the dose. Stochastic effects in cells that have the function of transmission of genetic information are termed 'hereditary' effects.^{62,70,72}

Acute effects of high doses of radiation are well documented, and three definite syndromes are recognised, i.e. the central nervous system syndrome, the gastrointestinal syndrome, and the haemopoietic syndrome. It is extremely unlikely, if not impossible, for workers to receive doses of a magnitude high enough to introduce these syndromes in the production of uranium.

Lymphocytes are the most sensitive cells, and after acute exposure a maximal effect can be expected from a whole body dose in the range to 2 - 2,5Sv. The granulocytes and the platelets both show an early rise, followed by depression maximal at about 4 - 6 days, and then slow recovery over the next 25 - 30 days.^{62,80}

The long-term effects associated with acute exposure, as well as to low chronic exposure is, as stated, an increase in the incidence of cancer which can be estimated in terms of an additive or a multiplicative risk model. The absolute risk is the number of excess cancers found for a given unit of time, and of dose for the population at risk, whilst relative risk is the ratio of risk in an irradiated population to that of a control group and does not state the number of individuals involved.^{62,72,73}

No increases in genetic defects were observed among atomic-bomb survivors. Studies on children exposed in utero at Hiroshima and Nagasaki have shown a dose-related increase of severe mental retardation. The number of cases is small, but the data indicates that the most sensitive period is 8 - 15 weeks after conception. A downward shift in the IQ of 30 points per Sievert was noticed, but no effect could be measured below 0.1Sv. The effect is believed to be deterministic.^{62,80}

No statistically significant demonstrable increase in major birth defects among the children of atomic-bomb survivors was found.^{62,80}

The most important late effect of radiation exposure observed among atomic-bomb survivors is an increased risk of cancer (including leukemias) associated with high doses of radiation. Survivors of Hiroshima and Nagasaki who received a dose of more than 0.6 Gy, showed a 5-fold excess of cancer cases.^{79,80}

Recent evidence of radiation-induced cancers in Japanese atomic bomb survivors shows an increase in some types of cancers, and it is now believed that the overall lifetime risk per unit dose may be larger than previously expected. The health effects of long-term exposure to low level radiation are not fully understood, and are controversial because of the difficulty in establishing dose-related effects. Most estimates for low dose radiation have been based on the assumption that dose response is linear without a threshold. This hypothesis is convenient for radiological protection but its predictions do not always correlate with epidemiological data. The argument for a threshold is based on the cell's ability to repair itself, and there are definite examples such as the deterministic effect of radiation-induced cataracts and erythema. Most cancer epidemiologists appear to consider environmental factors responsible for variation in cancer rates. These factors include (except for radiation), smoking, diet, habits and "practices". Radiation is known to be a cause, but not the only one.^{72,73}

Mancuso reported in 1977 that he found evidence of a risk of cancer for nuclear workers. Opposing reports by Kneale *et al*, and Gilbert *et al* heightened the difficulty in identifying small increases for risks of cancer in strictly controlled doses of nuclear workers.^{85,86} The US National Cancer Institute Study did not find an increase in cancer deaths around nuclear facilities. Research carried out by Massachusetts Department of Public Health traced all types of adult leukemia with the exception of chronic lymphocytic leukemia (believed not to be associated with radiation) to those who lived or worked close to the Pilgrim Nuclear Power Plant in Massachusetts during 1978 - 1983. The study was well designed, and one of the first to correct for confounding factors. They

suggest that there may be increased risk levels from radiation at low levels of exposure.⁸³

There have also been reports on leukemia clusters near nuclear installations (Italy, England, America and Argentina) and in 1990 MJ Gardner *et al* reported on a correlation between the cases of leukemia and the fathers' irradiation history. Other studies (Sorahan) do not support Gardner's study⁷⁹ claiming that other explanations have not been fully excluded.^{83,84}

Health effects arising from low dose external exposure of uranium miners is difficult to demonstrate. This is partly due to the low radiation levels generated by the ores mined, the safety precautions taken to limit the exposure, and the relatively small number of people employed in the production of uranium.⁹ Those who have the potential to be exposed to higher than acceptable levels of external radiation include pit grade control personnel as their task is to mark out those areas in the pit where the radiation levels are highest so that the uranium-rich areas can be preferentially mined as well as those employed in the production of yellow-cake (uranium oxide) (especially in the final process of recovery and concentration).^{9,13}

Available scientific data does not support concerns about the effects of exposure to low levels (below the recommended ICRP threshold limits) of radiation in the mining and milling of uranium. The consensus view is that there is about a 1 in 100 risk of fatal cancer developing for each Sievert of radiation dose received over and above the dose received from natural background radiation.^{74,75,76,78,79,80,81,82,83}

2.3.7.4 Internal Radiation

The inhalation of radioactive gases and dusts (with particle size in the range of 7 micron and less) constitutes the biggest potential problem associated with uranium mining. Inhalation of radioactive dust particles,

which are insoluble in lung fluids, contributes to a radiation problem. Even small quantities of radioactive materials, which represent an insignificant external hazard can give rise to an appreciable dose rate when inhaled. Uranium products, which are soluble in lung fluids, pose a chemical (toxic) rather than a radiological hazard. Once taken into the body the radioactive substance will continue to irradiate the body until it has decayed or has been excreted.^{62,71} The rate of decay of the radioactivity depends on its half-life which can vary from seconds to thousands of years. The rate of excretion depends on the chemical characteristics and the general condition of the human host. This can also vary from hours to many years.

Internal radioactive contamination can occur via inhalation, swallowing or through the skin. The major demonstrated health hazard associated with uranium mines is the inhalation of air containing the radioactive daughters of radon and radioactive dust. When deposited on the epithelial cells of the tracheo-bronchial airways and the lungs, the subsequent alpha decay delivers large radiation doses to the sensitive lung tissue increasing the risk of developing lung cancer.^{71,72,73} The associated alpha radiation could lead to the development of interstitial fibrosis and obstructive airways disease. Miners are furthermore exposed to other environmental pollutants such as silica, diesel fumes. It is extremely difficult, if not impossible, to separate the effects of radon from silica. Excessive mortality rates from non-malignant renal disease, cancer of the stomach, silicosis and COPD have been reported.^{9,11,13,14,17,22,26,34} To date the Environmental Protection Agency (USA) has no solid evidence that exposures to 4pCi/L of radon causes lung cancer in either smokers or non-smokers. The most recent ICRP publication (No 65 of 1993) differs from that of 1991 (No 68), by obtaining "a conversion from exposures to effective dose by a direct comparison of the detriment associated with a unit effective dose and a unit radon exposure."

They state in the recent ICRP publication (65 of 1993) that:⁶⁸

- * The Commission relies mainly on data from epidemiological studies on miners and does not recommend the use of the dosimetric human respiratory model for the assessment of radon exposure.
 - * The Commission adopted a nominal probability coefficient (fatality) for males of 8×10^5 per mJ.L.M³ (3×10^4 per WLM). 1 mJ.L.M³ is equivalent to an effective dose of 1.43 Sv for members of the public (1WLM = 5.06 mSv for workers and 3.88 mSv for members of the public).
 - * The detriment per unit effective dose is 5.6 mSv for workers and 7.3×10^5 per mSv for the general public.^{68,70}
- It is impractical, if not impossible, to consider the contribution of the various radiation doses separately. Estimates of the incomplete collective effective dose equivalents are referred to as "collective dose". Collective doses are expressed in the unit *man-Sieverts (or man-Rems)*. The Sievert is the SI unit of dose equivalent and replaces the old term, *Rem*. One Sievert equals 100 Rems. The unit of absorbed radiation dose is the *Gray* (1 Gy is 1 joule per kilogram is 100 Rad - old unit) which is numerically equal in the case of beta, gamma and x-rays to the biological active *sievert*.^{72,73} In the uranium mining and milling industry the unit for exposure is known as the *working level (WL)*. This term is used because the radiation dose to the bronchial epithelium cannot be determined directly or even calculated accurately. The WL is usually measured instead of the concentration of each of the short half-life radon daughters. It is defined as any combination of radon daughters in one litre of air that results in the ultimate release of $1,3 \times 10^5$ MeV of potential alpha energy. Accumulative exposures are expressed as working level months (WLM)-exposure at one WL for one month (176 working hours) is one WLM.^{65,66,69,70}

Radon exposure at home adds to the radiation dosage received, but this radiation dose varies considerably. On average the annual dose is 1,2mSv, but can be as high as 12mSv. As stated before, occupational exposures to radon and its decay products are found in those mining

uranium, hematite and fluospar - higher exposures (as is the case in uranium mining) is associated with an increased risk of lung cancer in smoking and non-smoking uranium mine workers. Numerous epidemiological studies in various groups of uranium mine workers showed a significant excess of lung cancer rates with the dose effect relationship and the attributable cancer risk significantly influenced by the age of first exposure, total accumulated exposure and cigarette smoking.⁶² Based on the AEC (Publication 9) publication 65 (1993), the fatality risk associated with the average indoor radon concentration in South African residences of 42 Bq.m^{-3} is therefore 5.25×10^{-5} , resulting in 1500 deaths per annum in a population of 30 million.^{69,70}

2.4 ENVIRONMENT AND THE RESPIRATORY TRACT

2.4.1 Introduction

The respiratory system, particularly the lungs, provide the body with oxygen and eliminate carbon dioxide at the rate required by tissue metabolism. The morphology of the lung is determined by genetic and environmental influences, and the total number of alveoli which is genetically determined can be correlated with height.⁸⁷ The origin of adult lung abnormalities can often be traced to insults received during the foetal and and/or early childhood periods. Conducting airways are formed during early gestation whilst alveoli are formed during late gestation, and during the first years of life. The number of alveoli during the first year of life is estimated to be 25×10^6 , and increases to 295×10^6 during adult life. Parental smoking, passive smoking, childhood infections and being under-weight in infancy is associated with impaired growth of lungs. Parenchymal lung injury can thus be closely correlated with the functional and structural unit of the gas exchange region; the pulmonary acinus.^{88,89,90}

The average adult inhales between 10 000-20 000 litres of air per day which weighs approximately 15kg. Inhaled air not only contains oxygen, but also a variety of environmental agents ranging from particles (organic and

inorganic), fibres, noxious gases, vapours and micro-organisms. Selectivity over the air inhaled is limited and the risk of developing lung diseases is enhanced by the exceptionally large lung parenchyma (70 metres square for an adult male), and the tissue barrier which is extremely thin (as little as 2 micrometres).⁸⁸

The lung is the target organ in most industrial settings. Polluted air inspired over time exposed to a large parenchymal surface, leads to various lung abnormalities broadly classified as occupational lung diseases.^{91,92,94}

Massive short-term exposures or sustained long-term smaller exposures, can have a significant effect on human lungs. The outcome of the interaction between environmental agents and the lung depends on the length of time the particle stays in the lung, and the dose delivered to sensitive parts. The potential to cause adverse effects in humans also depends on the physical and chemical properties of the pollutant, and the response of the multi-stage defense mechanism of the human host. The lung's response to environmental agents is not agent-specific – it shares general pulmonary defense responses such as neutrophilic invasion, initiation of cell mediator release and the development of antibodies. This could lead to impaired bronchociliary clearance, bronchoconstriction, gland hypertrophy, inflammatory reactions and colonisation with micro-organisms.^{92,93,94}

Environmental and occupational lung diseases have been recognised for hundreds of years, but were only focused on in a significant and purposeful manner since the Second World War. The relationships between environmental (occupational and general population) exposures and mortality (malignant and non-malignant), and respiratory morbidity, have been extensively studied and reported on since 1980. Although the environmental causes of many lung diseases have been identified, the pathophysiology and pathogenic mechanisms underlying the development of some of these diseases are still not fully understood. A number of unanswered questions still remain, i.e. the relative role of genetic factors, the role of cigarette smoking and atmospheric pollution.^{92,93,94,95,96}

Another complicating factor is the fact that environmental lung diseases are often not recognized and are thus under-reported. Davies of the N.C.O.H. states that a fundamental error in attempts to determine the prevalence or incidence of occupational diseases, is under-ascertainment or denominator difficulty. As a recent example he quoted that occupational asthma had to wait until 11 January 1993 before it was added to the list of occupational diseases in South Africa.⁹⁷

2.4.2 Air Pollution

Air pollution affects primarily the respiratory system, and results in increased rates of asthma, chronic bronchitis, emphysema and lung cancer, as well as acute respiratory infections such as pneumonia.^{98,99,100,101,102} These conditions have been among the most rapidly increasing health problems in the industrialised nations over the past decades. In industrialised areas of Southern Africa, death rates due to cancers of the trachea, bronchus and lung are thought to be increasing among the various population groups. Cigarette smoking remains the single most important causative factor, but in high pollution areas additional cancers may occur.^{99,101}

Air pollutants vary from visible particulates, for example, dust and smoke, to invisible, odourless gases such as carbon monoxide. Fine suspended particulates, aerosols and gaseous substances that remain in the atmosphere, are major causes of respiratory ailments. Although measurements of the criteria pollutants (SO_2 , NO_x , CO, O_3 , Pb and particulates (PM)) are sparse for South Africa, evidence exists in selected areas that levels of some of these pollutants exceed world health standards.^{98,99,100}

Particulate matter and sulphur dioxide emissions are probably largely responsible for the diminished air quality in many areas of Southern Africa. Sulphur dioxide is a form of air pollution that results from domestic and

industrial coal combustion and from ash that is discarded on smoldering dumps. The health effects of environmental agents, notably the sulphur dioxide/particulates complex, have been well demonstrated. Respiratory diseases are aggravated and decreases in lung function may occur.^{99,100,101,102}

Air pollution in Namibia is confined to the areas around the major mines. The influence of air pollution (other than from their work) in the Rössing population is minimised as all the houses are fitted with electricity and the residential areas are located far from the mines and outside the direction of the prevailing winds.

2.4.3 Particle Mechanics

Atmospheric pollutants penetrate the lung and the adverse effects depend largely on their physical and chemical properties. Particles or collections of particles (aerosols) penetrate the lungs, and the depth of penetration depends on their aerodynamic size (particle diameter), density and concentration. Those larger than 10 microns are effectively filtered out in the upper airways. Those between 1 – 10 microns penetrate the lung, and their deposition depends on gravitational sedimentation (force of gravity). Compaction usually occurs at the bifurcation where the aerodynamic forces impact the particle at the bend in the lung structure. Slow breathing increases sedimentation leading to uniform deposition in the lungs, whilst rapid and shallow breathing enhances compaction resulting in concentrated patchy depositions of particles at bifurcations.^{88,89}

The deposition of particles smaller than 1µ's depends on Brownian diffusion which increases with the length of airway, and is greatest in the terminal bronchiole. The deposition of fibres (particles with a length of 3 times the width) occurs mainly through interception and those with a large cross section align themselves with air streams allowing for deep penetration. The deposition of gases depends on their water solubility, concentration and breathing patterns. SO₂ and formaldehyde are, for instance, highly water

soluble and affect the upper airways, whilst nitrous oxide and ozone, which are less water soluble, penetrate deeper into the lung structure affecting the smaller airways and alveoli.^{88,89}

2.4.4 Defense Mechanisms

The human lung has a very effective yet complex multi-stage defense mechanism, but it can readily be impaired. In this dysfunction lies the pathogenesis of occupational lung diseases.¹⁰³

2.4.4.1 Physical

The structural characteristics of the upper respiratory tract prevents harmful environmental agents from deeper penetration. Mechanical filtering takes place in the nose, the nasopharynx and larynx, whilst the angulation of the bronchial tree increases the turbulence, and the slow flow rate enhances particle deposition in the mucous. Receptors in the airways are sensitive to irritant and noxious agents and lead to sneezing, coughing and bronchospasm.^{104,105,106}

The second line of physical defense is the mucociliary elevator mechanism. The system consists of ciliated epithelium cells with mucous produced by the submucosal and goblet glands. The terminal bronchioli contain non-ciliated epithelium cells which also secrete fluids (Clark cells). The mucous contains amino acids, electrolytes, immunoglobulins, alpha-1-antitrypsin and alpha-1-acidglycoprotein. The ciliated epithelial cells beat at a rate of 1000 to 1500 cycles per minute, and the particles deposited at the level of the trachea or the first bifurcation, are cleared within the half time of 30 minutes. Clearance distal to the terminal bronchioli is different for inert and cytotoxic particles. Inert particles are removed via the bronchial and lymphatic route (intra-pulmonary and hilar lymph nodes.) Cystic fibrosis, cigarette smoking, exposure to noxious gases and micro-organisms could lead to cilio-stasis and cilio-toxis.¹⁰⁴

2.4.4.2 Cellular (Cell Mediated) Immunity

Small particles and solubles can pass through the upper airway defenses and reach the alveolar region. The elimination of environmental agents in this region depends, to a large extent, initially on the phagocytic capabilities of the alveolar macrophages that are the main defense cells of the alveoli. The impairment of the alveolar clearing mechanism is related to the development of a number of occupational lung diseases.^{103,104}

The alveolar macrophage plays a pivotal role in the cellular defense system. They are large (14 - 19 μ), mononuclear phagocytic cells formed in the haemopoietic system and recruited as monocytes into the interstitium where they differentiate into interstitial and alveolar macrophages. Newly arrived cells are as small as monocytes, but when activated, develop new membranes, lysosomal enzymes and grow in size. Macrophages are recruited, according to demand, from the resident pool within the interstitium, and through local proliferation. The important role of both phagocytic and immuno-regulatory reactions of the macrophages, is well documented.^{106,107}

Chronic exposure to dust and other environmental agents provoke an inflammatory reaction in the lungs which is associated with an increased release of cytokines and complement fragments leading to the activation of prime leukocytes such as macrophages, neutrophils and eosinophils. There is a direct relationship between the size of the lung load of environmental pollutants, and the cellular output of phagocytes.^{107,109}

Once macrophages are activated they express Fc, C3b and C3b1 receptors for attachment to particles and produce higher levels of super-oxides and enzymes. Phagocytosis is a complex energy-consuming process and oxygen-dependent killing of micro organisms and

inactivation of other particles occurs within the phagosomes (membrane bound intra-cellular vesicles which contain phagocytosed materials).¹⁰⁹ When activated, enzymes from the phagosomes' membranes (nicotinamide-adenine-dinucleotide phosphate {NADPH} oxidase), catalyse the reduction of molecular O_2 to the superoxide anion (O_2^-). Catalysed by the enzyme superoxide dismutase - superoxide in turn dismutates to hydrogen peroxide H_2O_2 and molecular oxygen. If metal ions are present, reactive hydroxyl radicals (OH^-) are formed from superoxide and hydrogen peroxide, H_2O_2 . (Haber-Weiss or Fenton reaction). The lysosomes also contain peroxidases that convert halide ions in the presence of H_2O_2 to toxic halogen compounds.^{106,107,108,109,110,111,112,113}

The response of the macrophages is not an isolated event, but part of a general pulmonary reaction to protect the integrity of the lung. Exposure to ozone, oxides of nitrogen and cigarette smoke are associated with damage to type 1 bronchiolar epithelial cells, and a neutrophilic response. Macrophages release powerful neutrophilic attractants with the neutrophils; the first cells to respond.^{110,114} The release of the arachidonic acid from the bi-layer is believed to initiate chemotaxis. Just after phagocytosis, neutrophils undergo a burst of activity with increased oxygen demand and an increased hexosemonophosphate shunt with the production of oxides. Neutrophils and monocytes (myeloperoxidase dependent) produce hydroxyl radicals from hydrogen peroxide, whilst myeloperoxidase and chloroperoxidase from neutrophils and eosinophils respectively, are essential for the formation of cytotoxic hypochlorous acid (HOCL).^{110,114} To quote K L Maier: "the myeloperoxidase is an inflammatory marker, which substantially influences the composition of the oxidant pattern in the lung"¹¹³

2.4.5 Immunological Reactions

The immune response refers to all the responses of both T and B cell lymphocytes, to antigens. When the process of phagocytosis fails, the

immunologically specific mechanisms of the host defense responses are ultimately provided by the lymphocytes. The responses depend on the type of effector cell generated, and can be broadly divided into antibody and cytotoxic T cell responses, and activation of macrophages and other cells.^{110,111,112} This interaction of macrophages and lymphocytes is essential for initiating and modulating the pulmonary immune reactivity. Antigen presenting cells [APC] (macrophages, monocytes, Langerhans and dendritic cells) occur in lymphoid tissue throughout the body, including the epithelium of the airways and the skin. The particles and antigens become attached to antigen presenting cells (APC) which transport the antigen in an identifiable form to the specific antigen-reactive B-and T-lymphocytes, with subsequent proliferation and differentiation into effectors of humoral (antibody production) and cell-mediated (cytotoxic lymphocytes) immunity. The TH2/CD4 lymphocyte subset produce interleukin 4 (lymphokine) which stimulates the "switching on" of an uncommitted B-cell to produce IgE (TH2 cell type predominance). TH2 lymphocytes seem to regulate the inflammatory cascade and the cytokines recruit migrating inflammatory cells such as mast cells, eosinophils and macrophages to the site of inflammation releasing inflammatory mediators which cause smooth muscle contraction, inflammatory oedema, mucus production and the infiltration of inflammatory cells.^{109,110,112,113}

2.4.6 Immunopathology

Immunopathology refers to excessive immune responses when exposed to environmental agents which can damage the host's own tissues. It encompasses both the excessive response and the subsequent pathology which develops, and is implicated in the pathogenesis of occupational and other chronic inflammatory diseases.^{113,114} Hypersensitivity is the exaggerated and inappropriate immune response, and is subdivided into four major types by Gel and Coombes.^{115,116,117,118} The subdivision is based on the speed of reaction and the nature of the immune mechanism, and although they are described as four different entities, they may occur in isolation or may be subsumed in a single type. Type I is the immediate

hypersensitivity reaction; type II the antibody mediated hypersensitivity; type III the immune complex mediator hypersensitivity and type IV, the delayed hypersensitivity.^{116,117}

2.4.7 Allergic Diseases

Allergy can be defined as altered immune tolerance or reactivity on a second contact with an antigen, and usually means a type I hypersensitivity reaction.^{117,118} Atopy is the term used to identify those who are susceptible to hyperactivity to allergies. It predisposes individuals to develop IgE mediator sensitivity to allergens, and is a clinical syndrome first described by Coca and Coca that can be found in 10% of the general population. The Oxford Group defined *atopy on the basis of positive response to a prick test, positive specific IgE titre, a high total concentration of IgE or any combination of these.*^{116,117,118} Atopy manifests itself as eczema, hay fever, allergic conjunctivitis, urticaria, food and additive allergy, medication allergy, migraine and asthma. The expression of atopy is dependent on several genetic influences and a variety of environmental effects. It is usually an immediate hypersensitivity (allergic) reaction in susceptible individuals, with a release of mediators (histamine, leucotrienes, etc.) from the mast cells and the basophils. In the case of asthma both immediate and delayed immunological mechanisms are implicated - the acute asthmatic reaction being mainly histamine-driven.^{116,117,118,119}

Allergens are carried by antigen-presenting cells to local CD4 helper T-cells. They present the antigen via the surface MHC2 and CD4 markers, to T-helper cells surface receptors which in turn release the cytokine interleukin 4 (IL-4) which causes specific B-cells that have attached to the APC's, to undergo clonal proliferation, and to release IgE specific for the intruding allergen. The IgE can then cross-link with the allergen on mast cell and basophil surface which leads to degranulation and mediator release. The degranulation occurs when the mast cell granules fuse with the plasma membrane resulting in the release of the contents to the exterior.¹²⁰

CD-4 and helper cells can be subdivided into two main types according to their cytokine profile and function. The TH2 cells promote B-cell IgE production and proliferation by releasing interleukin 3, 4 and 5 and TH1 cells which produce interferon gamma (IFN-gamma) which retards IgE production.^{120,121} The opposite reaction, namely the reduction of IL4's stimulated IgE production is a function of gamma interferon (IFN), another lymphokine, but this time produced by the TH1/CD4 lymphocyte subset. The net result of the IgE response is thus determined by the balance in function between interleukin 4 and gamma interferon epithelial cells, and fibroblasts in the mucosa of the airway. These play an important role in the inflammatory process as it is believed that they can also reduce cytokines which could enhance the inflammatory process by "up regulating" the maintenance of chronic inflammation.^{121,122,123,124,125} The cause of "up regulating" is not always known, but atmospheric pollution and viral infections are implicated.¹²⁵ It is believed that the epithelial cells reduce pro-inflammatory mediators GM-CSF (granulocyte, macrophage colony stimulating factor) and interleukin 1. GM-CSF enhances eosinophil migration into the airways, and interleukin 1 promotes the inflammatory cascade. Of special importance are the adhesion molecules that play an important role in leukocyte attraction to the site of inflammation. It also plays an important role in cell mobility, cell communication, and immune regulation by recognising and activating phagocytes and T-cells.^{116,118,121,122} The major families of adhesion molecules include: the immunoglobulin super family ICAM 1 (intercellular adhesion molecule 1), VCAM 1 (vascular cell adhesion molecule 1), and the Integrin and Selectan family.^{118,119,120,121,122} The eosinophil products break down the adhesion molecules which hold the columnal epithelium together, and cleavage occurs at the base of the cell layer with the result that the epithelial cells drift apart. Fibrosis of the basement membrane occurs in chronic asthma when the myofibrills infiltrates the basal cell and induces scar tissue.¹¹⁸ They also increase the lifespan of the eosinophil from 3 to 60 days, and contribute to the whole inflammatory process by enhancing and propagating it.

Allergic diseases are multi-factorial and there are a number of well-identified risk factors for the development of allergic diseases. These include genetic predisposition, allergen exposure, and certain contributing factors influencing the phenotypic expression of allergy.^{122,126} There is little doubt that there is an increase in allergic diseases worldwide. The so-called "allergic march" is a process where a genetically pre-disposed person is sensitised as a foetus, fed on cow's milk, eggs and wheat, exposed to allergens such as the house-dust mite, moulds and animal epithelium cells, and who develops an allergic profile which is now well established. These individuals, when exposed in later life to environmental pollutants, progress from food allergies to upper respiratory infections, and lower respiratory infections with full-blown asthma.^{122,123,124}

2.4.8 Genetic Predisposition

The nature of inheritance of atopy is not fully understood. There is good evidence though that atopy is a genetic abnormality inherited as an autosomal dominant abnormality, and predisposes an individual to the development of immunoglobulin-E mediated hypersensitivity to allergens.^{122,126} The occurrence of asthma in families was described in the 17th century, and the understanding was strengthened in the 1800's when Correnz and Vries rediscovered Mendelsohn's work on genetic transmission of familial trends. A number of publications followed describing the increased prevalence of asthma and allergic tendencies in the offspring of asthmatics (Schwartz and Leigh and Marley). A family history remains an important predictor of atopy. Atopic individuals usually have a family or personal history of allergic rhinitis, atopic eczema and allergic asthma.¹²³ It is still not known why some atopic individuals develop asthma and others do not.¹²⁶ It has, however, been shown that if there is no family history of atopy, the chances for developing allergies are less than 5%. If one parent is atopic then the chance is 37%, and if both parents are allergic the child has a 62% chance of developing allergies. If both parents have the same allergic disease (for example, asthma) then the chances could be as high as 73%.^{123,125,127}

Goodheart looked at the hereditary nature of asthma in 1991, and a number of studies have revealed allergic concordance in 50% of monozygotic and 33% of dizygotic twins. Both recessive and dominant mendelian inheritance, and polygenetic modes of inheritance have been studied. Professor Bill Cookson and LP Ten Kate pointed out the strong maternal inheritance in their recently published work.^{122,127}

Professor Cookson found a marker for atopy on the long arm of chromosome 11 (D11S97) at position 11q13.¹²⁶ Another chromosome that was intensively studied was chromosome 5. At the 3' end is the site for the gene's interleukin 4 (IL4), interleukin 5 (IL5), interleukin 9 (IL9) and interleukin 13 (IL13) also known as the interleukin 4 gene cluster. Interleukin 4 is essential for isotype switching in B-lymphocytes from IgM to IgE production, and the others are important pro-inflammatory mediators in atopic disease. The gene for the Fc portion of the heavy chain of IgE is found on chromosome 14, and may be closely involved in the control of atopy. Another interesting association is the one between Alpha-1-proteases inhibitor (Alphalpha-1-antitrypsin), phenotypes, and atopic disease since the gene for Alphalpha-1-antitrypsin lies on 14q close by. The responsiveness of immunoglobulin-E to antigens is genetically controlled by immune response genes in the D region of major histocompatibility complex (MHC), and by non-MHC link genes (chromosome 6). These control the magnitude of the IgE response.^{122,126}

2.4.9 Allergen Exposure

IgE is produced by the foetus as from the 11th week of gestation. Intrauterine allergic responses are possible if the allergen crosses the maternal-placental barrier. Differences between IgE concentrations in cord blood of infants who have been sensitised, and those who are not, can be demonstrated. Gamma interferon which inhibits IgE production in normal individuals has been found to be secreted maximally by the healthy foetus during the second trimester of pregnancy - this may be a normal

physiological mechanism to prevent allergic responses.¹²⁴ Excessive maternal allergen exposure during the third trimester of pregnancy has been linked to increased T-cell proliferation to a number of allergens. A low cord blood interferon correlates with the later development of atopic eczema, but cord blood IgE estimates seem to be an insensitive measure of atopy. Smokers have higher IgE levels than non-smokers, and smoking predisposes atopic individuals to sensitisation.¹²⁵ Environmental tobacco smoke can cause increased bronchial hyper-responsiveness from as early as four weeks of age. In non-atopic parents, maternal cigarette smoking increases IgE and bronchial hyper-responsiveness to the same level as that attained when both parents are atopic non-smokers.^{124,127} Of all infants that wheeze, 20% will be atopic and go on to develop chronic asthma, while 80% will go into remission over 1 - 4 years. Those who remit can still run the risk of developing COPD in later life¹²⁵. An affluent lifestyle also means variety of foods, exposure to multiple allergens, pets and the house dust mite. This leads to allergic sensitisation during the first month of life. The month of birth also correlates well with seasonal allergens and allergic sensitisation. There is no doubt that maternal medication and smoking during pregnancy are among the first allergens that induce the allergic process in the child.^{124,125,126}

2.4.10 Contributing Factors

Small airway calibre is associated with low birth weight, male sex (smaller lungs), chronic lung disease, prematurity low IgE (immunologic defect), gastrointestinal disease such as Coeliac's disease, viral infections, pertussis vaccination and vaccination with aluminium-based vaccines. Exposure to tobacco smoke, SO₂, NO₂, and other environmental allergens contribute to the development of allergic lung disease.¹²⁵

The question whether atopes should be excluded from working in potentially hazardous environments is often debated.¹²⁸ It appears that the current consensual view of atopy is that those in whom the likelihood of inducing an "inappropriate or altered immune response" resulting in an allergic

occupational disease, should be excluded. A more practical guide-line seems to be to employ those with positive skin prick tests to allergens and with a high IgE levels, but without symptoms.

2.4.11 Eosinophils

Eosinophilia is defined as more than 400 eosinophils per mm^3 or 8% of total white cell count. (Others prefer to define it as 250 eosinophils per mm^3 or 5% eosinophilia). Eosinophilia is associated with a long list of human diseases which can be subdivided into four broad groups of ailments, ie: IgE mediated hypersensitivity, allergen induced asthma, allergic rhinitis, allergic broncho-pulmonary aspergillosis, metazoan infections (helminthic in particular), drug reactions, and connective tissue diseases and malignancies.^{130,131}

Eosinophils are bone-marrow derived phagocytes with secretory functions, and have membrane receptors for immunoglobulins and complement. They preferentially damage helminthic larvae in-vitro when opsonized by antibody and/or complement. It is well documented that eosinophils play an important role in the pathogenesis of bronchial asthma, and have been associated with obstructive airways disease.^{132,133} Dutch investigators speculated in the 1960's that allergy and bronchiole hyperactivity could predispose some individuals to develop COPD. Van der Lende (1969) and Burrows *et al*¹³² showed, and confirmed, an association between eosinophilia and lower levels of FEV₁. Horn *et al*¹³³ (1975) confirmed the association between blood eosinophilia and air flow obstruction, whilst Durham and Kay¹³² (1985) showed inverse correlations between blood eosinophilia and the degree of non specific bronchiole hyper-responsiveness.¹³⁹ Kaufmann *et al*¹³⁴ found that absolute numbers of eosinophils were significantly related to a history of childhood eczema and asthma, as well as to current smoking. Whilst the percentage of eosinophils was related to the occurrence of eczema and asthma, FEV₁ (adjusted for smoking) was significantly related to the percentage of eosinophils, current respiratory infections and asthma. The association between eosinophils

counted, and smoking, was related to people who never smoked. In the never-smoked group (without respiratory infections and asthma), both eosinophil percentages and counts were significantly related to the level of FEV_1 , suggesting that "eosinophilia might be a risk factor for COPD among adult non-smokers (Kaufmann *et al*)".¹³⁴

Frette *et al* reports in 1990 that eosinophilia was primarily associated in non-smokers with a lower FEV_1 .¹³⁵ A difference of 400ml was observed in never-smokers with eosinophilia (> 5%) compared to those without. (Controlled for atopy, asthma and bronchiole hyper responsiveness). They concluded that "association between eosinophilia and FEV_1 loss cannot be explained on the basis of asthma or asthma-like diseases, and that the role of eosinophils in respiratory disorders can go beyond its intervention in allergy." Annesi *et al* (1992) correlated IgE (an objective allergy marker) skin prick test with FEV_1 and metacoline bronchio-hyper responsiveness.¹³⁷

IgE levels were not associated with bronchial hyper-responsiveness, but with FEV_1 score in non-smokers (after exclusion of asthmatics). A longitudinal five-year FEV_1 decline was related to IgE non-smokers and ex-smokers, but not to current smokers. The relationship was present after exclusion of those who had a positive test, and those with a history of asthma. Anessi *et al* concluded that "IgE production reflects factors other than allergy; possibly non allergic inflammation).^{137,138}

2.4.12 Oxygen-radicals, lung injury and repair

Oxidants are compounds capable of withdrawing electrons from atoms or molecules and free radicals are atoms or molecules that contain one or more unpaired electrons which makes it more reactive.^{112,113,114} The body makes its own oxygen radicals ie. Superoxide (O_2^-), and uses 1-3% of the oxygen we breathe for this purpose. The active oxygen species are derived from endogenous sources, phagocytic cells and from exogenous sources.¹¹⁴ Partially reduced oxygen species (oxygen derived free radicals) are involved in metabolic reactions. The release of active toxic metabolites

of oxygen is also implicated in many diseases. They tend to react with non-radicals resulting in a free-radical chain-reaction with the formation of new radicals, which in turn can react with membranes, trigger lipid peroxidation and attack DNA, leading to lung abnormalities through oxidant-mediated lung injury.^{111,112,113,114}

There has been considerable debate about the role played by activated phagocytes (macrophages, neutrophils, monocytes and eosinophils) in the overall protection of the lung.¹¹⁴ They respond on demand with a rapid outpour into the alveoli where they modulate the inflammatory processes and, if unchecked, could act as a potential destroyer of lung tissue through the secretion of proteases and the stimulation of fibroblasts.¹⁰⁸

However several cellular antioxidant systems are also in place to neutralise unwarranted reactions, and to protect and maintain normal lung function and structure. The balance between these opposing forces (redox balance) is delicate and disturbances can lead to dysfunction. For instance, when macrophages are injured or killed the cells may release lysosomal enzymes (including collagenase and elastase) to the exterior which in turn may damage normal lung tissue and could play an important role in the pathogenesis of emphysema and hyper-responsiveness of the airways. Elastase is a protease found in PMNL (polymorphonuclear leukocytes) together with lysosomal enzymes interferes with elastin and changes the elastin-connective tissue adhesion which is found in patients with emphysema.^{114,139}

2.4.13 Alpha-1 Antitrypsin

Alpha-1-antitrypsin, a defense glyco-protein, is mainly synthesised in the liver with a small amount produced by macrophages and lymphocytes. As an acute phase protein, its concentrations rise rapidly during acute inflammatory conditions, pregnancy, tumour activity, and with oestrogen and corticosteroid therapy. Smokers exhibit higher than normal levels of alpha-1-antitrypsin which is thought to be associated with a chronic low grade

inflammatory response. An abnormal level of alpha-1-antitrypsin is associated with lung and 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.¹⁴¹

Emphysema is the lung disease most commonly associated with abnormal levels of alpha-1-antitrypsin. The elastin in the alveoli is destroyed through 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 emphysemas. The panlobular (aciner) type of emphysema is thought to be associated with A-1-anti protease deficiency. Environmental pollution likewise increases the risk of developing premature emphysema.^{141,142}

2.4.14 The Role of Smoking and Environmental Pollution

Alveolar macrophages are highly active metabolically, and secrete large amounts of proteases. They increase in number when exposed to cigarette smoke or environmental pollution, and increased numbers are found in patients with COPD and interstitial fibrosis. Cigarette smoke is known to stimulate macrophages to secrete neutrophil chemo-attractants such as C5a.¹²⁰

Peripheral blood leucocytosis can be found in smokers (20% > 9000 cells/ml), and may be an important determinant of the levels of pulmonary functions. The white cell count shows a significant inverse correlation with forced vital capacity (FVC), and forced expiratory volume in one second (FEV₁) adjusted for age, height and smoking habit.

Tobacco smoke contains nicotine, carbon monoxide, tar and more than 50 toxic and cancer causing chemicals. "Cigarette smoke is a heterogeneous mixture of gases, uncondensed vapours and liquid particulate matter. The known compounds in tobacco smoke exceed 4 000, including pharmacologically active, toxic, mutagenic and carcinogenic compounds."¹⁴³

Cigarette smoke contains 2×10^{15} free radicals per “drag” as well as 800ppm oxides of nitrogen (NOX), which can react with H_2O_2 produced by lung phagocytes to produce even stronger free radicals (Dooley and Pryor). This can lead to alpha-1-antitrypsin anti protease/protease dysfunction with subsequent lung abnormalities.^{143,144,145,147}

Oxidants produced by cigarette smoke and environmental pollution can inactivate the TIO ester group in the active part of the alpha-1-antitrypsin molecule. This can lead to proteases/antiproteases dysfunction with subsequent lung abnormalities. It is generally accepted that nitrogen oxides and sulphur, as well as ozone, can produce direct mediated tissue damage as well as damage via the indirect inactivation of alpha-1-antitrypsin.^{103,141,142}

The pathogenesis of emphysema in heterozygotic Z individuals is 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).^{141,142} In summary it can be said that cigarette smoking, and air pollution cause a chronic inflammatory response in the lungs associated with the initiating or exacerbating of recognised lung abnormalities. However the combined effect of a heterozygotic genetic profile with exposure to environmental agents, passive and active cigarette smoking, is also 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.

2.4.15 The Net Effect

In summary it can be stated that individuals and groups of individuals exhibit different responses to environmental stressors (chemicals, infections and environmental agents etc), and that the range of responses can be large. The response, and the intensity of the response, depend on the net effect of

the interplay and modulation between genetic and environmental factors, and its influence on the metabolic capability of the individual, as well as the effect of the host's repair mechanisms. Sustained impairment of the host defense mechanisms could lead to environmental lung diseases that can be classified in a number of ways. For the purpose of this thesis it was decided to use four broad categories: acute irritation and inflammatory lung diseases; chronic inflammatory lung diseases; progressive fibrotic lung diseases and carcinogenic lung diseases.

2.5 ACUTE IRRITATION AND INFLAMMATORY LUNG DISEASE

The inhalation of biologically active substances can give rise to irritation, inflammation and asthmatic response, whilst exposure to biologically inert substances cause asphyxia. The epidemiology is almost always associated with accidental exposures, and usually symptoms are of short duration with measured pulmonary volumes and flows returning to normal within 24 hours.^{148,150,151} Exposure to environmental irritants such as sulphur dioxide, ozone and nitrogen dioxide can lead to a temporary non-specific hyper-responsive state of the airways. Bronchial hyper-responsiveness is found without clinical evidence of symptoms or signs of asthma. There are different individual responses of non-specific hyper-responsiveness. The prevalence varies from 3 - 23% in non-smokers and up to 35% in smokers when tested with methacholine, histamine or cold air challenges. Peat *et al* showed familial predisposition and twin studies point towards a genetic component.¹⁴⁹ Childhood chest infections increase the likelihood of developing bronchial hyper-responsiveness, and epidemiological studies showed that passive smoking might be related to increased bronchial hyper-responsiveness. Bronchial hyperactivity or hyper-responsiveness describes the tendency of airflow limitation (FEV_1 and PEF reduction) or specific airways resistance (Sgaw) to increase in response to a lower dose of inhaled bronchoconstrictors (methacholine and histamine) than that needed to cause the same airflow limitation in normal subjects.^{150,151} The mechanisms of bronchial hyper-responsiveness include inflammation, immunological liberation of bronchoconstrictors, abnormal calcium flux,

alterations to cholinergic anti-cholinergic controls, and damage to epithelium junctions.^{150,151}

Bronchial hyper-responsiveness is considered to be a sentinel "abnormality", and marker, for airway dysfunction in asthmatics and in non-atopic subjects. Those with bronchial hyper-responsiveness are postulated to have more permeable airways with an increased risk to develop irritable and sensitising asthma. Exposure to high doses of SO₂ has also been associated with non-allergic asthma, whilst exposure to uranium hexafluoride, ammonia and smoke inhalation, has been shown to cause bronchial epithelium injury with inflammation (without eosinophils, gland hyperplasia and smooth muscle hypertrophia) leading to a clinical entity first described in 1985 as *reactive airways dysfunction syndrome* (RADS).¹⁵¹ The criteria for RADS are:

- * No history of asthma-like respiratory disease.
- * Onset follows a high level of exposure; usually an accident.
- * Toxicant is an irritant gas, vapour, fume, aerosol or dust in high concentrations.
- * Onset of symptoms is abrupt, developing within minutes or hours, but always within 24 hours.
- * The clinical picture stimulates asthma, with unremitting cough (bronchial irritability) complaints and wheezing.
- * Results of pulmonary function test may be normal or show reversible airflow limitation.
- * Results of challenge with methacholine (or other agents) are positive in the range typical of asthma (i.e. less than 8mg per ml).
- * Other respiratory disorders that simulate asthma are ruled out.

(Taken from Environmental and Occupational. Rom W.H. (ed) 2nd Edition, Boston, Little, Brown and Co;1992;143)¹⁰⁸

Tarco and Broder's¹⁵² recent report on RADS-like cases in patients with repeated low dose exposure to irritants leading to the so-called "low dose RADS" was most interesting. Information about this condition could provide new insight into the etiological explanation of irritant (non-allergic) asthma.

Bronchial hyper-responsiveness remains the hallmark of asthma, but the links between transient increases in airways responsiveness, and the more persistent hyper-responsiveness that characterises asthma, is unclear.^{150,151}

2.6 CHRONIC INFLAMMATORY LUNG DISEASES

Acute inflammatory reactions usually resolve, but chronic inflammation can progress to scarring with the effector cell, the fibroblast, migrating, proliferating and producing collagen and matrix proteins.

Most of the chronic inflammatory lung diseases are associated with bronchial hyper-responsiveness (BHR), and obstruction to airflow. Obstruction to airflow is a common problem and it affects 34% of men over the age of 60 years. It is extremely difficult to apply a diagnostic label to airflow limitation.^{6,34,96} - there are two different schools of thought. Certain European countries (especially the Netherlands) tend to group all obstructive respiratory diseases together as *chronic non-specific lung diseases (CNSLD)*.¹⁹² The Americans and British prefer to make a distinction between two main disease groups, namely asthma and chronic obstructive pulmonary disease because of the different etiologies, pathophysiologies and clinical outcomes. It must, however, be stressed that neither the clinical features nor the pulmonary function test normally used, can successfully distinguish between the two groups.^{172,173,174}

At the first Ciba guest symposium on chronic obstructive pulmonary diseases and related conditions in 1959, asthma was defined as a "reversible" obstruction versus the "non-reversible" obstruction of chronic obstructive pulmonary disease. These definitions have been redefined

taking into account evidence of more recent studies. Some studies found no correlation between bronchodilatation responsiveness and any of the clinical features such as age, allergies, blood or sputum eosinophilia, cigarette smoking or metacholine response. Thus the distinction between asthma and COPD on the basis of pulmonary function testing and bronchodilator responsiveness, is based more on random choice than actual fact.^{172,173,174,175}

2.6.1 Asthma

Asthma is often ill-understood, under diagnosed and inappropriately treated although it was already known to the Greeks. Occupational asthma was described in the 18th century by Ramazzini as "the irritant effects of organic dust which caused both shortness of breath and allergic skin reactions"⁴⁵. A critical issue in the pathogenesis of asthma is the role of allergens and the question whether asthma is a manifestation of atopy or whether it has separate genetic bases, was addressed by various researchers (Pepys, Gerrard *et al*, Ferguson *et al*)¹¹⁷. Sibbald and Turner-Warwick specifically tried to find a different genetic basis for extrinsic and intrinsic asthma.^{127,160} The consensus of opinion points towards a common mode of inheritance for both clinical syndromes. The hypothesis that explains most of the questions is that "asthma and atopy are inherited independently, but that atopy may enhance the likelihood of a genetic predisposition to asthma being expressed". However the evidence for the hypothesis remains, however, circumstantial. Conflicting reports were published on the association between the HLA system and asthma, but there seems to be an absence of detectable association.^{121,132,133}

2.6.1.1 Clinical

Asthma is a chronic, non-stable inflammatory disease of the lungs, and is on the increase world-wide. Airflow limitation and hyper-responsiveness remain the main features of asthma. Asthma, according to the American Thoracic Society, is a "*disease characterised by*

increased responsiveness of the bronchi to various stimuli, manifested by widespread narrowing of the airways that changes in severity either spontaneously or as a result of treatment". It is now almost universally accepted that asthma has at its core, airway inflammation.^{116,155,161,166}

Although the symptoms of asthma are often reversible, the disease is not.¹⁵⁹ The allergic inflammation leads to functional and structural changes. The typical pathological features of asthma include hypertrophy of smooth muscle, vasodilatation, desquamation of epithelium cells, thickening of the basement membrane, oedema of mucosa and submucosal infiltration of eosinophils, plasma cells and lymphocytes.¹¹⁷ The incidence of asthma has increased from 3% to 8% to 10% in the industrialised countries.¹⁵³ The increased prevalence is also associated with an increase in severity in mortality. The reason for this is thought to be a change in lifestyle and the increase of exposure to exogenous factors such as outdoor pollution, indoor pollution and the world-wide increase of allergens. It is also coupled with a decrease in host resistance associated with diet changes (increased alcohol consumption) and a reduced intake of anti-oxidants.¹⁵³

Asthma is expressed in various clinical patterns ranging from asymptomatic to severe. Conventionally asthma was subdivided into allergic (extrinsic), and non-allergic (intrinsic) forms. The allergic form had a positive family history of allergy and asthma, onset in early childhood, affects boys more than girls, has a positive immediate reaction to skin prick for common environmental allergens and tends to improve in adulthood. The non-allergic variety was found in non-atopic parents with fewer familial allergies, and negative skin-prick tests, no sexual preferences and appeared later in life.¹⁵⁵

The emergence of occupational asthma (OA) is of great importance in the industrialised world. "This phenomenon was already described by Ramazzini but it was only recently (1992) declared as an occupational disease in South Africa.^{45,101,156,159,160,161,163} There are a number of

definitions for this condition now regarded as the most common occupational respiratory disorder in the technically advanced world. It is usually defined as “variable airway narrowing causally related to the working environment”. The British Industrial Injuries Advisory Council defines it as “Asthma which develops after a variable period of symptomless exposure to a sensitising agent at work”.^{158,159,160,161,162,163} The list of sensitising agents is long and well documented, and a number of subsets of diagnostic criteria exist. In essence two requirements must be filled in order to diagnose this condition:

- * The diagnosis of asthma must be confirmed in a previously unsensitised person and;
- * A relationship between asthma and the environment must be established; either through specific inhalation challenges (the golden standard) or by serial expiratory peak flow rates (PEFR).^{158,163,164}

2.6.1.2 Epidemiology

Since the 1960's the prevalence of allergic diseases seems to be on the increase. Studies, for instance, in Australia showed that the incidence of asthma there has increased from 4,4% in 1980 to 11,9% in 1994. The incidence of allergic diseases, and specifically asthma, differs from country to country. It varies from 0% in Indonesia, 2,3% in Japan, 7% in Europe, 11% in Africa to 33% in parts of Australia.¹⁶⁰ This cannot be explained on the basis that the genetic pool of asthma is stable, and that the environmental factors responsible for the differences in asthma prevalence are different. The problems of comparison of studies conducted in different geographical areas are hampered by differences in methodology and diagnostic criteria. There are, however, recent studies which indicate that there is a world-wide increase in the prevalence of asthma, particularly in urban communities and communities undergoing westernisation.^{158,160,161} This is explained on the basis that these phenomena are associated with pollution and change in living conditions which increase allergic exposure. The effect

of the house dust mite might increase with urbanisation and animal danders are often found in the homes of developed communities. Studies performed by Van Niekerk *et al* and Keeley found evidence of an increased prevalence of reversible airway obstruction in school children in South Africa.¹⁵⁴ No community prevalence studies have been done in a major black city, such as Soweto, but a study among children in Soweto performed recently, indicated that they are exposed to antigen levels sufficiently high to cause IgA-driven allergic diseases.¹²⁴

Geographical areas also play a role in the so-called "coastal asthma". In these conditions the asthmatic symptoms are either diagnosed, or aggravated in coastal areas. Cookson noted that IgE levels were higher in rural non-asthmatic controls than in urban asthmatics, and it was thought to be associated with parasitic infestations. Carswell concluded after he did a study on Tanzanian children, that the low prevalence of asthma in the tropics could be due to the immunosuppressive effect of malnutrition or the immunosuppressive effect of malaria. The Zimbabwean study contradicted the malnutrition theory, as they were unable to show any differences of mean height and weight for age in children with or without reversible airway obstruction.¹²⁴

Studies done in Finland, Sweden and Scotland, as well as the UK, show that there is an increase in allergic disease. Professor R J Davis (Scotland) showed that the prevalence of hay fever increased from 3% to 12% over the last 25 years. The Swedish Conscript Studies showed a prevalence increase from 1981 to 1991, and in South Africa, the incidence of exercise-induced asthma increased from 3,1% in 1979 to 5,9% in 1985.^{124,126,133}

Asthma could thus be added to the list of so-called diseases of civilisation and is less prevalent, and later in onset, among people who maintain traditional and technologically primitive ways of life: one of the most important factors is the change of lifestyle which is conducive to greater house-dust mite exposure resulting in increased sensitivity and

susceptibility to the development of asthma. Air pollutions (both indoor and outdoor) seem to be an important contributing factor to allergic sensitisation.¹²⁵ The main indoor pollutants are tobacco smoke, and maternal smoking in pregnancy, as well as the burning of coal products producing CO₂ and particulate matter. Formaldehyde has been linked to respiratory allergies and NO₂ is another indoor pollutant that is released from gas stoves. Western lifestyles seem to be associated with improved hygiene and the use of various propellants (type I pollution). Outdoor pollution is characteristic of urbanisation and westernisation, with high levels of ozone, SO₂, NO₂, and exhaust particles.¹⁷² The allergenicity of type II pollution was investigated and it was shown that NO₂ attracts eosinophils into the nasal epithelium, and that these cells, when exposed to ozone, also produced increased levels of interleukin 8 in atopic individuals (interleukin 8 is an eosinophilic chemo-attractant). Therefore it is assumed that type II pollution is allergenic.^{156,159,163}

Another interesting association is the existence of an inverse relationship between allergy (especially bronchial asthma) and the susceptibility to develop lung cancer.¹⁶⁵ This has been debated and there are well documented pro and con arguments. IgE antibodies with anti tumour activities were, however, found in mice and high IgE levels are associated with prognostic significance in lung cancer. Sanchez-Borges *et al* reported a significantly lower prevalence of personal atopy history observed in cancer groups (compared to two other groups) but with significantly high IgE levels.¹⁶⁵ Slovak, (in a balance of opinion article in 1993), raised the question whether atopic employees should be excluded from specific occupations. He concluded that atopes comprise over one third of the work-age populations, and that he does not support discrimination against those with atopy.¹²⁸

2.6.2 Chronic Obstructive Pulmonary Disease

The collective term "chronic obstructive pulmonary disease" (COPD) refers to a disorder of expiratory airflow limitation that does not fluctuate markedly over long periods of observation.^{167,168,169} This definition is intended to differentiate it from asthma. COPD includes small airways disease, chronic bronchitis (with or without airflow obstruction) and emphysema. According to the definition of the American Thoracic Society (1987) localised obstruction, bronchiectasis and cystic fibrosis are excluded from the definition of COPD.¹⁶⁷

2.6.2.1 Small Airways Disease

Small airways disease was first described about 20 years ago for a lung condition with goblet cell metaplasia, and inflammatory infiltration in the airways which were smaller than 2mm in diameter. A major contribution in the understanding of the pathophysiology of COPD resulted from the work of Hogg *et al.*¹⁷³ This showed that early in the evolution of COPD the membranous bronchiole may be considerably affected without there being any appreciable effect on routine ventilatory function tests. The term "small airways disease" was originally taken to include only diseases in non-alveoli related airways of less than 2mm internal diameter, but common usage now includes inflammatory changes in the respiratory bronchioles as well. The absolute magnitude of this peripheral airways resistance, both in normal and diseased lungs, may be equal to, or greater than, the central component - even in the normal lung.^{176,177,178} The constellation of morphological abnormalities identified in the small airways probably does not represent a single disease entity, but is caused by different factors of varying etiologies. The use of the term "small airways disease" persists for lack of a better term.¹⁷⁹

In any epidemiological and/or etiological study it is important to recognise that in COPD the increase in flow resistance is in the

peripheral, and not the central airways.^{180,181,182} Several follow-up studies have been done to investigate the natural history of COPD. Clinical studies have shown that once disability is evident, COPD worsens at a fairly predictable rate that is not affected by presently available therapy.

The disease passes through a stage in which there is considerable peripheral airway obstruction without airway resistance rising above, or maximal expiratory rates falling below, expected normal values. Thus it is not surprising that the disease is incurable when symptoms develop. If the diagnosis could be established at an earlier stage, removal of the causal agent and/or treatment might be more effective.^{183,184}

Abnormal small airway morphology can be correlated with abnormal physiology.^{176,177,178} The correlations vary in strength between individual morphological abnormalities and function tests among studies. This is probably due to differences in methods and source of materials, or to chance alone. Considering all the possible sources of measurement error there is, on balance, a consistent relationship between indices of airflow obstruction and lesions of the small airways. The severity of emphysema correlates strongly with clinical state, whereas small airways disease and other abnormalities of the conducting airways, do not. For pre-clinical detection it is therefore necessary to include some method to determine the extent of small airways impairment.^{185,186,187}

2.6.2.2 Chronic Bronchitis

Chronic bronchitis is defined clinically as *an increase in mucous production by the lower respiratory tract, presenting as a persistent cough with sputum production for more than three months in each year of the previous three years.*^{187,188} This definition was developed for epidemiological studies and it has been shown that hyper-secretion of mucous (hyper-secretory disorder) does not shorten one's life

expectancy. Chronic airflow limitation (lower FEV₁ or PEF_R) is however associated with reduction of life expectancy.^{189,190,191} Chronic bronchitis is associated with inflammation of the mucosal surfaces of the bronchi, an increase in the amount of mucous secreted as well as with an increase of the secretory cells (by definition chronic bronchitis is associated with the inflammatory process of the larger cartilaginous airways). In the case of chronic bronchitis the main cells of inflammation are the neutrophils, and goblet cell metaplasia is a prominent feature. In the case of asthma, infiltration is mostly eosinophils with no, or very little, goblet cell metaplasia.¹⁷⁶

2.6.2.3 Emphysema

Emphysema is defined in pathological terms as *the dilatation of the air space lying beyond the terminal bronchioles of the lung, with destruction of the walls*. It must be stressed that both chronic bronchitis, and emphysema, are nearly always associated in any individual patient.

To sub-classify emphysema into "pink puffers" (alveoli abnormality) or "blue bloaters" (abnormality in the airway conduction system), is not scientifically correct. Pathologically these sub-types are indistinguishable.^{173,174,175}

2.6.2.4 Epidemiology

The diseases causing chronic limitation of airflow (COPD) are a serious problem in any community, and the most common cause of loss of work worldwide. COPD is an important cause of both mortality and disability, and in South Africa more gold miners are compensated for disability associated with COPD than silicosis and lung cancer combined. It is only during the last four decades that these diseases have been intensely investigated.^{191,192,193,194} Predominant factors that have influenced the incidence of respiratory disease in recent years include: exposure to infective agents; exposure to air pollutants; social factors;

nutrition and the causal role of cigarette smoking. Studies done among the general population in China, Norway, Italy, France and the USA (controlled for the “healthy worker effect”), showed a significant excess risk with occupation, and with dust exposure (relative risk 1.5). A number of longitudinal studies among the general population in a number of cities (Paris, Cracow, Bergen and Zutphen) were done, or are underway. The longitudinal analysis of data from the Zutphen study found accumulative 25-year incidence of CNSLD (27.9%). Incidence density ratios for smoking increased from 1.5 for light to 4.5 for heavy smokers (more than 20 cigarettes a day).^{195,196,197,198,199,200}

The Medical Research Council in the UK stated in 1966 that the intensity of dust exposure did not seem to play an important role in determining the prevalence of bronchitis and airway obstruction in workers exposed to dust. This statement is no longer valid or accepted and various researchers have shown that chronic exposure to dust causes chronic airways disease. Clinical experience provides no evidence of the existence of different types of chronic bronchitis that can be related to individual and environmental conditions, i.e. air pollution, cigarette smoking or occupation. The disease has the same characteristics whether found in a coal miner or agricultural worker, male or female. It is not possible to determine in any particular individual with established COPD, precisely how much of the illness is attributable to a particular environmental factor.^{191,192,193,194}

In the UK morbidity and mortality from chronic airways disease have fallen only slightly since 1935 (from the annual reports of the Ministry of Health and Department of Health and Social Security statistics. There is, however, no reason to believe that this could also be the case in Southern Africa, indicating that important etiological factors remain uncontrolled. COPD and lung cancer are at least in part caused by inhaled materials, and to this extent might be preventable. It seems that controlling the smoking of cigarettes will be the most difficult aim to achieve as after 40 years of warnings about the adverse effects of

smoking, and more than two decades of intensive anti-smoking campaigns; more cigarettes are being manufactured today than at the time of the first report on the consequences of smoking and health.¹⁹⁹ In the UK conditions in coal mining, and iron and steel industries, are now such that exposure contributes little to morbidity or mortality compared with the workers' working habits.¹³⁵ A study involving 31 coal mines scattered throughout the USA reported the prevalence of bronchitis to be significantly higher in smoking miners than in non-smoking, or ex-smoking, workers. Surface workers had less bronchitis than underground miners, reflecting a lower exposure to dust. The difference was significant only for non-smokers and ex-smokers. Similar results have been shown by cross sectional surveys of dusty occupations in West Germany. A number of South African studies have clearly shown that occupational exposure to underground dust has been associated with an increased prevalence of respiratory symptoms, COPD and emphysema.^{198,200} The dose response relationship has been established, but the relative role of each pollutant remains unclear. The role of silica exposure in the development of COPD has been studied by a number of researchers. The association between COPD, abnormal lung functions and environmental pollution emerged over the past five years as additional information became available. The bulk of published data suggests that the inhalation of siliceous dust per se contributes towards the development of COPD.^{201,202,203,204,205,206}

Some genetic predisposition to COPD has been shown, and the possible effect of this on workers in high risk areas, must still be investigated.^{142,143,208} The same is also true for cigarette smoking because only 20% of cigarette smokers develop disabling airway obstruction.^{172,175} Of special importance is the role of cigarette smoking in the pathogenesis of environmental diseases, especially as smoking represents the largest proven preventable cause of illness.¹⁸⁸ Tobacco smoke is by far the major air pollutant of health significance in Southern Africa (and elsewhere), and both direct and passive effects are important. Tobacco smoke has been established as the dominant

respiratory carcinogen in man and is associated with a higher incidence of chronic obstructive airways disease, cardiovascular disease, other cancers, and may also act as a synergistic agent with toxic substances found in the environment. Cigarette smoking remains the number one determinant of lung function levels in most studies. Some show a definite dose response relationship between the number of cigarettes smoked and FEV-1 lost. The accelerated loss with age in smokers was on average 35ml lower per each 100 cigarette-years compared with that of non-smokers. Chronic obstructive pulmonary disease is primarily a smokers' disease which worsens with age. It clusters in families and only becomes symptomatic when more than 30% of the lung is affected. The disease develops when the delicate balance between proteolytic enzymes, oxidative proteases and its inhibitors are impaired. This leads to a loss of elastic recoil, air-trapping and hyperinflation. Bronchiolitis is the predominant feature during the early stages of the disease. Emphysema dominates the clinical picture towards the end.^{148,175}

The most important risk factors are family history, smoking and environmental pollution (occupation). The person's family history (his genetic susceptibility), immune status, childhood respiratory infections and socio-economic status play an important role in the development of the disease.^{177,179,207,208,209,210,211,212} The genetic disorder, alpha-1-antitrypsin deficiency (especially in the P1Z variant), is associated with COPD.¹⁴¹ The alpha-1-antitrypsin molecule is sensitive to environmental agents and cigarette smoke which are rich in oxidising agents. It inactivates the active centre of the alpha-1-antitrypsin molecule. Anti-oxidants such as vitamin A, C and E may inhibit lung damage caused by oxidants released by inhaled particles.^{142,145} COPD has a long asymptomatic phase and abnormal clinical findings, abnormal lung functions, x-rays etc. are not features of the early stages of the disease. In non-smokers the decay in FEV₁ after 30 years of age is approximately 20ml per year. The decay of a susceptible smoker is 80 - 100ml per year.^{148,175} If a patient quits smoking at a stage when the FEV₁ is still

75% of predicted, the subsequent rate of decline of FEV₁ is reduced to that of a non-smoker and the person will most probably only develop disabling symptoms at the age of 75 years. If he quits smoking when his FEV₁ is 25 - 50% of predicted, therapy will have a minimal effect on his longevity and his quality of life will remain poor.^{172,173,174,175,188,213}

2.7 LUNG DISEASES ASSOCIATED WITH PROGRESSIVE FIBROSIS

2.7.1 Introduction

Pneumoconiosis is a generic term that refers to a number of lung conditions with a non-neoplastic reaction to inhaled dust particles (mineral and non-mineral), and the resultant fibrosis. It includes among others: silicosis, asbestosis and the condition known as *dust reticulation* but excludes asthma, bronchitis and emphysema.^{214,215,216}

A large body of published literature has dealt with this group of diseases already known to the Greeks and Romans (Pliny, Agricola, Ramazzini, Johnson, Thackwray, Peacock etc.). Schneeberge Bergkrankheid was a combination of respiratory diseases which included silicosis and tuberculo-silicosis.^{41,42} Uranium miners are also at risk of silicosis and there is some evidence that chronic radiation may enhance the effect of silica in producing generalised pulmonary abnormalities. A review of x-rays done on Colorado Plateau uranium miners (Archer *et al*) and New Mexico uranium miners (Samet *et al*) showed abnormalities compatible with silicosis in 90% of miners surveyed.^{10,11,13,26}

Exposure to silica (and to other agents such as asbestos and coal) is characterised by an alveolar macrophage alveolitis.¹¹⁰ Alveolar macrophages appear in increasing numbers and are activated and aggressive, readily releasing above-average doses of mediators such as oxidants, chemotoxins for neutrophil and fibroblast growth factors.¹¹⁰ Chemotoxins attract neutrophils and the subsequent release of mediators

by macrophages and neutrophils can damage host tissue, especially the alveolar epithelial cells. Fibroblasts infiltrate into tissue where they increase in numbers with an increased production of collagen that stimulates fibrosis. The fibrosis of the alveolar wall leads to generalised pulmonary fibrosis. The process is perpetuated by the re-uptake of the environmental agent such as silica, with the subsequent release of oxidants and resultant inflammatory and fibrotic process.^{110,111,112,113}

2.7.2 Silicosis

Silicosis, a chronic inflammatory and fibrotic lung disease, is one of the oldest pneumoconioses and results from the inhalation of silica, one of the most abundant agents in nature. Most of it is in free crystalline state (alpha quartz, cristobalite and tridymite).^{214,215,216}

Three clinical syndromes are described: classic type which develops over 10 - 20 years; sub-acute or accelerated interstitial variant which develops over a couple of years and the acute variant where the disease can develop over a period of one year after massive exposure.²⁰¹ Alveolar proteases may also develop, and in all cases the process of fibrosis can continue without further exposure.²⁰¹

Massive pulmonary fibrosis (PMF) refers to a condition where large lesions develop with fibrosis and collapse. Combined with rheumatoid arthritis feature it is referred to as *Caplan's Syndrome*.²⁰¹

2.7.2.1 Determinants of Fibrogenesis

Typical silicotic changes are observed when the quartz in the dust exceeds 18%, and is most severe if the particle range is between two to five micron. A mixture of quartz and cristobalite appears to be the most fibrogenic, but fibre and particle burden, and fibre and particle type, are all important.^{201,205,206} All forms of asbestos are fibrogenic to humans. Canadian crysotile and anthophyllit are the most fibrogenic among the

asbestos fibres.^{236,237,238} Investigations into the fibrogenic impact of fibre dimensions generates much controversy. It appears, however, that short forms (< 5 microns) are less fibrogenic than those between five and ten micron. There is, however, official ground to challenge the exclusive role of the longer fibres in fibrogenesis.^{239,240} There is some evidence that the tetrahedra structure of crystalline silica adds to the toxicity of silica and published data also suggests that particle charge could be related to its toxicity.

2.7.2.2 *Individual Predisposition to Silicosis*

Differences in health-outcomes of persons employed in the same environment and receiving the same silica exposure are well known. Factors that are believed to influence the susceptibility of an individual are subject to much speculation. The probability of developing silicosis depends on a complex influence of many factors that are both environmental and intrinsic for the individual. One's genetic predisposition is one of the most important factors that determine one's risk to develop silicosis and/or silica tuberculosis²⁰⁴. Other factors which were studied were a balanced diet, smoking, alcohol intake, accompanying diseases, exposure to other environmental agents, particularly sulphuric acid, and last but not least, exercise.^{218,219,220}

2.7.2.3 *Pathology*

Central to the process of silicosis, and the other institutional lung diseases (pneumoconiosis) caused by chronic occupational exposure, is the interaction between silica and lung macrophages.²⁰¹ Particles capable of reaching the alveoli are smaller than five micron. They are engulfed by pulmonary macrophages and removed via the mucociliary system. Macrophages, the first line of defense against particles that have reached the alveoli, found silica to be cytotoxic. The function of macrophages is thus impaired. Baghi²⁰⁸ postulates that the positive charge of the respirable silica particle combines with the macrophages

leading to the release of collagenase: "Fibroblasts are activated through various factors to lay down collagen." Lauri and Davis^{205,206,207} however feel that macrophages ingest small amounts of silica which alter metabolism and functions such as the release and/or production of mediators and cytokines. In vitro studies give some evidence of hydrogen bonding between the surface of silica particles and the macrophages membrane phospholipids. This leads to the release of lysosomal enzymes with subsequent autolysis.¹¹²

The process is perpetuated by the re-uptake of silica, release of oxidants with the resultant inflammatory and fibrotic process and is characterised by an alveolar macrophage alveolitis.^{110,219} Alveolar macrophages appear in increasing numbers and are activated, become aggressive, and release above average doses of mediators such as oxidants, chemotoxins for neutrophils and probable growth factors. Chemotoxins attract neutrophils and the subsequent release of mediators by macrophages and neutrophils can damage hurt tissues, especially the alveolar epithelial cells.^{117,220} Fibroblasts infiltrate the interstitium where they increase in numbers coupled with an increased production of collagen which stimulates fibrosis. The fibrosis of the alveolar will lead to reduced diffusion.¹¹⁰

2.7.2.4 Silicosis and Symptoms

Patients in the early stages of simple silicosis do not usually have any significant respiratory symptoms. Symptoms associated with bronchitis are found equally in those with radiological silicosis, and those with normal chest x-rays.²¹⁴ Reports on an increased frequency of respiratory symptoms were, however, found in studies of working populations of silica exposed workers.²¹⁹ The frequency of sputum production (chronic bronchitis) was present in 62% of all men, and in 45% of those who have never smoked.²¹¹ This was well correlated with a reduction of all indices of lung functions (with silica as an independent variable) even when they were controlled in the intensity of underground

exposure and for smoking. Dyspnoea on effort is, however, the symptom most often associated with advanced degrees of silicosis.^{209,210,211}

2.7.2.5 Silicosis and COPD

COPD is a more important cause of disability and mortality among South African underground workers than silicosis.²¹¹ Inhalation of siliceous dust can contribute towards the development of COPD through the process already described. The relative contribution of silica *per se* in the overall process leading to the development of COPD is, however, not clear. In a study done by Eva Hnizdo, she pointed out that white South African gold miners have a higher mortality from COPD than the general white South African population.^{211,212,213,219} She showed that the SMR (standardised mortality rate) is 165,5 (with a 95% CI 108 to 243). She found that smoking was associated with COPD in 34% of cases. Where people were exposed to the combined effect of dust and smoking, the association was 59% and with dust alone, only 5%.^{211,212,213}

2.7.2.6 Lung Function in Silicosis

The effect of silica on the lung function of miners has been studied by investigators. Several epidemiological studies focused on lung function impairment and silica. Most concluded that there is a significant correlation between siliceous dust exposure and accelerated lung function loss.^{215,216,217,218,219}

Whether exposure to high levels of silica dust or simple silicosis are associated with lung function abnormalities are still being debated. Some believe that the exposure to dust, and not the disease entity silicosis, is responsible for abnormal spirometric values. Wiles *et al*²¹⁶ point out that the observed impairment of lung function in some of the studies is not necessarily the direct result of silicosis *per se*, but may

have been co-incidental airflow limitation associated with greater exposure to silica dust. Support for this statement comes from Bucca *et al*²¹⁴ who state that "no relationship could be found between the slopes of ventilation parameters and that of the RX score." (RX score reflects the progression of nodular abnormalities.) Irwing and Rocks, Burkman *et al*, Moore *et al* support the Wiles' *et al*¹⁹⁹ observation that *except for the alveolar plateau and closing volume, radiological silicosis did not impair lung function.*

Becklake,²¹⁷ however, found significant differences between the lung function of miners with normal chest x-rays, and those with radiological silicosis. Her finding was supported by Banks *et al* and Glover *et al*. Cowie and Mabena^{210,215} in their cross-sectional survey of 1197 gold miners with silicosis as an independent variable, found a reduction in all of the indices of lung function (even when controlled for intensity of exposure and smoking). Cowie's final conclusion is that *simple silicosis is associated with significant pulmonary dysfunction.*²¹⁰ Hnizdo, Sluis-Cremer and Abramovich²¹³ studied 1553 mine workers with the specific purpose of determining whether silica dust exposure, in the absence of tobacco smoke, causes a significant degree of emphysema. They found that tobacco smoke potentiates the effect of silica dust on emphysema and that silica dust exposure, in the absence of tobacco smoke, is rarely associated with a significant degree of emphysema.²¹³

FEV₁ was the strongest predictor of mortality in a study done by Hnizdo, and the estimated loss attributable to 25 years of underground mining was estimated to be 200ml.²¹⁹ Many unanswered questions beg further investigation and the book on the relative contribution of smoking, dust exposure, silica and combinations of the above remains open.

2.7.2.7 Silica Exposure and Tuberculosis

The association between silica exposure and tuberculosis is well established.^{223,224,225,226} The increased activity of macrophages with

exposure to silica, and the subsequent release of proteolytic enzymes is associated with proliferation of mycobacterium tuberculosis in lung tissues. Patients with the accelerated interstitial variant of silicosis (usually with high dust exposure indices) are especially at risk of developing lung tuberculosis.²²³

In both in vitro and in vivo studies, the increased risk of contracting mycobacterium tuberculosis infection in silicotic individuals has been established. Sherson and co-workers²³⁰ also demonstrated that those exposed to heavy silica exposure, and without definite radiological silicosis, have an increased risk of developing tuberculosis. Studies in Sweden could not demonstrate the same degree of risk profile, but confer an increased risk with heavy accumulated silica exposure. In conclusion: the bulk of evidence points towards the fact that silica dust exposure creates an ideal ground for the activation of tuberculosis and silico-tuberculosis.^{225,226}

2.7.2.8 Silica as a Carcinogen

Goldsmith *et al* put forward the hypothesis that *silica is either a carcinogen or a co-carcinogen*.^{223,224} They postulated that cancerous changes develop in the fibrotic scars caused by silicosis. This view was supported by the International Agency For Research On Cancer (I.A.R.C.). It was refuted by Hepplestone²⁰³ and questioned by others^{8,222,223,224} on the basis that confounding factors and biases were not properly controlled.

The results of the most important studies can be summarised as follows:

- a) Historical cohort failed to make a strong association between silicosis and lung cancer. It also failed to demonstrate any carcinogenetic effect from exposure to silica.
- b) Case controlled studies could not find an association between lung cancer and any index of silica exposure.

- c) Studies of silicosis and record linkage studies produced conflicting results and do not support an increased risk of lung cancer in silica exposed workers.
- d) De Klerk and Musk⁸ (1998) also could not find evidence that exposure to silica caused lung cancer in the absence of silicosis. However they found that the onset of silicosis conferred a significant increase in risk for subsequent lung cancer. The situation at present is that the I.R.A.C. as reclassified crystalline silica inhaled in the form of quartz or cristobalite as on a class 1 carcinogen. Previously silica was regarded as a Class 2A carcinogen (limited evidence existed).

In a balance of opinion statement in 1992, Agius reviewed all the available evidence and came to the conclusion that *available evidence does not consistently support the fact that silica is a carcinogen*. However, it does not eliminate the possibility definitely.²²¹

2.7.3 Asbestos Related Diseases

2.7.3.1 Asbestos Exposure

The mining of asbestos does not only affect the workers; it is also a potential source of environmental exposure among populations living in the vicinity. South Africa produces a high percentage of the world's crocidolite (blue asbestos)²³⁵. Crocidolite exposure is regarded as carrying a higher risk of mesothelioma than other types of asbestos. Death rates in the general population living in certain mining areas of Southern Africa have been shown to be higher than in control areas - particularly death rates from asbestosis, mesothelioma, and cancer of the bronchus, lung and stomach.^{235,236}

Asbestos exposure is associated with the risk of the development of the so called asbestos related diseases which include: parenchymal asbestosis; bronchogenic carcinoma; mesothelioma of the pleura;

pleural asbestosis; laryngeal carcinoma and mesothelioma of the peritoneum.²³⁵

2.7.3.2 Asbestosis

Asbestosis is diffuse interstitial fibrosis that is usually accompanied by pleural fibrosis. The genesis time is usually 15 to 20 years, but could be shorter if exposure was excessive. It is primarily an occupational disease.

Experiments carried out on animals indicated that the disease is caused by fibres longer than five microns, and there is a correlation between the degree of asbestosis and the fibre load. The initial lesion is an interstitial pneumonitis affecting the alveoli of the respiratory bronchiole; extending and leading to a diffuse interstitial fibrosis. The main complaint is usually dyspnoea on exertion with cough symptoms, crepitations, ronchi, clubbing and cyanosis as late manifestations.^{236,237}

Abnormal lung function with reduced volumes and flows at 50% and 75% of predicted vital capacity is well documented.²³⁷ Gas exchange abnormalities are a late finding and radiological changes occur later in the development of the disease. In the beginning, the changes are too fine, and too diffused, to produce radiological abnormalities. The typical radiological picture is that of a fine reticulation seen in the lower two thirds of the lungs.^{238,239}

2.7.3.3 Pleural Asbestosis

Pleural asbestosis is the term used when a person exposed to asbestos develops pleural fibrosis with the presence of asbestos fibres. The fibres found in macrophages reach the visceral pleura via direct spread, and the parietal pleura via the lymphatic system.²³⁵ This may lead to diffuse or focal fibrotic changes (fibrous plaques). The distribution of these plaques are characteristically found on the lower parts of the

visceral pleura and the diaphragm, and are usually bilateral.²³⁸

Exposure to anthophyllic asbestos in particular, is associated with pleural thickening and pleural plaques, and is found in people who are not occupationally exposed to asbestos.²³⁹ The dose effect relationship is best described by Selikoff and Lee who state that *as the dose decreases, pleural responses develop less rapidly than dust parenchymal responses so that we have many incidences where low or even apparently trivial doses have been found to have resulted in plaque formation, after a long interval, with minimal or virtually no corresponding parenchymal involvement.*²³⁵ The so-called asbestos bodies were first described by Cook in 1924 and named "asbestos bodies" by Stewart in 1930, and Gloyneu in 1933. Asbestos bodies are retained asbestos fibres, coated with an iron protein complex found in 40% of people with asbestos exposure.²³⁵

2.7.3.4 Bronchogenic Carcinoma

Carcinoma of the bronchus is usually an adeno-carcinoma but all types of primary lung cancer can be found. It is associated with asbestos exposure and dose.^{235,240,241} It is possible for bronchus carcinoma to develop before asbestosis becomes apparent. According to Doll and Peto²⁵³ "the relative risk of bronchogenic cancer from asbestos exposure increases linearly during constant exposure, remains constant after exposure stops, and is independent of age and smoking". Although it is extremely difficult to be accurate on the magnitude of the increased attributable risk, a rule of thumb is *that there is a 1% increase in the standard mortality rate for lung cancer per year of exposure to one related fibre per millilitre.*^{235,236,240}

2.7.3.5 Mesothelioma of the Pleura

Mesothelioma, a malignant tumour usually of the pleura, (generally associated with crocidolite) has a history of exposure to asbestos in 85% of cases. Cigarette smoking is not related to mesothelioma and

evidence of metastases is rare. The prognosis is very poor with 50% mortality within 12 weeks of diagnosis; few patients survive more than two years. The characteristic feature of mesothelioma is the long lag period between exposure and the development of the pathological finding. The lag period is usually 20 to 30 years but it has been described as short as three years, and as long as 50 years, after exposure. Exposure does not have to be long or excessive and the threshold is not known. The patients usually complain of a pleuritic pain or symptoms associated with the unilateral pleural diffusion.^{235,239,241}

2.8 LUNG DISEASES ASSOCIATED WITH CARCINOGENESIS

2.8.1 Introduction

Cancer rates in Namibia are not readily available but are believed to be on a par with South African statistics. According to Dr F Sitas (personal communication), cancer in South African adults (15-64 years) was the third most common cause among whites, coloureds and asians if one excludes deaths from "ill-defined conditions".

He pointed out that the high frequency of cancer in black populations was illustrated in the cancer registries of Johannesburg 1953-55 (Oettle and Higginson 1966); in Durban 1964-66 (Schoonland and Bradshaw 1968) and oesophageal observed in the Transkei (Jaskiewicz *et al* 1987).^{244,245}

Agricola (1494 - 1555)⁴³ was the first to describe occupation-induced cancers among Carpathian mine workers. It remained, however, a relatively rare disease until the early twentieth century. From the 1920's onwards, a number of researchers started to focus on the increasing rate of bronchogenic cancers associated with exposure to environmental agents (Uhlig, 1921;⁴⁰ Hueber,⁴⁶ 1943; Wynder *et al*, 1950)²⁵⁴ and since the 1950's a number of epidemiological studies confirmed the relationship between lung cancer and uranium mining (New Mexico, Newfoundland, Czechoslovakia and Navaho miners).¹³⁻²⁶ Publications by Alderson (1986),

NCI Oncology Reviews (1986), Cotes and Steele (1987), and Doll (1994),²⁵³ strengthened the association between the environment and cancer through their publications.

2.8.2. Histology

Cancer is, according to Joan Austoker,²⁴⁹ *a genetic disease at the cellular level* with the basic abnormality being the incorrect transfer of information at the level of cellular growth and proliferation. Most genetic abnormalities are acquired through exposure to environmental carcinogens such as chemicals, radiation, infectious organisms and dietary factors. Only a small number are inherited in the gene line (Joan Austoker, Oxford University, 1995).^{247,250,251}

It is still uncertain why certain individuals develop cancer at a given level of exposure, while others do not. The susceptibility factor varies in populations and the search for susceptibility markers shows some promise: in most cases the mechanisms that govern mutagenic metabolic activation and DNA repair ability, remain unclear.^{248,250} Clustering of cancers in families is explained on the basis of a shared genetic pool and exposures in the same environment. Genetic predisposition to cancer is thought to be associated with inherited mutations in genes responsible for proliferation and growth. The roles of oncogenes (promoters) and tumour suppressor genes are intensely studied. Proto-oncogenes and tumour suppresser genes play a critical role in normal cell activities and dysfunction can result in cancer. The activation of proto-oncogenes can thus enhance the probability of neoplastic transformation. In 1990 a gene line mutation in 5 families (Li-Fraumeni) was found. The mutation occurred in the p53 tumour suppressor gene alteration of the tumour suppressor genes and its encoded proteins are known to be the most frequently encountered event in human malignancy. These genes are found on the short arm of chromosome 17 and can be damaged or "switched off" through mutations. The gene manufactures a transcription protein "which activates other genes by binding to DNA". This gene "instructs" cells that are about to become

cancerous, to self-destruct, or stop dividing. Chemical carcinogens require metabolic activation by enzymes such as cytochrome P450. The altered chemical carcinogens bind to DNA leading to mutations and subsequent DNA synthesis errors.^{244,245,246,247,248,249}

Carcinogenesis is considered to be a multi-stage process from carcinogen exposure through mutation, promotion and progression towards overt malignancy, with two main types of carcinogens: genotoxic and non-genotoxic. Radiation, viruses and other environmental agents can cause damage to DNA and mutational changes in cells. It was generally believed that most human carcinogens are genotoxic but it is likely that this is not necessarily so.^{246,250}

2.8.3 Lung Cancer

Lung cancer is the most common cancer in both men and women; resulting in a million fatalities annually. In 1985 lung cancer overtook breast cancer as the leading cause of death in females worldwide. It accounts for approximately 33% of all cancer deaths in males in the USA and 17% in females. In South Africa lung cancer accounts for 24% of all cancer deaths in men and 10,6% cancer deaths in females²⁴⁵. Data for Namibia is not available, but it is believed to be lower because the country is less industrialised with fewer cigarette smokers.²⁵¹

Unfortunately the morbidity and mortality of lung cancer has not changed over the past decade. Bronchogenic carcinoma is a major preventative cause of death in developed countries, and remains one of the most important challenges to primary health care. The five-year survival rate of lung cancer is less than 10% and has remained the same for a number of years.²⁴⁴ Lung cancer rates have increased dramatically among urbanised Africans along with an increase in indoor pollution and environmental tobacco smoke. The median age for this cancer to be diagnosed is 59 years of age (31- 89) 25% occurring below the age of 50.²⁵¹

It is usually diagnosed late in the natural history of the disease offering patients limited treatment options. Surgery remains the preferred form of treatment, but only 15% of patients referred to Groote Schuur Hospital in Cape Town with lung cancer are suitable for surgery.²⁴⁴ In general, only 33% of patients in the western world are susceptible when diagnosed, and since it is regarded as an environmental disease, caused by readily available environmental agents, much needs to be done.^{146,251,252}

2.8.3.1 Causes of Lung Cancer

a) Tobacco Smoke

The association between cigarette smoking and lung cancer is firmly established.^{253,254} Tobacco smoke is regarded as the dominant cause of lung cancer world-wide and although first reported in 1950, the watershed evidence was provided in 1964 by the US Surgeon General's Advisory Committee on Smoking and Health. "Smoking is causally associated with lung cancer and the most important exogenous factor in the development of lung cancer". This was followed by the 1982 statement blaming 25% of all US cancer deaths, and 85% of all cancer cases on cigarette smoking (US Surgeon General).²⁴⁵

In 1994 Sir Richard Doll²⁵³ reported that 50% of all smokers will eventually die as a result of smoking regularly, and showed a definite dose effect relationship with 7,5 times higher cancer rates when 1-14 cigarettes per day are smoked; 14,9 times higher when 15-24 cigarettes are smoked, and 25,4 times higher when more than 25 cigarettes per day are smoked. Lung cancer contributed 31,8% of all neoplastic deaths among current smokers, 18% among former smokers and 4,6% among non-smokers.^{248,249,252,253,254,255}

b) Radiation

The inhalation of radioactive gases and dust, leads to the major demonstrated health hazard associated with uranium mining and milling: lung cancer (especially the undifferentiated small cell carcinoma).^{256,257,258,259,260} Although radiation to the epithelium of the lungs includes alpha, beta and gamma radiation; 96% of the radiation dose is alpha radiation produced by the daughter products ^{218}Po and ^{214}Po . The lung cancer produced by exposure to radon daughters is normally an upper bronchial cancer that is readily separated from the lung cancer generated by other causes.

2.8.3.2 Histology

The inter-relationship between exposure and effect, in the case of lung cancer, is sometimes concealed by the relative frequency of the disease. It is not easy to obtain definite pathological evidence of the association unless there is an unusual histological feature or site of tumour. Unfortunately, the bronchial cells have a limited range of neoplastic expression (Harrington and Levy).²⁴² According to Cameron (1986), 82% of cancers of the lung are of this squamous (non-small cell) variety which is associated with cigarette smoking. The guidelines given by Ives, Buffer and Greenberg (in 1983) still offer the best association on possible relationships.^{242,243}

Table 1 – Association between exposure and lung cell type

	Arsenic Exposure	Different lung cancer cell types predominate in different studies.
	Beryllium	Adenocarcinoma or small cell carcinoma predominates in a single study.
	Chromates Nickel BIS (chloromethyl) ether	Squamous carcinoma. Squamous carcinoma. Small cell carcinoma
	Uranium Miners	Small cell carcinoma (particularly high proportion)
	Asbestos	Three out of four studies showed predominance of adenocarcinoma.
	PVC dust	Greater proportion of large cell and adenocarcinoma found.

Although all types of bronchogenic tumours have been found in uranium miners, the undifferentiated type is the most common and it is generally accredited that the occurrence of excess undifferentiated lung cancers, which are rare among the general populous, are directly related today to radon exposure.

2.8.3.3 Epidemiology

Health effects on humans in the form of excess lung cancers were first observed in the uranium miners in Czechoslovakia and later also in the American and Canadian miners.^{259,260} In the beginning the exposure effect relationship was uncertain because the actual exposures were not well documented. The long genesis period of 5-15 years between exposure; the development of radiation induced cancers; the effect of smoking and the role of other synergistic agents, complicated the initial research. Since then several epidemiological studies have shown that there is a relationship between exposure to radiation and the prevalence of lung cancer.¹³⁻²⁶ Excessive exposure to radon and its daughter products increases the risk of lung cancer in smoking and non-smoking uranium mine workers.^{259,260} Epidemiological studies in various groups of mine workers showed a significant excess of lung cancer rate. There is a definite dose effect relationship. The attributable cancer risks are significantly influenced by the age of first exposure; total accumulated

exposure and cigarette smoking. In the early United States studies, almost every miner was a smoker, but recent studies have shown that it only has an additive relationship.⁴⁹⁻⁵⁶ In 1987 a task force of the National Institute for Occupational Safety and Health (NIOSH) produced a document on recommended standard of occupational exposure to radon progeny in underground mines. They reviewed published data and subdivided available studies into two categories.²⁴²

The 6 Primary and 10 Secondary Epidemiological studies in the primary studies were those done in the United States, Czechoslovakia, Ontario; in iron miners in Sweden and fluospar miners in New Zealand. Although the studies lacked accurate radon primary exposure data for individuals, the data could be used to categoric exposure. The association of radon progeny exposure and lung cancer (in spite of various methods and study populations) was obvious. Elevated lung cancer rates showed a direct relationship with radon progeny.^{242,243}

TABLE 2: SUMMARY OF PRINCIPAL STUDIES OF LUNG CANCER MORTALITY IN UNDERGROUND MINE WORKERS EXPOSED TO RADON PROGENY

TYPE OF MINE (LOCATION)	REFERENCE	MEAN LIFETIME CUMULATIVE EXPOSURE (WLM)	PERSON – YEARS	LUNG CANCER DEATHS		
				OBSERVED	EXPECTED	SMR
Uranium United States	Waxweiler <i>et al.</i> [1981] Lundin <i>et al.</i> [1971]	821§ (median = 430)	62,556	185	38.4	482
Uranium Czechoslovakia#	Placek <i>et al.</i> [1983]# Kunz <i>et al.</i> [1978]	289**	56,955	211	42.7	496
Uranium Ontario, Canada	Muller <i>et al.</i> [1985]	40-90††	202,795††	82††	56.9††	144††
Iron Sweden	Radford & Renard [1984]	81.4§§	24.083§§	50	12.8§§	390§§
Fluorspar Newfoundland	Morrison <i>et al.</i> [1985]	--##	37.730##	104	24.38##	427##
Uranium Saskatchewan, Canada	Howe <i>et al.</i> [1986]	16.6***	118,341†††	65†††	34.24†††	190†††

Comparisons between these studies, especially for purposes of risk assessment, should be made with caution because of differences in the calculations of person - years, expected deaths, and SMR values in the various studies.

· $p < 0.05$ except in Muller *et al.* [1985], Radford & Renard [1984], and Morrison *et al.* [1985]; because p-values were not provided in these three studies, they were estimated from the observed lung cancer deaths and the Poisson frequency distribution.

§ Lifetime cumulative exposures ranged from less than 60 to greater than 3,720 WLM.

! Studies are of uranium mine workers who started work underground between 1948 and 1952.

* Lifetime cumulative exposures ranged from less than 50 to approximately 1,000 WLM.

† Values are for uranium mine workers with no previous gold mining experience; exposures were lagged up to 10 years; lifetime cumulative exposures ranged from 0.1 to greater than 340 WLM.

§ Person-years for the first 10 years of mining experience were excluded; expected deaths were adjusted for smoking status; exposures were lagged 5 years; lifetime cumulative exposures ranged from 0 to greater than 200 WLM.

Person-years for surface and underground mine workers were included; person-years for the first 10 years of mining experience were excluded; radon progeny exposure levels were recently re-estimated (Corkill and Dory 1984); lifetime cumulative exposures ranged from 0 to greater than 2,040 WLM.

** Value was based on underground workers (surface workers received a mean exposure of 2.8WLM); lifetime cumulative exposures ranged from 0 to greater than 250 WLM.

† Values were based on surface and underground workers.

TABLE 3: SUMMARY OF ADDITIONAL STUDIES OF LUNG CANCER MORTALITY IN UNDERGROUND MINE WORKERS EXPOSED TO RADON PROGENY*						
TYPE OF MINE LOCATION	REFERENCE	ESTIMATED CONCENTRATION OR EXPOSURE	COMPARISON GROUPS	LUNG CANCER DEATHS OBSERVED/ EXPECTED		RATE RATIO† FOR LUNG CANCER DEATHS
IRON Grangesberg, Sweden	Edling and Axelson [1983]	0.3 to 1.0 WL	Underground miners aged 50 and above vs. non-exposed individuals in the parish aged 50 and above	33	2.87§	11.50
Zinc-lead Sweden	Axelson and Sundial [1978]	1 WL	Underground miners vs non-exposed individuals in the parish	21	1.28§	16.4
Iron Kiruna, Sweden	Jorgensen [1973, 1984]	0.5WL	Underground miners vs Swedish males	28	9	3.11
Iron Kiruna and Gallivare, Sweden	Damber and Larsson [1982]	0.095 to 2.025WL	Underground miners vs non-exposed individuals in the Kiruna and Gallivare parishes	20	2.74§	7.3
Metal U.S.	Wagoner <i>et al.</i> [1963]	0.05 to 0.40 WL	White male underground miners vs white males from the same States	47	16.1	2.92
Uranium U.S.	Samet <i>et al.</i> [1984]	Lifetime exposure: 30 to 2,698 WLM; median exposure: 1,207 WLM (values are for 14 of 23 uranium miners)	Navajo males with uranium mining experience vs Navajo males listed in the New Mexico tumour registry that died of cancer other than lung cancer.	23	0	NA#
Tin Cornwall, United Kingdom	Fox <i>et al.</i> [1981]	1.2 to 3.4 WL	Underground miners vs English and Welsh males	28	13.27	2.11

* These studies contain limitations in study design, radon progeny exposure records, smoking history information, follow-up, etc. Comparison between these studies, especially for the purposes of risk assessment.

† $p < 0.05$ (some p-values were estimated from the observed lung cancer deaths and the Poisson frequency distribution): rate ratios depend on lung cancer mortality in the comparison population and are sensitive to error in rates that are based on a small number of expected deaths.

§ The expected number of deaths was estimated from the rate ratios provided by the authors.

Not applicable. The 95% confidence limits of the rate ratios range from 14.4 to infinity. (NIOSH .88, 1987)



The value of the mean lung cancer excess risk rate, according to various epidemiological studies, covers a range from 2-20 cases per year per million miners exposed to one WLM. And the ICRP suggests a total life-time risk for lung cancer of between $15 - 140 \times 10^{-6}$ per WLM. The average annual exposure to environmental radon of the order of 0,22 WLM which associates with a risk of 22 lung cancer deaths per million of the general population.

TABLE 4: RELATIVE RISK ESTIMATES OF LUNG CANCER AT AGE 60 BY ANNUAL AND LIFETIME CUMULATIVE EXPOSURES TO RADON PROGENY			
Annual mining exposure above background (WLM/year)	Cumulative exposure* (WLM over a 30-year working lifetime)	Relative risk†	95% confidence limits
0.5	15	1.31	1.23-1.39
1.0	30	1.57	1.42-1.74
2.0	60	2.04	1.74-2.40
3.0	90	2.45	2.00-2.99
4.0	120	2.81	2.23-3.56

* Values are exclusive of background exposure.

† Estimates are based on a log-relative risk model fitted to age at initial exposure, time since cessation of exposure, and the natural logarithms of the following variables: cumulative mining and background exposure to radon progeny, cumulative cigarette smoking and background smoking, and rate of exposure to radon progeny. NIOSH 88 (1987).

Professor Jacobi from the German Institute for Radiation Protection developed a (time since exposure)-model to determine lung cancer rates depending on exposure, age at exposure and age at lung cancer incidence. It does not distinguish between smokers and non-smokers. For those who worked in the German Uranium mining companies Wismut, the model states that for those who worked since 1970 and

who has accumulated 4 WLM the probability of causation for a lung cancer as occupation-related is dependant on period of exposure, age at exposure and age at lung cancer incidence.²⁴²

2.8.3.4 Other Environmental Causes

In 1986 the National Cancer Institute reviewed available published data on occupational lung cancer and concluded that asbestos, arsenic, chloromethyl ethers, chromium, mustard gas, nickel and polyaromatic hydrocarbons are accepted as carcinogens.²⁴⁶ The relationship between silica exposure, silicosis and lung cancer is the subject of numerous South African publications. The relation risk of lung cancer associated with 1 000 particle year was established at 1,023 (95% confidence intervals 1,005 to 1,0042). Hnizdo concluded in their recent publication of 1991 that it is extremely difficult to identify the independent role of silica in the presence of confounders such as cigarette smoking and radon found in underground mines of South Africa.²⁴⁸ In the "balance of opinions" statement, Agius²²¹ concluded that human evidence does not consistently support the proposition that silica per se is carcinogenic. There is, however, epidemiological evidence that it may synergise potent environmental carcinogens such as cigarette smoking and that the disease process is associated with or leading to silicosis might carry an increased risk of lung cancer.¹⁷⁵

CHAPTER THREE

3.1 PULMONARY FUNCTION TESTS

3.1.1 Introduction

In essence pulmonary function tests (PFT) measures the movement of air in and out the lungs during various maneuvers. It also includes the measurement of lung volumes, airway resistance, carbon monoxide diffusion capacity and arterial blood gases.^{261,262} For the purpose of this discussion we will concentrate on the measurements used for this epidemiological study.

Although PFT's have been used for than 150 years or more (J Hutchinson 1846), it's clinical application lagged behind till the 1950's because PFT's were not regarded as definitive diagnostic tests for lung abnormalities. The general view is that it only indicates functional abnormality and the results must be integrated with other clinical data to make a diagnosis.^{261,262,263} When accurately performed and properly reported, pulmonary function tests can however provide objective and quantifiable measurements of lung function and can demonstrate pre-clinical abnormalities. PFT's are now widely used by both clinicians and researches to detect departures from "normality", to measure severity of disease and to monitor the progress of a patient's condition.

Serial pulmonary measurements combined with clinical evaluation are essential for the medical surveillance of the exposed worker, especially where the lung is the target organ and are now performed for a variety of reasons such as:^{264,265}

- 3.1.1.1 To establish reference baseline function values for individuals and groups.
- 3.1.1.2 The detection of early abnormalities in individuals and groups of workers under surveillance.
- 3.1.1.3 To assist with health promotion programs and the placement of vulnerable individuals.
- 3.1.1.4 To quantify and monitor the degree of pulmonary impairment and to determine an individual's ability to perform specific tasks (fitness for duty).
- 3.1.1.5 To assist with evaluation of impairment and disability assessment.
- 3.1.1.6 To provide information on the health status of persons with occupational exposure to injurious substances. (Epidemiological surveys).²⁶⁵

When PFT's are used in epidemiological studies and for the screening and detection of early lung disease in people working in high-risk areas in industry and mining, it is essential to have a clear understanding of the factors that determine an individual's lung volumes and flows, and the many sources of variation that may confound the test results. The significant differences in test results obtained by various laboratories using the different types of equipment, techniques, or normal values make it essential that the more basic technical aspects of spirometry must be addressed prior to the important issues of the clinical usefulness, indications for testing and the interpretation of results.^{264,265}

3.1.2 Standardisation

Although PFT's are relatively easy to perform and are widely used, poorly performed tests, and a lack of insight into test interpretation can create tremendous problems in the occupational health context. One of the

major problems encountered was a lack of internationally accepted standards and guidelines for pulmonary function testing.

The need for comparable lung function data necessitated standardisation of pulmonary function tests. The American Thoracic Society's (ATS) first statement on standardisation of spirometry was published in 1980 (shortly after the well-known Snowbird Workshop in 1979).²⁶⁶ The initial statement was updated in 1987²⁶⁷ and again in 1994.²⁶⁸ Recommendations for standardisation from the European Respiratory Society (ERS)²⁷⁰ and British Thoracic Society²⁷¹ (BTS) also contributed towards universally accepted well-developed guidelines and practices. Of special note is the official statement of the European Community for Steel and Coal (ECSC) published in 1993.²⁷⁰

These statements have contributed largely to combat technical sources of variations as well as the largest sources of inter-subject variability - namely improper performance of pulmonary functions test and poor quality control. It cannot be stressed enough that where the aim is to detect early changes, before symptoms develop in the exposed worker, accuracy and repeatability are of the utmost importance. It is essential to use reliable equipment and quality control is vital.^{268,269,270,271,272}

3.1.3 Spirometry

The first and still the most widely used lung function test, spirometry, measures the volume of air an individual inhales or exhales as a function of time (volume/time curve). The spirogram makes a number of measurements and subdivides the vital capacity into its subdivisions. It registers volume changes as a function of time that is a good measurement of airflow obstruction. It measures the maximal volume of air exhaled from a point of maximal inhalation or volume of air inhaled

from a point of maximal exhalation which is the forced vital capacity, (FVC) inhaled. It also registers the maximal volume of air that can be expired from the lungs in one second of forced expiration from a position of full inspiration which is the forced expiratory volume in one second (FEV₁).^{261,273}

Measuring FEV₁ requires a spirometer capable of measuring at least 8 litres within accuracy of at least 3% of reading or approximately 50ml (whichever is the greatest) with flows of 0-14 liters per second. The accuracy validation limits for volume (FVC/FEV₁) are 3,5% of reading or 70ml (whichever is greatest) and the mechanical syringe must be accurate within approximately 24ml for FVC and FEV₁.^{265,268,269,273}

FVC is reduced in more serious diseases of the lung, but lacks discriminatory power. The FVC must be distinguished from the relaxed VC where the emphasis is on completing the maneuver and not on speed. In certain conditions such as emphysema the relaxed VC is greater than the FVC (the emptying rate is determined by airflow limitation).^{265,268,269,273}

FEV₁ is extensively used as an indicator of airflow obstruction. It has a good index of reproducibility. The FEV₁ can be standardised for the VC in the relation $FEV_1 \times 100 / FVC = FEV_1\%$. Normally 75% of the FVC is exhaled in one second and expressed as $FEV_1 / FVC \times 100 = 75\%$. Some researchers and clinicians prefer to express the FEV₁ as the % of the relaxed (slow) VC in the case of severe air flow limitation disease (where the relaxed VC is greater than the FVC).^{265,268,269,273}

These tests are relatively easy to perform, are highly acceptable to the patient, the results are reproducible and the coefficient of variation (CV) is often less than 5%. FEV₁ is only partially influenced by subject effort (determined by both effort dependant and independent portions of the

MEFVC). FEV_1 is more reproducible than other indices and is more sensitive in detecting airflow obstruction than PEFV.^{261,262,263,264,273}

3.1.4 The maximal expiratory flow volume curve (MEFVC)

Flow or the rate at which the volume is changing as a function of time can also be measured. The MEFVC is the graphical presentation of the flow versus volume signal recorded from the maximal forced expiration starting from full inspiration, which is immediately followed by a maximal inspiration.^{34,274}

The maximal expiratory flow volume curve yields more information than the spirogram (volume/time curve) by permitting easier pattern recognition of airflow abnormalities. Obstruction of peripheral airways is readily detected from the increased convexity of the volume axis in the descending portion of the flow volume curve, but may be overlooked in the standard analysis of the expiratory spirogram. A flow volume curve test with a 1 second timer (and with registration of the tidal volume) allows measurement of not only the conventional indices of the direct spirogram such as the forced vital capacity (FVC) and the forced expiratory volume in 1 second (FEV_1), but also of peak expiratory flow rate, peak inspiratory flow rate and flows at 50% and 75% of the expired volume.^{34,261,262}

3.1.4.1 Time Factors in Relation to the MEFV Curve

Although the MEFV curve is a plot of flow against volume, the FEV_1 can also be measured by adding a 1-second time signal on the volume axis or by computer programming techniques. In order to determine the beginning of expiration or zero time, back extrapolation (as described for volume time curves)²⁶⁵ is not practical for flow volume curves. Time zero can be defined as the time at which flow exceeds a threshold value (e.g. 50 ml/s) or when a threshold volume (25-100 ml)

has been delivered. These measures provide values that are similar to those obtained by extrapolation when effort is optimal, but smaller values are obtained when initial effort is submaximal.²⁶⁵ If the subject hesitates after the initial commencement of the test, the FEV_1 may be smaller.

The FVC manoeuvre is considered at an end when either the volume change is less than 25ml or the flow rate is less than 0,05 l/s with a half-second interval. If this end-point has not been reached, recording should continue for at least 10 seconds. Many expiratory efforts are terminated before full expiration is reached and this has an influence on several measurements derived from or expressed in terms of the FVC, including the forced expiratory flow at 50% (FEF_{50}) and 75% (FEF_{75}) of the expired volume and the FEV_1/FVC ratio.^{265,273}

3.1.4.2 Shape of the MEFV Curve

The shape and the size of the MEFV curve varies considerably among healthy subjects and patients with lung disease. No single mathematical expression fits all variations and the experienced clinician uses the shape of the curve as a pointer towards abnormality. Three patterns describe the majority of curves in healthy subjects. (i) In young persons the descending portion of the curve is approximately linear or slightly concave to the volume axis. (ii) In older persons the descending part of the curve, especially near residual volume, is slightly convex to the volume axis. (iii) Some young and healthy subjects have a small intermediate plateau ("knee") on the curve at high lung volume - this is thought to result from a shift in the site of flow limitation from extra-pulmonary to intrapulmonary airways.^{273,274}

In all instances there is a gradual decrease in expiratory flow towards zero at residual volume. A sudden reduction of the flow to zero before the end of expiration is usually due to a sub-optimal effort, but could also be caused by rigidity of the chest wall. Sub-maximal effort is suggested by the reduction of flow rates at high volumes, flattening of the expiratory portion of the curve and poor reproducibility. The shape of the MEFV curve may also be distorted by technical factors, i.e. when the response time of the flow channel exceeds that of the volume-recording channel.^{273,274}

FIGURE 1: RELATIONSHIP BETWEEN THE SPIROGRAM AND MEFV CURVE

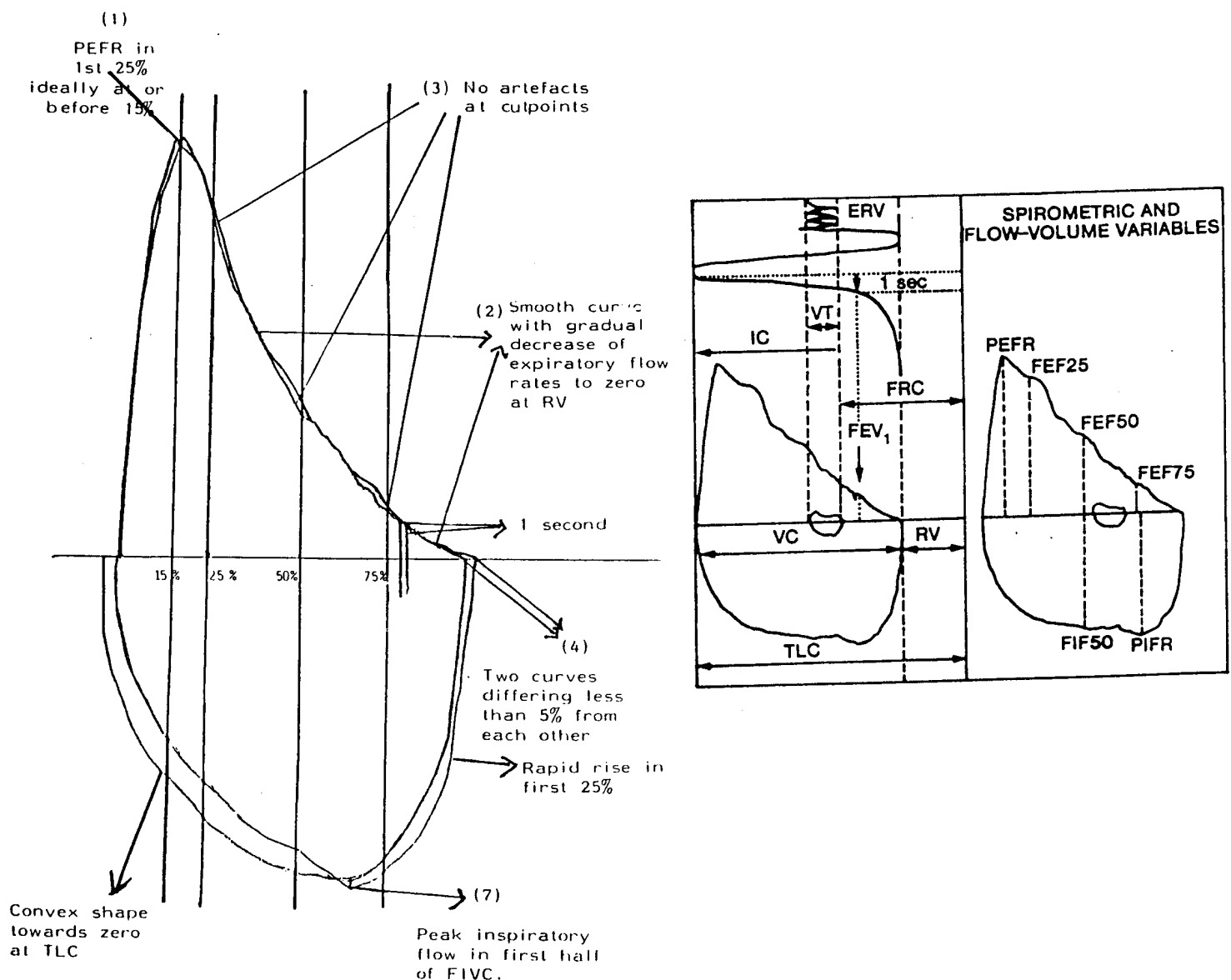
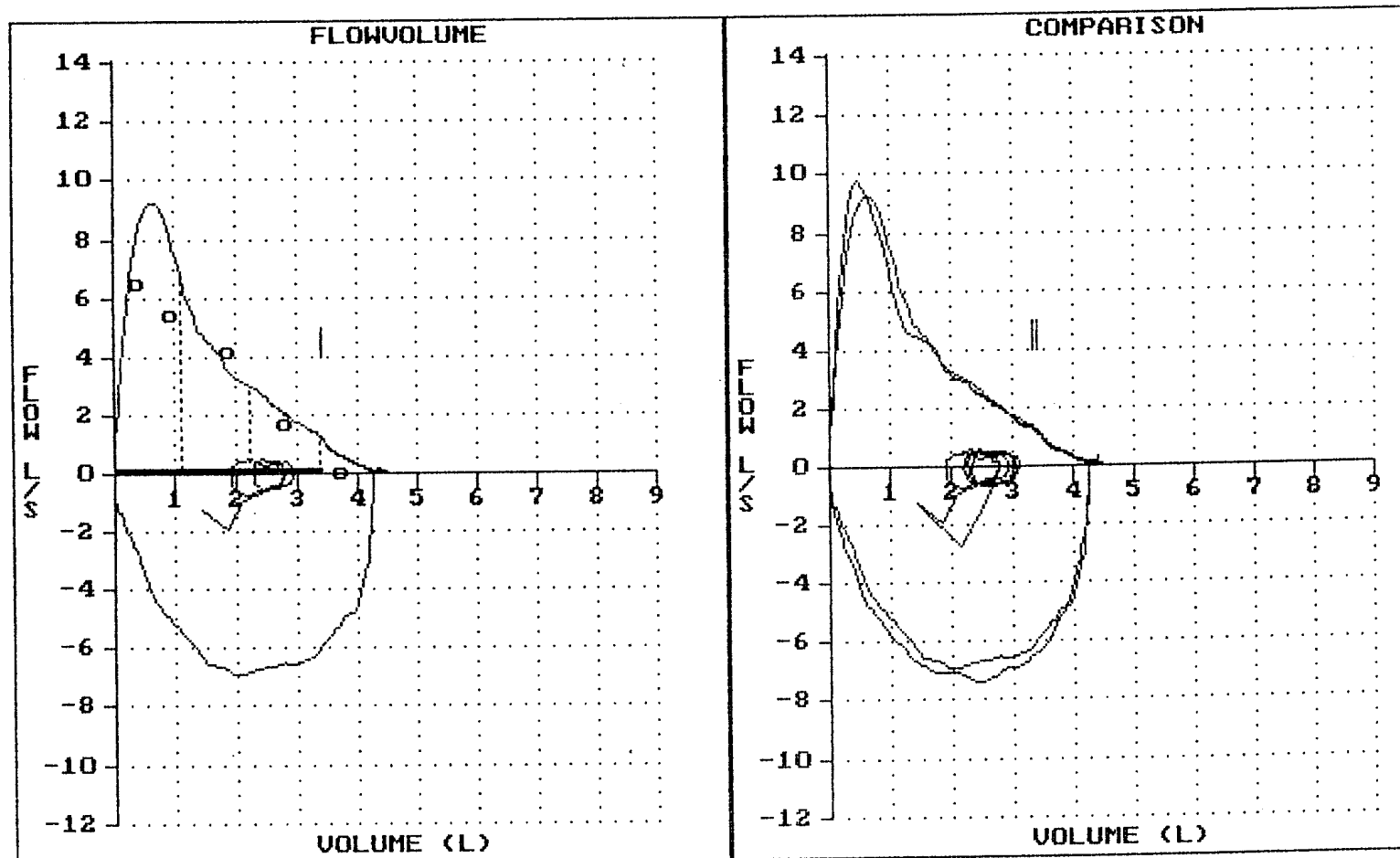


FIGURE 2 – STANDARD RÖSSING LUNG FUNCTION TEST

FLOWSCAN SYSTEM LUNGFUNCTION EVALUATION

Date :17-04-97 Id :P.E 190 Pack years :0
 Name :NARIB J.K Height :166 cm Weight :76 kg
 Age :28 Sex :Male Ethnic code :N
 Work :10 Doctor :VAN STADEN Technol :GU
 Flowtable 930802V last calibrated on Thursday 17 April 1997



Temperature 22°C Barometric pressure 707 mmHg

Time 09:58:12

09:59:36

Measure	Test1	Pred	%Pred1	Test2	%Ch
Fvc	4.48	3.70	121.2	4.47	-0.2
Fivc	4.26	3.70	115.2	4.28	0.5
Fev1	3.41	2.98	114.6	3.35	-1.8
Fev1%	76%	82.58	92.0	75%	-1.3
Fef25	6.70	5.40	124.0	5.66	-15.5
Fef50	3.03	4.20	72.3	2.93	-3.5
Fef75	1.28	1.71	75.1	1.25	-2.2
Pefr	9.23	6.49	142.3	9.81	6.3
Pifr	6.86	6.91	99.3	7.40	7.8
RV		1.04			
Frc		2.31			
Tlc		4.74			

Prediction values : Schoenberg
 Note : BEST OUT OF MANY ATTEMPT



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3.1.4.3 *Peak Expiratory Flow Rate (PEFR)*

The PEFR is the largest expiratory flow achieved with a forced effort from a position of maximal inspiration expressed in liters per second. The most commonly measured flow rate is the PEFR. PEFR is highly sensitive to effort and may vary considerably within the same subject. PEFR reflects the conductance of large upper airways and is largely associated with the size of the subject's trachea rather than the small airways and is insensitive to low levels of airway obstruction. Thus, a normal PEFR does not exclude significant lung disease, and PEFR frequently underestimates airway obstruction. The peak expiratory flow should be produced within the first 15% of the volume expired from maximum inspiration and sustained for 10 milliseconds. Although the PEFR can usually be reached within the first 15% of the FVC, it is our experience that a significant number of normal subjects have difficulty in achieving this and as long as PEFR is reached before 25% of expired volume, it does not appear to influence other measurements.²⁶⁹ When PEFR is reached after 25% of expired volume, the MEFV curve must be rejected.³⁴ Pneumotachograph-derived signals virtually eliminate the measuring device as a source of this distortion. A PEFR which is not easily identified or which is delayed and reduced in amplitude may indicate upper airway obstruction or poor initial effort. If the latter is the case, instantaneous flows occurring later in the same curve may be higher than on a true maximal expiratory curve because dynamic airway compression is less. Apart from a sub-maximal effort, PEFR can also be reduced if the manoeuvre was not started from total lung capacity (TLC), as maximal flow is also volume-dependent. A clue to the existence of this latter problem is a forced inspiratory vital capacity immediately after the MEFV that exceeds the forced expiratory vital capacity.^{261,262,269,274}

3.1.4.4 Flow Rates at Lower Lung Volumes (Forced Expiratory Flow {FEF} at Specified Volumes)

Flow rates at lower lung volumes are often surprisingly repeatable in spite of considerable variation in initial effort. This phenomenon has prompted the description of the descending portion of the curve as effort-independent, but this term is confusing since effort does influence this part of the curve. At any volume, a certain minimal effort is required to achieve maximum flow, but at lower lung volumes (beyond 25% of expired volume) flow is independent of further effort once this minimum has been attained. At high volumes, isovolume pressure flow curves³⁴⁴ do not show plateaux, and flow continues to increase until the limit of expiratory muscle power has been reached. When flow is plotted against volume, instantaneous flow can be noted at any specified lung volume. The flow rate is called the FEF when the reference volume is FVC and maximum flow (V_{max}) when the reference volume is TLC.³⁴⁴ The most commonly reported FEFs are at 50% (FEF_{50}) and 75% (FEF_{75}) of FVC and at 60% of TLC. By consensus, these percentages refer to the volume of air expired when FVC is the reference or remaining in the lungs when TLC is the reference.^{273,274}

Instantaneous flows at low lung volumes (near or below functional residual capacity) are useful in the detection of small-airways disease as well as having a role in epidemiological studies and in following the natural history of disease. The maximal flows at 50% and 75% of the expired volume may be low in the presence of a normal FEV_1 and PEFR, and in epidemiological studies this forms a group that warrants special attention. The FEF_{50} and FEF_{75} are inherently more variable than FVC and FEV_1 and are sensitive to relatively small record artifacts. The FEF_{50} and FEF_{75} are also influenced by early termination

of expiration (FEF_{50} and FEF_{75} taken from expirations with a low FVC because of incomplete expiration may have values that are falsely elevated). Another source of “inaccuracy” is less forceful initial effort, which may also be associated with erroneously high flows at 50% and 75% of expired volume. It is therefore absolutely essential to obtain the best repeatable MEFV curve when instantaneous flows are measured. Careful attention to these factors can improve the reproducibility of the FEF_{50} and FEF_{75} to near to 5%, even when airway obstruction is present.^{264,273,274}

The maximal mid expiratory flow (MMEF) or force mid expiratory flow (FMEF) is the mean forced expiratory flow during the middle half FVC. It is used extensively and sensitive to diagnose minimal airflow obstruction. It is however difficult to interpret if the VC is abnormal or after bronchodilatation. The forced late expiratory flow (FEF_{75} to 85%) has a poor reproducibility and is seldom used. In the European nomenclature the FEF_{50} and FEF_{75} is equivalent to their MEF_{50} and MEF_{25} .²⁷¹

The slope of the descending portion of the MEFV curve shows differences in various lung diseases - it is steep in patients with restrictive disease and flat in those with airways obstruction. However, measuring instantaneous flow at specific volume levels, as described above, is more satisfactory than assessing the slopes of MEFV curves.^{261,262,273}

3.1.4.5 Evaluation of the Maximal Inspiratory Flow Volume (MIFV) Curve

Although the MIFV curve provides useful information, many laboratories do not routinely record it, one of the reasons being that most commercially available instruments do not allow for this. The

MIFV is effort-dependent but in itself this should not detract from its value because the MEFV curve per se is also effort-dependent, although possibly not to the same degree. It is, however, true that many subjects have more difficulty in performing a maximal inspiratory effort from residual volume than the maximal expiratory effort from TLC.

For the more accurate interpretation of lung function there are valid arguments why MIFV curves should be recorded together with the MEFV on every subject tested:

- * An MIFV loop can provide that first “clue” or the most easily obtained confirmation of an obstructive process in the trachea, larynx, or pharynx. Different types of upper airways obstruction can be recognised by flow volume loops.
- * Although most of the present standard values have been calculated from the FVC, it is of value to register the slow expiratory vital capacity. In standard spirometry the subject expires slowly to residual volume before taking a deep inspiration to TLC and then performs the FVC manoeuvre. The inspiratory vital capacity thus measured may be equated to the slow expiratory vital capacity. The same procedure can be followed with the flow volume curve. When the curves thus obtained are monitored on an oscilloscope or computer screen, it helps the operator to ensure that the subject exhales totally and to detect early closure of airways. If $FEVC < FIVC$, when the maximal inspiratory manoeuvre precedes the maximal expiratory manoeuvre, the early closure of the airways is indicated.^{34,262,273,274}
- * Changes in inspiratory versus expiratory flow may be used to separate emphysema from chronic bronchitis. The rationale is that the

mechanism for airway obstruction in chronic bronchitis (secretions, inflammatory thickening of the bronchial mucosa) will affect inspiratory flow more than the prevailing mechanism for obstruction in emphysema.

In emphysema there is insufficient elastic support of the airways, resulting in severe compression when positive pleural pressure is developed during forced expirations. On the other hand the peak inspiratory flow in emphysema may be higher than the predicted normal level on account of the loss of elastic recoil of the lungs.

- * All inspiratory flows are reduced in restrictive lung disease due to the increased elastic recoil or “stiffness” of the lungs. At the same time the increased elastic recoil enhances the expiratory flow, resulting in an increase of PEFR, FEF₂₅, FEF₅₀, and FEF₇₅ relative to the lung volume.

An inspiratory manoeuvre performed from residual volume with a maximal effort produces an hemi-elliptical MIFV curve. There is an initial rapid increase in flow from the starting point at residual volume, reach MIFR in the first one-third to half of the inspired volume. If PIFR does not occur before 50% of inspired volume, the cause for this should be sought. Typically, the curve is concave to the volume axis from the point of peak flow to zero flow at TLC.^{34,261,262,274}

3.1.4.6 Tests for Detecting the Extent of Small Airways Impairment

Laboratory tests for the detection of small-airways impairment include.^{328,329}

- * the single-breath oxygen test from which is calculated the slope of phase III and the volume at which phase IV begins ("closing volume")^{278,279,280,281};
- * the frequency dependence of dynamic compliance;
- * the flow-volume curve using gas mixtures other than air,^{282,283,284}
- * the maximal flows at low volumes (FEF₅₀ and FEF₇₅) measured by the flow-volume curve. The flow-volume curve yields more information than the spirogram by permitting easier recognition of abnormalities confined to large or small airways. Obstruction of peripheral airways is really detected from the concave shape of the flow-volume curve,^{274,276,277} but may be overlooked in the standard analysis of the expiratory spirogram.

The small non-cartilaginous airways are those distal to the eighth generation and the elastic recoil of the parenchyma maintains their patency. Recoil pressure is greatest at total lung capacity (TLC) and decreases progressively as lung volume diminishes. Thus the resistance of the small airways increases in relation to that of the large airways as lower lung volumes are reached during a forced expiration. Flows at low lung volumes are thus greatly dependent on the calibre of the small airways.²⁶⁵

Some authors maintain that the FEV₁ is quite sensitive to morphological variations in the peripheral airways both in normal and diseased lungs, and that the clinical relevance of the greater sensitivity of the "tests of small disease" is at best marginal^{275,276,277} and appears to have only limited application for either clinical or epidemiological use. There are, however, still those patients in whom the tests that indicate small airways impairment are abnormal in the presence of a normal FEV₁, and in a longitudinal study conducted in higher-risk areas they will form a group that justifies special attention. Tests for the

detection of early impairment of the small airways will have a more important role in future if it can be shown that these abnormalities are caused by occupational exposure and that these tests can identify those subjects who will develop significant functional impairment if they remain exposed.

The test of frequency-dependent compliance and tests involving low-density gas are not quite suitable as screening tests for a large number of subjects. A flow-volume test with a 1-second timer permits the registration of all the conventional measurements of the spirogram including the FVC and the FEV₁, as well as measuring flows at 50% and 75% of VC. The single-breath oxygen tests are also relatively easy and quick to perform.^{278,279,280}

3.1.4.7 Prediction of “Normal” Values for Lung Function Measurements

For a test to be clinically useful, and to make decisions about changes in lung function being due to disease or to the effects of height, weight, age, or ethnic group, it is essential to standardise for these latter variables by predicting values based on the effects of these variables.²⁸⁵ As long as normal values for lung function are used mainly to detect gross abnormalities of function in patients with overt disease, the drawbacks of many of the existing prediction equations will not immediately be apparent. When lung function tests are being used in epidemiological studies to detect early lung disease in people working in higher-risk areas, it is essential to have a clear understanding of the concepts of normality, the factors that determine the extent of an individual subject's lung function, and the many sources of variation that may confound the test results. This requires a more complete knowledge of the determinants of lung function than is presently available.^{286,287}

The accuracy of measurement and of prediction is determined by the accuracy required for the specific application.²⁸⁶ Failure to recognise important variables that determine lung function can lead to erroneous interpretations of results.²⁸⁸ A few measurements of pulmonary function, e.g. the pH of blood, have a narrow range of normal values and are independent of physical characteristics such as height or age. Selection of useful upper and lower limits of normal values of such measurements are, therefore, relatively simple. For most pulmonary function tests (including spirometry and maximal flows) the range of observed values in a population of normal subjects is much broader, thus making selection of the limits of normal values more difficult.^{289,290} Because normal predictive values for many of these measurements correlate significantly with selected physical characteristics, regression equations can be developed from studies of large populations in normal subjects. These may be used to predict a narrower range of normal values for subjects with specific physical characteristics. Recognised factors for the prediction of many pulmonary function measurements include age, height, weight, sex, and ethnic background.^{288,289}

*

Age

Vital capacity (VC) increases until the age of about 23 to 27 years, then steadily decreases. The precise relationship between aging and decrements in pulmonary function is obscured somewhat by the interactions of height and age.²⁸⁵ Any prospective study is complicated by the deteriorating effect of aging on lung function measurements. It is still controversial how much the reference values, derived from cross-sectional population data, reflect the true aging process. These values are liable to be confounded by secular changes such as the

progressive increase in height of the population over a period of time and by the selective mortality, which results in survivors who have superior function and a slower rate of aging, living longer than their contemporaries. High-quality longitudinal data covering a sufficient time-span to define the aging pattern with a sufficient degree of certainty are unavailable.

* Height and Mass

In children, many pulmonary function measurements can be better predicted from height than from age, and are often best related to curvilinear regression equations. For adults, published regression equations that include height almost always use linear correlations.²⁸⁵

* Sex

For many pulmonary function measurements there are differences in predictive normal values related to the sex of the subjects and independent of differences in height and weight. For such measurements, separate regression equations for each sex are usually defined.²⁸⁵

* Ethnic Background

Differences in predictive values related to ethnic backgrounds are often overlooked in pulmonary function testing and are not adequately documented. In countries with heterogeneous populations such as the RSA and Namibia, where people of many ethnic backgrounds live in different climates and where altitudes range from sea-level, it would be important to know to what extent lung function varies in relation to ethnic group, climate, and altitude.

Since Gould made the observation in 1869 that height being equal, young black males had a lower VC than comparable white males, pronounced differences in pulmonary functions in various ethnic groups (including Caucasians, American Negroes, blacks of African descent in the UK, blacks in Africa, and Asians) have been reported by various authors.²⁹⁶⁻³¹² The lung function values for Indians and African blacks in Guyana living side by side in a uniform environment but remaining ethnically distinct, were significantly different after standardising for age and body size.²⁹² The arguments for uniform prediction formulae for all, proposed by Myers, are therefore not supported by the finding of the majority of investigators.^{307,308,309,310}

Ethnic differences are thus clearly important in determining lung function. This knowledge has not consistently been applied in the clinical interpretation of pulmonary function tests or in epidemiological screening.²⁶⁵ This has created a problem for the large number of users of computer-based pulmonary function testing systems that incorporate prediction equations derived from North American and European whites, because these are not valid for blacks, Asians and other ethnic groups.²⁸⁵ The difference in trunk/leg ratio among the various ethnic groups may be an important cause of differences in reference standards for test ethnic groups, but there may be additional genetic or acquired differences, perhaps relating to physical activity, socio-economic or environmental factors.^{307,308,309,310.} Louw, Golden and Joubert³¹³ found evidence to incorporate sitting height and socio-environmental status (SES) indicators in prediction equations to reduce the impact of "race" on spirometric values.³¹³

Whatever the causes, these differences clearly emphasize the need to use ethnic-specific reference values, many of which are now available. Although the ATS²⁷² is not specific in its recommendation, the official

statement (1993) of the ERS²⁷⁰ makes definite recommendations. They state that the lung's relation to the body size varies with both age and ethnic group. The generally accepted view is to apply approximate conversion factors for adjusting European reference values for application to other ethnic groups. For people of African origin the predicted value of FVC and FEV₁ should be multiplied by a factor of 0,87 or to subtract 0,45 liter from FEV₁ and 0,70 liter from FVC.^{270,271} In a study at the Tygerberg Hospital it was found that the prediction formulae for blacks of Schoenberg *et al* were the most suited to predict the standard values for blacks in Cape Town area (unpublished data). It was therefore decided to apply the Schoenberg formula to the different ethnic groups at the Rössing uranium mine.^{34,262}

3.1.4.8 Interpretation of Pulmonary Function Tests

There are considerable differences in criteria used to define abnormality and to grade the severity of lung diseases. It is complicated by the fact that "abnormal pulmonary function tests" are not always associated with significant clinical symptoms. The boundaries of normality remain difficult to determine, but any pulmonary surveillance programme requires a selection of an endpoint to define an abnormal level for a lung parameter. The interpretation of lung functions involves the classification of the derived values with respect to a reference population and assessment of the reliability of the data as well as the integration of the lung function values into the diagnoses and management of the individual. Several methods exist for comparing measured values of an individual with the reference values. To quote a few:

- * Fixed percentage of the predicted values (limits of normal as the predicted value plus/minus 20%). This method is in common practice, and is valid if the scatter is proportional to the level of the lung functions, which is true in children but not always in adults. This method implies that all measurements have the same coefficient of variation (CV) around the predicted mean. The method tends to over-classify abnormality, for instance in older and shorter individuals who have lower cut points for abnormality.
- * Cut-point based on the mean and standard deviation of the reference value. The most frequently method used for determining the cut-point is based on the mean plus-minus standard error of the estimate of the reference value. The lower limit of normal can be determined with a 95% degree of confidence by the mean predicted value minus the standard error of the estimate multiply by 1,65.
- * Lower point of normal by means of percentiles. All the values are placed in numerical order and the cut-point of the poorest values are determined.
- * Normalising individuals to a single value for each function. Sobol and Sobol suggested a method of "normalising" all individuals to a single value for each separate function.
- * Method using the residual. This method utilises the residual (difference between the measured and predicted value) to determine the cut-point of normality.
- * The relative operating characteristic curve (ROC). This is a modern epidemiological approach to the evaluation of the efficacy of diagnostic tests based on the concept of sensitivity and specificity. It slows the

relationship and trade off between the true positive and false positive results.

Multiple linear regression is the model used by most to describe lung function data. The prediction equations derived from linear regression take into account the effects of both age and height.²⁶⁴

In the occupational setting the use of percentiles (ATS)²⁶⁸ and standardised residuals (ERS)²⁷⁰ as well as the means minus two standard deviations are commonly used. Reference values are usually given as means (SD's) which is the residual SD about the regression equation (RSD). The RSD is nearly constant throughout adult life therefore an abnormal FVC or FEV₁ is one which is reduced by at least 1.64 RSD compared with the reference value. The probability of any given result differing from the reference value can be expressed in SD limits (difference of observed from expected divided by RSD) when a deviation of one or more 1.64 is considered abnormal.^{263,264}

3.1.4.9 Clinical guidelines

The standards for normal spirometry in the clinical setting is a FVC, FEV₁ and FEV₁% = or > than 75% of predicted value (using an appropriate set of reference values such as Schoenberg or to apply the ECSC standards with an ethnic correction factor of 0,87 for FVC and FEV₁). Some clinicians allow adjustments for age: 75% ≤ 30 years; 70% ≤ 30 to 60 years; 65% ≤ 60 plus years.

Airflow obstruction is often also graded as follows:

Mild:	FEV ₁ greater or = 70% of predicted
Moderate:	FEV ₁ greater or = 50% – 69% of predicted
Severe:	FEV ₁ greater or = 50% of predicted

Non-smokers lose FEV₁ at an accelerated rate with age at plus minus 30–35ml per year. In susceptible smokers the decline is 50–90ml per year and in a small group of smokers the decline is between 100–150ml per year.^{265,273} In general a loss of FEV₁ of more than 50ml per year suggests accelerated progression of disease. The FEV₁ value that is reduced relative to FVC (FEV%) usually points towards an obstructive abnormality. If FEV₁ and FVC are both reduced (with a normal FEV₁%), the mechanism is probably non-obstructive.^{273,274,287,288}

3.1.4.10 Pulmonary Function Tests in an Epidemiological Study

It is of interest to note that almost 50 years ago Gilbert *et al*²⁶¹ launched the first full-scale occupational respiratory health survey. In today's epidemiological survey PFT's must be accurately performed and properly reported in order to provide valuable clinical information.^{34,262} Quality control is essential in pulmonary function testing and requires frequent checks and calibrations of all instruments. The pulmonary technologist must be trained to ensure that each individual performs reliably. Serial studies done on the same patient avoid some of the problems in interpretation caused by the wide range of inter-subject variability, and are a useful way of studying the course of a disease and/or its response to treatment. These tests can be used to estimate the occupationally caused fractional loss in the individual, rather than by using comparisons with population norms. Estimation of pre-exposure values is easy when accurately performed pre-placement pulmonary function results are available. Unfortunately, few industries perform any such pre-placement examination (even though such testing would clearly pay dividends in the prevention of disease and savings in worker compensation costs).^{262,264}

CHAPTER FOUR

4.1 METHODOLOGY

4.1.1 Formulation of Problems and Hypotheses

It is well documented that prolonged exposure to high levels of uranium and its daughter products (notably radon gas) is associated with an excess of lung cancers (especially small cell carcinoma).¹¹⁻³² Likewise, prolonged and excessive exposure to siliceous dust is associated with the risk of silicosis, lung cancer and chronic non-specific lung disease (CNSLD).²¹⁰⁻²¹⁹ Exposure to criteria pollutants (SO₂, NO_x, CO, O₃, Pb and particulates) is associated with decreases in lung function and aggravation of respiratory disorders.¹⁸³⁻²⁰⁰

The main question is whether prolonged exposure to low levels of uranium and/or silica causes an excess of respiratory abnormalities such as pneumoconiosis (in particular silicosis), lung cancer and chronic non-specific lung disease (CNSLD). The broad concern was with the entirety of health effects of uranium and its daughter products as well as silica in smokers and non-smokers.

If an effect could be demonstrated, the strength of association had to be investigated. Studies were launched at specific intervals when the majority of the workers had been “sufficiently exposed” (between 10 and 25 years of exposure) to accommodate latency and to consider specific intervention measures to prevent the effects of further exposure.

These observations were the basis for the hypothesis **that uranium miners at Rössing Uranium Mine are at a greater risk than the general public of developing lung cancer, silicosis and chronic non-specific lung disease (CNSLD).**

4.1.2 Study Plan and Time Frame

4.1.2.1 Introduction

The first ground in the Open Pit was broken in 1974 but a multitude of technical problems and a devastating fire in 1978 postponed meaningful production until 1979. In 1979 Namibia (South West Africa) was politically isolated and an embargo on virtually all commodities (including technical information and assistance) existed.⁵⁵

The combination of low levels of occupational and non-occupational exposure; active environmental control programs, anti-smoking campaigns and personal protective equipment programs, as well as the long genesis time associated with the development of most occupational related respiratory disorders made the detection of abnormalities extremely difficult. The level of technology available in 1980, controversy about applicable reference values, false-positive results of tests, and the influence of extraneous factors complicated this.^{55,316}

Although health screening and periodic medical examinations were introduced in 1978, the emphasis in the period 1978 - 1980 was mainly on occupational hygiene and safety. In 1980 a proper and modern occupational surveillance programme was phased in. All workers on the mine undergo pre-employment medical examinations which include a relevant history, full clinical examination by medical doctors, chest radiograph (reported on by visiting occupational health consultants), ECG, audiometry, eye evaluation, a flow volume curve, full blood count and kidney and liver function tests. Periodic medical examinations include special investigations that are done regularly once or bi-annually. The occupational programme links with a public health

section that deals with the prevention of home accidents and social problems such as smoking and alcoholism. Contagious diseases are treated and immunisations are carried out.^{55,316}

Labour turnover dropped from 30.1% in 1978 to 8.1% in 1985 and to 2% in 1995 and it remains low. Forced by a reduction in worldwide uranium sales, a retrenchment exercise was carried out in 1991. This was done on the basis of "first in - last out" which meant that the long-serving workers were least affected.

4.1.2.2 Project Organisation

The two team-leaders, an occupational health physician and a consultant pulmonologist jointly planned the studies at various stages. The team included various other members of the occupational health unit and statistical analysis was done by outside consultants. The projects were put into effect with the cooperation of management and the workers.

4.1.2.3 Time Frame

The project commenced in 1979 and ended in 1999. The table below shows schematically the overall time frame of the project.

The **first phase** involved studies of respiratory health of workers in various occupations in order to identify vulnerable individuals and high-risk groups, to evaluate different reference values for lung functions and to standardise procedures and equipment.

The **second phase** comprised of a number of pilot studies to determine the prevalence of alpha-1-antitrypsin deficiency, to

determine the lung burden of uranium workers, and to evaluate the effectiveness of sputum cytology as a screening test for lung cancer.

The **third phase** included a descriptive cross-sectional study to develop predictive equations for the Rössing work force. This was followed up with an analytical cross-sectional study in which the essential confounding factors were controlled for by design and matching. The purpose was to determine the independent effect of uranium mining (utilising the results of the previous study) on the respiratory health of the workers after more than 10 years of exposure to the Rössing environment.

Phase four was a case-control study to investigate the relationship between exposure to uranium and silica-bearing dust and lung cancer, pneumoconiosis and chronic non-specific lung disease (CNSLD), after more than 23 years of exposure).

Table 5 Time Frame of Respiratory Health Study together with Reporting Dates			
Years of Study		Type of Study	Reporting Year
I First Phase	1982 - 1985	Exploratory respiratory health survey and a cross-sectional study	1985
II Second Phase	1985	Pilot studies (various)	1985
III Third Phase	1987 1996	Cross-sectional prevalence study and a descriptive and analytical cross-sectional study	1987 1996
IV Fourth Phase	1999	Case-control study	1999

4.1.3 Study Design

To achieve the objectives outlined, more than one study design was used. The pilot studies were exploratory in nature and are discussed separately.

4.1.3.1 Cross-Sectional Studies

In the first studies descriptive cross-sectional designs were used. The main purpose of these studies was to standardise procedures, to evaluate various methodologies and to focus on a cross-sectional survey of respiratory morbidity. The effects associated with dust and cigarette smoke were explored and the prediction of unstandardised (raw) lung function data of the three major ethnic groups in the population was investigated. The strength of these studies was the accuracy of the lung function data obtained, the weakness, the fact that although the sample size was large it was primarily selected on the basis of the quality of lung functions and not on a random basis of the population studied. Initial results obtained were used for preliminary analysis.

4.1.3.2 Analytical Cross-Sectional Study

Cross-sectional prevalence studies of lung diseases and confounding variables in cohorts of Rössing employees were done. The populations chosen received estimated exposures and subsequent health outcomes were measured. The rate of abnormalities was compared with those in less exposed sections. In analytical cross-sectional studies confounding factors are controlled for by design and matching. Retrospective data on exposure (level and time) to occupational factors are taken into account. Analytical cross-sectional studies provide cost-effective information and may assist with the verification of a working hypothesis.

The classic retrospective cohort study designs were not used, as it is highly likely that an unacceptably low response rate would occur among past employees. The study could however serve as a baseline for a prospective cohort that will detect health effects with long latencies.

4.1.3.3 *Criteria for Admissibility*

Those eligible for inclusion as the population at risk were all the males who had completed a fairly lengthy service at Rössing Uranium. The number of years of service was different for the various studies (time-related variables). The percentage of women was small and it was decided to exclude them.

It was decided to exclude those with short lengths of employment and only to include those with long periods of exposure because the latency period for most occupational disease is in excess of 10 years' exposure. It is accepted that the studies will have a high probability of under-estimating the true risk of lung cancer because the disease will not have had time to develop.

In the third study, those who had more than 15 years employment history were not subjected to the same exclusion criteria (pre-employment medical examinations) as the group with 10-14 years service (healthy worker effect). It was a small group and it was decided to group them together to enable statistical analysis. To control for "different drop-out rates", a random sample of ex-employees (those who have left the mine) were examined to ascertain the prevalence of abnormalities studied.

The study group was subdivided into those who were employed in operational areas (and exposed) and those who were in administrative positions (unexposed group). It is accepted that this group is not the ideal control group. However, a suitable alternative group could not be found (i.e. a sufficiently large enough group of males whose medical parameters were available for matching purposes).

In the case control study (phase four) all men fulfilling the following criteria were included:

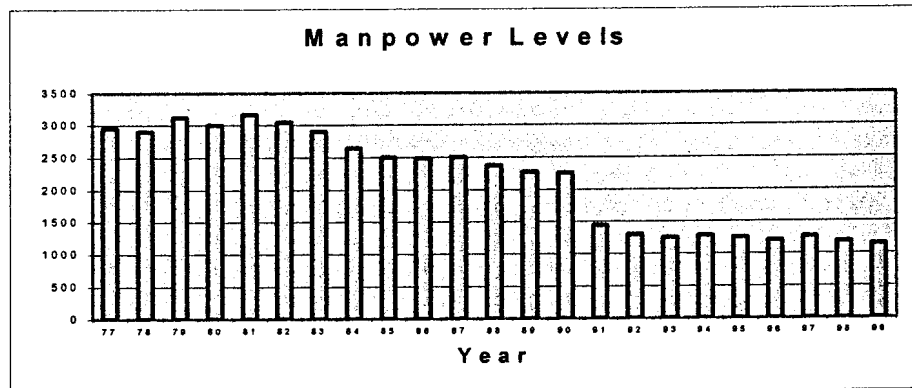
- * Aged 35 years and more;
- * Twenty-three years of continuous or uninterrupted service;
- * Also included were workers who worked for more than 23 years and who had left the employ of the mine.

This group had been employed before the mine instituted strict selection criteria (before 1979) and this group was least affected by retrenchment because of the policy of first-in-last-out.

4.1.3.4 Population and Sample Size

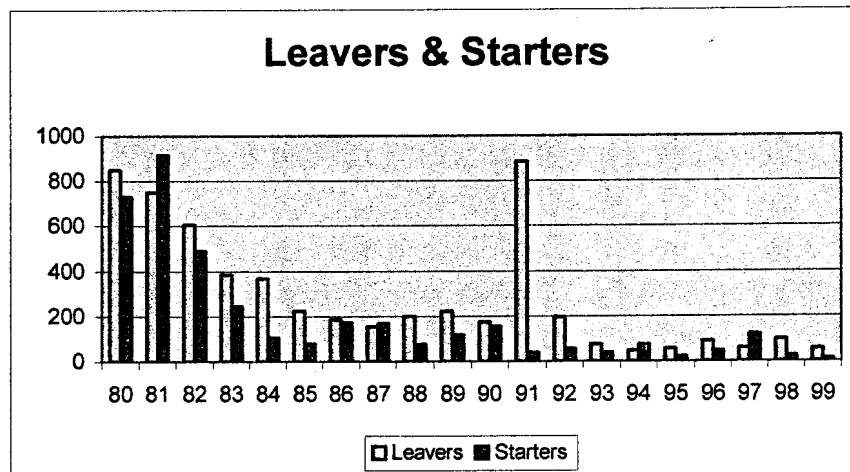
The manning levels at Rössing have varied considerably over the past twenty years. Total manning levels are best reflected by the following graph.

Graph 1



Initially the labour turnover was high but remained stable until the retrenchment exercise in 1991.

Graph 2



The sample size is considered to be representative because it is large enough and the population had adequate exposure and the observation period was long enough to allow for the development of respiratory disorders. This latency assumption is based on known occupational carcinogens such as radon progeny. The sample size allows for a type 1-error level at 0,05 and a power at 0,90 with an arbitrary relative risk of 2,0.

4.1.4 Assessment of Health Effects

All workers are medically examined before, during and when their services are terminated. The health evaluation of each subject is accomplished by means of a questionnaire on previous employment history, general and respiratory symptoms questionnaire, physical examination, spirometric examination, chest x-rays, sputum cytology and haematological indices. Selected samples were investigated for uranium lung burdens and for the identification of susceptible individuals (alpha-1-antitrypsin).

All the equipment was purchased on the basis of best available, and is calibrated on a regular basis and to agreed protocols. Laboratory quality controls are audited regularly by internal and external auditors. The staff at the medical centre is all qualified and part of a stable workforce.

4.1.5 Respiratory Function Measurements

4.1.5.1 *General Comments regarding Equipment and Quality Control*

The confusion caused by the large number of different devices available for lung function testing was aggravated by the advent of computers in the lung function laboratory. Several methods are applied to measure the same variable, e.g. hot wires; low-inertia rotating vanes and resistive-type pneumotachographs are all used for the measurement of air-flow. Some methods integrate flow/time to obtain volume; others differentiate volume/time to obtain flow, while spirometers can vary from conventional wet-cylindrical to dry-wedge types. The investigator should choose the equipment that suits his purposes best, but must ensure that it meets the minimum internationally accepted performance standards, such as those

recommended by the American Thoracic Society.^{267,268} Briefly, these minimum requirements are.^{262,263,264,266,267,268,269}

- * The volume range should be at least 7,0 litres and the accuracy should be within 3% or 50ml when gas is injected at any rate between 0,2 and 12 litres per second.
- * The instrument must be capable of accumulating volume for at least 10 seconds.
- * Resistance should be less than 1,5cm H₂O litres per second at a flow of 12 litres per second.
- * Flow should be measured within 5% over a range of 0,12 litres per second.

To this we would add that real-time viewing of the curve on the computer screen and the facility to store and recall the registered curves facilitates the selection of the “best” repeatable curve.

All equipment should be calibrated with a 3 - 5-litre syringe.

The concept of accuracy implies that there is a “correct” value around which repeat measurements scatter in a random Gaussian manner. The closer the mean of these measurements is to the correct value, the greater the accuracy. Accuracy of a measuring device is usually ensured by meticulous attention to the calibration procedures. Precision is an index of reproducibility of repeated measurements, regardless of how close the mean value is to the “correct value”. The standard deviation or coefficient of variation (SD/mean x 100) of repeated measurements is commonly used as an estimate of precision; the smaller the standard deviation or coefficient of variation, the greater the precision. The assessment of precision is an essential component of quality control programs. It serves to define not only the

capabilities of the instrument but also those of the technologist and the subject during the entire testing procedure. In the determination of instrument precision, the use of devices such as large syringes for simulating forced expirations clearly offers the advantage that repeated test "samples" will be more reproducible than the repeated forced expirations of a subject whose possible fatigue, airway spasm, and lack of co-operation will adversely affect the magnitude of random error of measurements with a specific spirometer or pneumotachograph. Even though the accuracy and precision of a particular instrument may be within acceptable limits, significant problems in accuracy and precision can occur as the result of faulty techniques and non-compliance of the subject. Few other laboratory tests are so dependent on subject co-operation as this.^{262,263,264,268,269}

4.1.5.2 Procedure for the Flow Volume Curve

A period of quiet breathing is maintained until a constant end-tidal point is reached for three consecutive breaths. The subject is then instructed to exhale slowly and maximally. When expiration is maximal, that is, when residual volume (RV) has been reached, the subject is told to breathe in as fast and as deeply as possible to total lung capacity (TLC), to hold the inspiratory effort at TLC for 1 or 2 seconds, then to exhale as rapidly, forcefully, and completely as possible.

A minimum of three acceptable FVC manoeuvres must be obtained. An acceptable manoeuvre demonstrates a "crisp", unhesitating start; smooth, continuous expiration; absence of cough, glottis closure, second inspiration, leak (e.g. at the mouthpiece), or blockage (e.g. by the tongue); and complete effort. Early termination of effort, before RV

is reached, can be easily missed. The same principles apply for the inspiratory maximal effort.

In selecting the best curve the following criteria require special attention:

- * Peak expiratory flow (PEFR) should be produced within the first 15% of the volume expired. The steeper the ascending part of the curve to peak flow, the better. All curves where peak flow is reached at, or after, the first 25% of the expired volume, should be rejected. A PEFR that is not easily identified or that is delayed and reduced in amplitude may indicate upper airway obstruction or more commonly poor initial effort. If the latter is the case, instantaneous flows later in the same curve may be higher than on a truly maximal expiratory flow volume curve.
- * The down curve should be smooth and free of recording artifacts, including coughing and the RV reached by a gradual decrease in expiratory flow rates towards zero. A sudden reduction of flow rates at the end of the expiration may be due to a sub-maximal effort not exhaling to RV and should only be accepted if totally reproducible. Sub-maximal effort is suggested by reduction of flow rates at high volumes, flattening of the expiratory portion of the curve and poor reproducibility.
- * As an indication of peripheral (small) airway involvement, the $FEF_{50\%}$ and $FEF_{75\%}$ are measured. The instantaneous flows at middle and low lung volumes are increased by recording artifact, by early termination of expiration, and by less forceful initial effort. They are inherently more variable than FVC and FEV_1 . A full expiration to RV is essential for accurate measurement of these values. An erroneously smaller FVC due to an incomplete expiration will result in erroneously high $FEF_{50\%}$ and $FEF_{75\%}$. The curve is checked especially for

artifacts coinciding with the cut points at 25%, 50% and 75% of the expired volume so that the accuracy of the measurements of FEF_{25%}, FEF_{50%} and FEF_{75%} is not affected.

- * The aim is to register at least 2 more or less identical curves differing not more than 5% in the FVC and FEV₁. A special effort is made to reproduce the curve with the largest FVC that was produced with a maximal effort.
- * If the above criteria are fulfilled, the expiratory curve with the largest sum of FVC and FEV₁ is selected and all flow measurements made from this curve.
- * The inspiratory VC (FIVC) after a slow expiration to RV can be assumed to be the same as a slow expired VC and is equal to or larger than FVC. The FIVC is unlikely to be smaller than the FEVC when the test is properly done.
- * The peak inspiratory flow (PIFR) should be reached within the first half of the inspiratory volume and the inspiratory curve towards TLC is usually convex.
- * The best expiratory and best inspiratory efforts are selected and may not necessarily be from the same manoeuvre.
- * If acceptable curves are not possible due to inability or lack of co-operation of the subject, the test is abandoned and redone at a later date.
- * Bronchodilatation medicine is stopped before a test is performed:
 - Inhalers 4 hours
 - Theophyllin 12 hours and;
 - Theophyllin slow release 24 hours.
- * A positive bronchodilator response is regarded:
 - > 200 ml increase in FEV₁
 - > 15% FEV₁ from baseline
 - > 10% in FEF₅₀ and FEF₇₅

4.1.6 Descriptive Cross-Sectional study

A Cavitron-SC-20 spirometric computer (including a DP-30 data printer and a CR-84C recorder) and a Gould model 80 computerised spirometer were used to produce a flow-volume loop. The Gould apparatus was used for the single-breath nitrogen wash-out curve. The calibration procedure included the setting of room temperature, barometric pressure, and relative humidity. Volume was calibrated by using a calibrated syringe (6 litres) with an accuracy of 2ml) for expiration and inspiration. Frequent recalibrations were performed due to the fact that in the Namib desert temperatures vary appreciably during the day in spite of the air-conditioned room.

The following measurements were obtained from the flow volume curve: FVC, FEV₁, peak expiratory flow, FEF₂₅₋₇₅, FEF₂₅, FEF₅₀, FEF₇₅ and the peak inspiratory flow. The acceptability of the test was determined by the operator's observation on the basis that the subject understood the instructions and that he performed the test **with**:

- * a smooth continuous escalation and inhalation;
- * apparent maximal effort;
- * a good start;
- * **and without:**
- * coughing;
- * a Valsalva manoeuvre;
- * early termination of expiration;
- * a leak;
- * an obstructed mouthpiece;
- * an unsatisfactory start of expiration characterised by excessive hesitation or false start;
- * an excessive variability among the acceptable curves and loops.

The aim was to obtain two identical loops whenever possible. When two identical loops could not be obtained in spite of good technique and maximal effort, the one with the largest sum of the FVC and FEV₁ was selected. All the curves were inspected by one of the authors before being included in the analysis to minimise operator error.

4.1.7 Analytical Cross-Sectional and Case-Control Studies

In order to simplify and optimise quality control so that optimum MEFV and MIFV curves could be obtained a flow volume apparatus was developed. It is based on an IBM compatible PC with an interface for a pneumotachograph, Spirostat and Flow Scan. In addition to fulfilling all the criteria recommended by the American Thoracic Society, the following functions of the apparatus facilitated the procurement of the best, satisfactory repeatable curves and promoted quality control:

- * The inspiratory and expiratory graphs were displayed in real time.
- * If the curve was acceptable it was stored and, if not, it was rejected.
- * Curves could be stored or rejected according to the quality of the effort.
- * When three acceptable curves were obtained, it was possible for the operator to recall each individual curve separately on the screen or to superimpose them whenever it was thought necessary in order to select the best curve.
- * The following measurements of all three efforts were displayed on the screen: FVC₁, FEV₁, FEF₂₅, FEF₅₀, FEF₇₅, PEF_R, FIVC, and PIFR.
- * The manoeuvre with the largest sum of the FVC + FEV₁ and the largest inspiratory vital capacity (FIVC) (which may not have come from the same manoeuvre) were indicated on the screen. If all other criteria were met, these curves were selected. The operator had the option to overrule the computer.

- * The selected MEFV and MIFV curves were printed together with the predicted values, actual measured values and measured values expressed as a percentage of the predicted values. (The predicted values were calculated from formulae decided on by the specific laboratory). In our case the Schoenberg *et al*, the Rössing formulae and the European Steel and Coal Miners were used. With some equipment it was not possible to select or change the prediction formulae.
- * On the graph of the selected curve, lines were drawn through the points at 25%, 50% and 75% of expired volume in order to check that the artifacts (such as commonly occurring flow oscillations) did not affect the flow at these points and also to control for the volume coinciding with PEFR.
- * In the final report all three curves were also superimposed and printed to the right of the selected curve, together with the actual values of the measurements as specified above.
- * A hard copy of the curves and all measurements was printed out and all the information stored on a computer diskette.

To overcome variation in equipment used (spiostat and flow scan) five pulmonary function test result variables for each of the two instruments was obtained from thirty-one subjects.

The table shows the skewness coefficient and chi-square values as calculated for each of the pulmonary function variables for each of the instruments.

A skewness coefficient of less than 1.0 can be considered as very acceptable. The critical value for the chi-square distribution with seven degrees of freedom and at a significant level of 10% is 12.02 and this was only exceeded for the FEF₅₀ for the flowscan and the PEFR for the spiostat.

In the former two cases however, the skewness coefficients were low which indicated an acceptable distribution of values about the mean, even if they were not necessarily gaussian. In the latter case, both the chi-square value and the skewness co-efficient were higher than desirable but were included in order to avoid a break in continuity.

The correlation coefficients determined for each of the regression analyses were acceptable as they all exceeded 0.8 which is generally accepted as constituting a satisfactory "goodness of fit" of the regression line to the data.

Table 6 Pulmonary Function Variable										
	FVC		FEV ₁		FEF ₅₀		FEF ₇₅		PEFR	
Inst	sk	X ²	Sk	X ²	sk	X ²	sk	X ²	sk	X ²
Spst	-0.24	6.1	-0.39	6.1	0.53	9.3	0.14	6.7	1.18	15.8
F Sc	0.03	10.0	-0.03	1.6	0.43	18.4	-0.31	4.2	0.74	7.4

4.1.8 Radiological Examination of the Chest (Chest x-rays)

All chest x-rays were taken with the same equipment by the same qualified radiographer. An iontomat was installed to ensure constant exposure with a 140 kV exposure to obtain full-size films at 3 metre distances and 18cm air-gap. Each participant had a full size postero-anterior chest x-ray.

The presence or absence of pneumoconiosis according to the International Labour Organisation (ILO) coding of pneumoconiosis (ILO, 1980)³¹⁷ was recorded and read by two persons experienced in ILO coding (with at least one reader not being a resident in Namibia). The readings were performed independently and without knowledge of exposure status. As well as ILO coding for pneumoconiosis, each x-ray was ILO coded for the presence of other diseases (e.g. silicosis,

siderosilicosis, asbestosis, carcinoma, mesothelioma, and pleural plaque as well as pleural effusion). The median reading of the two readers was the one used for analysis. Films with abnormalities were compared with previous films of the same individual to assess the time-course of the development of the abnormality, particularly in relation to dust exposure history.³¹⁷

All x-rays with suspected abnormalities (>0/1) were sent to the South African Medical Bureau for Occupational Diseases (MBOD) in Johannesburg for interpretation. Their ruling was accepted as the final verdict.

4.1.9 Sputum Cytology

Sputum specimens were collected from a number of Rössing workers. Patients were carefully instructed to produce sputum by several deep coughs after mouth hygiene and eating. Sputum was expelled into a standard container containing the pre-fixative ethanol and 2% Carbofax. Each container was identified by company number, initials, name and date of collection. It was then sent to Tygerberg Hospital. All specimens were processed by the "Stripper" and modified Saccomanno Technique, blended and certified, prepared and post-fixed in 95% ethanol, and stained according to the Papnicoloau method.^{331,332,333}

The cytology slides were screened and interpreted by cytotechnologists and cytopathologists of the Cytology Department of the Tygerberg Hospital in Cape Town (Director: Dr J Deale).

4.1.10 Alpha-1-Antitrypsin

Blood was collected from those who had "abnormal" lung functions (lower than predicted), and sent to the Genetic Department Laboratory

(Dr H Hitzeroth) in Pretoria. Radio-immuno diffusion methods were used to identify the phenotypes (SANOS - Pasteur diagnostics).

4.1.11 Determination of Uranium in the Lung

A selected number of employees were examined in South Africa at the Tygerberg Hospital (Radiation Decontamination Unit) to determine the retained lung burden of uranium. Four Na (TI) crystal detectors were used in a low background counting chamber constructed from pre-World War II steel and lined with lead. Signal processing was done by an ND68-MCA system (details are reported on in the chapter - Uranium in Lungs).³²⁵

4.1.12 Clinical Management

Every patient with an "abnormality" as defined in the following protocol was clinically evaluated and treated if indicated. Where applicable, the worker was advised to stop smoking and, if necessary, he was removed from a higher-risk area with no financial loss.

Table 7- Abnormal Lung Function Management Protocol

Grade 0		Normal in all respects
Grade I		FEF₅₀ or FEF₇₅ < 75% of predicted or abnormal general pattern
	a)	With no symptoms – follow up 6 monthly
	b)	With symptoms – see clinically
	c)	If a smoker, must be advised to stop, advise on environmental protection
	d)	Investigate environment and possible causative factors
Grade II		FEF₅₀ and FEF₇₅ < 75% of predicted
	a)	See clinically and assess exposure to dust or irritant gases
	b)	If he has symptoms do histamine provocation test and "body box"
	c)	No symptoms – follow-up 6 monthly, advise on smoking
	d)	Investigate environment and possible causative factors, advise environmental protection

Grade III		FEF₅₀ and FEF₇₅ < 75% of predicted, reduced FVC and/or FEV₁ and/or a PEFR (without symptoms)
	a)	Full clinical examination
	b)	Investigate environment and possible causative factors
	c)	Chest x-ray
	d)	"Body box" and CO dif
	e)	If FEV ₁ > 70% do histamine provocation test
	f)	If FEV ₁ < 70% do after bronchodilator
Grade IV		Grade IV is as for Grade III plus symptoms
	a)	Manage as for Grade III but consider a transfer and/or retirement

4.1.13 Assessment of exposure

Rössing is a low-grade, high-tonnage mining operation with an open pit, a metallurgical plant, engineering workshops and an acid plant. It is situated in a harsh and dry desert.

The ore containing pegmatitic granite is called alaskite. Uraninite is the dominant primary radioactive material and is included in quartz, feldspar and biotite. The average ore grade is 0,035% with uraninite comprising 53% of the ore-body, betaphyte 5% and secondary minerals 40%.

Industrial hygiene monitoring data for airborne agents and gases, as well as occupational history of subjects in various areas both during and prior to joining Rössing was used. Quantitative industrial hygiene data was used for two purposes, namely: to assist in the allocation of work areas or occupation into exposure categories, and to provide a quantitative estimate of the exposure of individuals allocated to the different exposure categories.

A more detailed description of the Rössing working environment is given as an appendix with special reference to geology, climate, operation and environmental characterisation.

4.1.14 Environmental Characterisation

The Rössing environmental surveillance programs were developed around a risk-based approach based on the type and frequency of monitoring the degree of exposure; the target organ involved; the type of work carried out; meteorological conditions; the location of residential areas, and are in line with legal requirements.

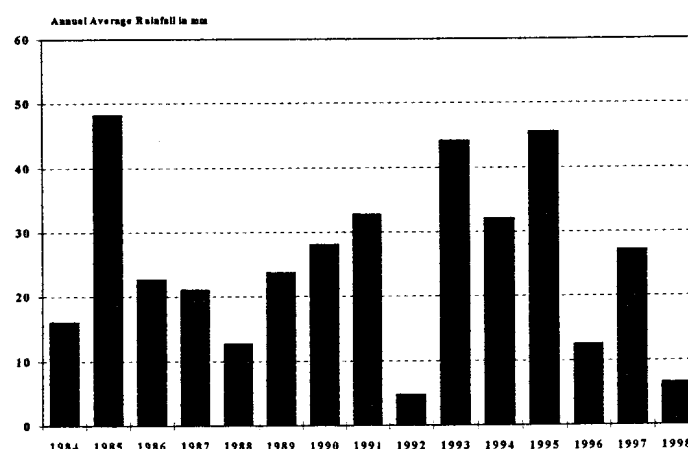
4.1.15 Meteorological Monitoring

There are three meteorological stations in operation: Point Bill, located in the plant area, one at the Arandis Airport and the other at the Open Pit. The variables measured hourly by these stations include the wind direction, wind speed, temperature, solar radiation, pressure, relative humidity, evaporation and rainfall.

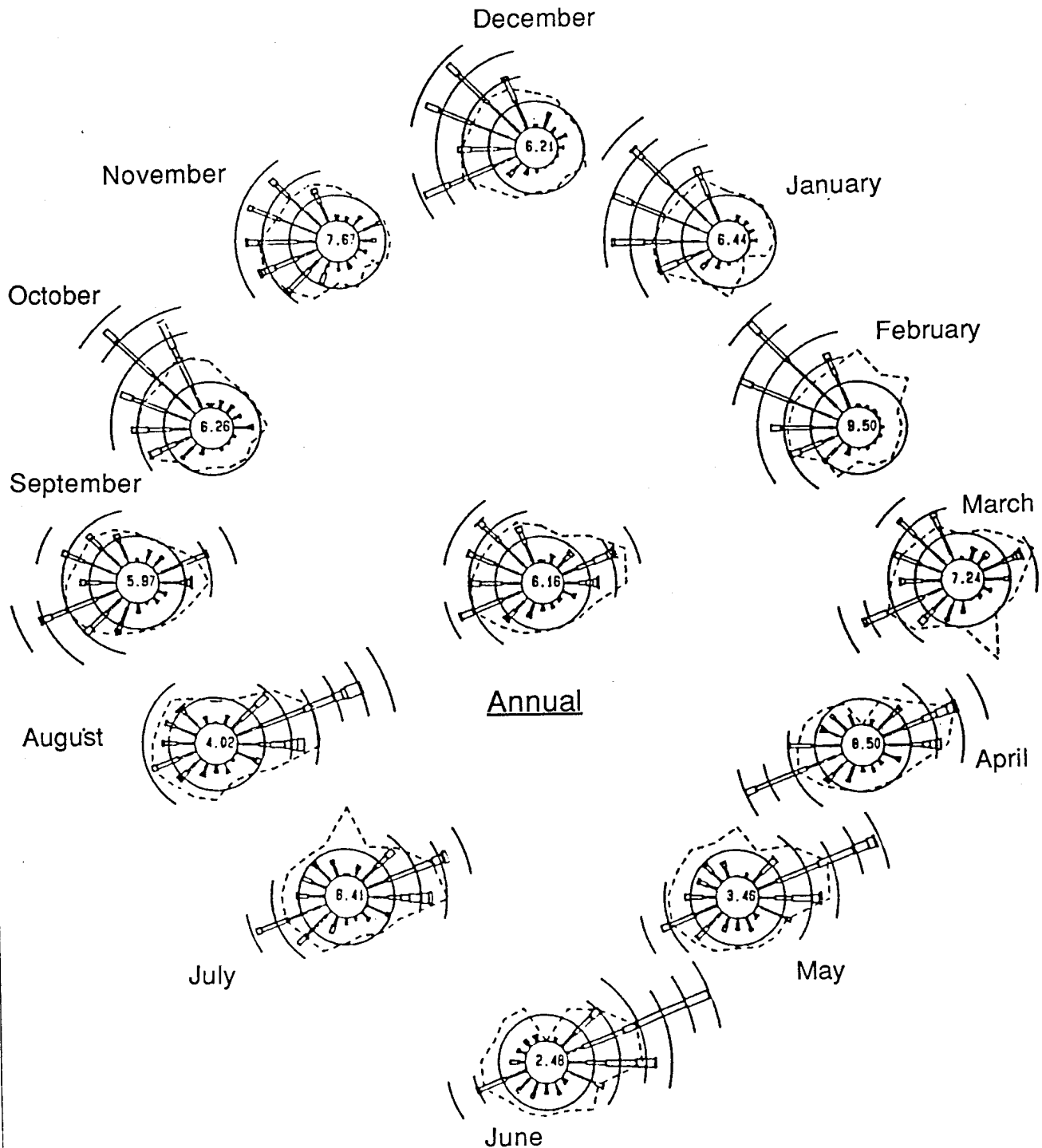
Graph 3



Rainfall at Rössing



Annual and Monthly Windroses Rossing Uranium



KEY :

1.1-1.5 1.6-3.3 3.4-5.4 5.5-7.9 8.0-10.7 10.8-12.5 12.6+

CIRCLES REPRESENT 5% FREQUENCY INTERVALS AND

2.0 m/s AVERAGE WIND SPEEDS (DASHED POLYGON)

PERCENTAGE CALMS WITHIN THE INNER CIRCLE



UNIVERSITEIT VAN PRETORIA
UNIVERSITY OF PRETORIA
YUNIBESITHI YA PRETORIA

4.1.16 Radiation Monitoring

The natural background radiation or external radiation measured 1 metre above the ground averages 3,5mSv per year at the mine and in the surrounding areas. It is approximately five times greater than the average natural background radiation in the United Kingdom (0,7mSv per year). This is as a consequence of the higher uranium concentration naturally occurring in this area.

Table 8 Background Radiation mSv/a					
	United Kingdom	Windhoek	Swakop	Arandis	Rössing
Background (terrestrial and cosmic)	0.7-1.2	1.6-1.7	1.4	1.6-1.75	2.19
Internal (Food, water, air)	0.37	0.37	0.37	0.37	0.37
House (material)	0.45-0.8	0.45-0.8	0.45-0.8	0.45-0.8	0.45-0.8
	1.52-2.37	2.42-2.87	2.22-2.57	2.42-2.92	3.01-3.36
	1.95	2.65	2.39	2.67	3.19

Occupational exposure to radiation can reach much higher levels, for example, up to 0,015mSv per hour (equivalent to 30mSv per year in a 2000 hour working year) has been occasionally measured. Occupancy factors are however low and the dose to personnel is kept within ICQP annual dose limits.

- * Background Radiation: External beta and gamma background radiation levels are measured by exposing thermoluminescent dosimeters (TLD's) and portable monitors in different areas on and off the mine site.
- * Radiation Surveys, Beta/Gamma Dose Levels measured at contact and at the 1m level, and source contamination: Beta/gamma rates and source-alpha emissions are measured at all areas on the mine site.

- * Personal Radiation Dose Levels: The personal external radiation doses of all registered radiation workers are measured with the TLD's issued and read by the South African Bureau of Standards (SABS). The Environmental Control Department also issues and reads TLD's of employees undertaking tasks that may result in enhanced personal exposures.
- * Leakage tests of sealed radioactive sources on the mine site: All radioactive sources are inspected and smear samples taken to determine any leakage. Training of employees in the safe handling of these sources is conducted on an annual basis.
- * Radon, Thoron and Progeny: Radon (and its daughters) is a significant contributor to radiation dose on the mine. Measurements of radon working levels, radon concentrations and the radon/radon-daughter equilibrium factors are used in determining the radon dosage. The thoron dosage is obtained from thoron working-level measurements. Radon concentrations are measured by the modified TSIVOGLON and the Rolle methods as well as track-etch detectors exposed over four months to obtain a time-averaged value. In areas exhibiting high concentrations, exposure only lasts for two months. Grab sample measurements are also done to supplement the track-etch results. The measurement of radon exhalations with the activated charcoal detectors is conducted in all areas identified as showing an enhanced exhalation of radon.

Average radiation levels are as follows:

- * External radiation: In the non-operating area the natural background external radiation measures 1 metre above ground, average to 2,2mSv per annum. In Arandis the average dose level is 1,7mSv per annum.
- Internal exposure: A major potential hazard arises from inhalation of radon and its daughters. Radon exposure is greatly influenced by ventilation that is associated with open pit mining. The maximum continuous

exposure to radon daughters in the operating areas is 0,1 working level, with an average exposure of 0,031 working level, which equates to 0,37 working level months per annum. In the non-operational areas of the mine, the maximum continuous exposure to radon daughters is 0,006 working level, with an average exposure of 0,003 working level corresponding to the 0,036 working level per annum. Measurements of radon daughter working levels taken in residential areas averaged 0,0003 working level.

Table 9 – Radiation Exposure in Working Levels in Residential Areas

Operating Areas	Dose Rate	Annual Dose
Maximum Continuous Exposure	0,1WL	1,2WLM
Average Exposure	0,031WL	0,37WLM
Non-Operating Areas	Dose Rate	Annual Dose
Maximum Continuous Exposure	0,006WL	0,072WLM
Average Exposure	0,003WL	0,036WLM

Table 10 – Radiation Exposure in Working Levels in Operational Areas

Radon Measurement Operational Areas			
	Radon Concentration – WL		
	Average	Lowest	Highest
Open Pit	0,015	0,001	0,06
Crushers	0,030	0,001	0,10
Metallurgy	0,031	0,001	0,09
Final Product Recovery	0,018	0,001	0,04
Tailings Area	0,047	0,001	0,31
Engineering	NA	NA	NA
Administration	0,006	0,0001	0,014
MPL	0,33WL	0,33WL	0,33WL

- * External and internal radiation: Potential occupational exposure to external and internal radiation is highest in the final product recovery area where a maximum annual dose recorded is 7,5mSv. The annual dose excludes the respiratory protection factor which, when applied, reduces the total dose to about 3,5mSv. The average annual dose for the Rössing workforce is 2,0mSv. (The permissible intake of radon daughters for

radiation workers is 4 working level months per annum. This corresponds to an average concentration of 0,33 working levels {WL}}

Uranium dust in the final product drying and packaging department can become airborne and may present a dual hazard: as a toxic metal and as a source of internal radiation. Protective clothing and respirators control the chemical (uranium) exposure. Urine analysis for uranium is regularly carried out.

Table 11 Annual Radiation Internal Dose of a Worker and Estimated Risk

	Internal Dose				Total Internal	Annual Collect. Dose	Risk
Location	Dust mg/m ³	mSv	Radon WLM	mSv	mSv	Sv	
Final Product	.052	4.2	.095	.95	5.15	.108	.0018
Crushers	1.2	.388	.135	1.35	1.74	.312	.005
Grinding/ Leaching/ Washing/ SIX/SX/Labs	.30	.097	.1044	1.044	1.14	.251	.004
Tailings	.50	.052	.162	1.62	1.67	.033	.001
Open Pit	.62	.20	.191	1.91	2.11	.958	0.15
Other	.05	.010	.076	.76	.77	1.158	.019

Table 12 - Annual Radiation External Dose of a Worker and Estimated Risk

External Dose Annual Risk			Total Collect Dose Sv	Individ. Risk	Total Risk	Total Individ Dose mSv
TLD MSv	Collect. Dose Sv	1.65×10^{-2} Sv				
2.48	.052	.0008	.160	1.2×10^{-4}	.0026	7.63
1.39	.250	.0041	.562	5.1×10^{-5}	.0091	3.13
1.52	.334	.0055	.585	4.4×10^{-5}	.0095	2.66
1.39	.028	.0005	.061	5.1×10^{-5}	.0010	3.06
1.41	.640	.0105	1.598	5.8×10^{-5}	.026	3.52
.45	.676	.0112	1.834	2.0×10^{-5}	.030	1.22
Average Individual Dose = 2.00			Average Individual Risk = 3.2×10^{-5}			

4.1.17 Dust Monitoring

High dust levels present a problem in most open cast mines and crushers. Ambient dust level monitoring comprises the determination of the respirable and the total dust concentration. The dust concentration results combined with the sizing, uranium content and the total alpha activity are used to assess and control health and radiological hazards from this source. Respirable dust is monitored with personal samples in the breathing zone and in the different working area. The high volume samples measure dust concentrations in air, and the directional samples and fall-out plates are used to determine the dust contribution from crushers and stockpiles. Samples of the dust collected from these monitors are sent away for radionuclid analysis which includes the determinations of gross alpha, gross beta, quantitative gamma and radium, uranium and thorium content.

There are four high volume samples in operation. These samplers are located at the Arandis Valve House, Arandis Airport, Namib Lodge and on the mine site, east of the fine crushing circuit. The latter is mainly used to monitor dust from Fine Crushing while the other three are used to determine the environmental dust.

Directional samplers and fall-out plates are located in the Open Pit, coarse ore stockpile, fine ore stockpile and the tailings dam. Samplers are placed in the four principal directions for each area. Samples are collected monthly or when necessary and results reported annually.

The background dust levels in the area around Rössing have been measured at positions off site and average 17 to 19mg/m^3 at Arandis Airport and the Arandis valve house respectively. However, during the windy months dust levels at these two stations can go up to 49mg/m^3 .

Exposure to dust containing silica and radioactive materials is a potential health hazard at Rössing. High dust levels present the most severe environmental problems in open pit mining. Precautions taken to minimise the problem include the wetting down of muck piles and haul trucks. In conditions where the standard cannot be met for the general environment, the worker is required to wear a suitable respirator.

The standard for respirable dust was set using the guidelines of the American Conference of Governmental Industrial Hygiene list (ACGHI) and the UK Health and Safety Executive (HSE). It is based on the free silica content of the ore. Frequent analysis of free silica in respirable fraction of samples is conducted; on which basis the standard is determined. The average free silica content of the material varies between 3% and 35% with an average of 18%. The respirable dust standard, based on the percentage concentration of free silica, is 0,5mg per cubic metre.

Table 13 – Average Annual Respirable Dust Levels in mg/m³ (MPL = Maximum Permissible Levels – 0.5mg/m³)

	Mean	Minimum	Maximum
Open Pit	0.42	0.01	2.62
Crushers	1.33	0.02	12.68
Plant	0.52	0.08	4.23
Final Prod Recov	0.17	0.10	0.64
Tailings	0.26	0.01	4.52
Acid Plant	1.45	0.04	1.63
Engineering	.24	0.18	1.90

4.1.18 Gases/Fumes and Acid/Alkaline Mist

The main exposure to gases, fumes and acid mist (excluding radioactive radon) has been identified in the Acid Plant (SO_2/SO_3). Leaking (H_2S , H_2SO_4 mist, caustic mist) and Boilermakers/Welders (metal fumes).

During 1987 an intensive SO_2 monitoring programme was launched. SO_2/SO_3 emissions from the Acid Plant are monitored in-plant as well as in the environment. Chemically reactive passing monitors (Huey plates) are placed in a pattern covering the predominant wind directions. Plates are placed and returned monthly to laboratories for analysis and the concentrations are correlated with the monthly meteorological wind-rose to determine direction of plume.

TWA limits of SO_2/SO_3 are exceeded when there is a leak in the gas clean steam or during a plant crash and subsequent start-up. Exposures in the Mine Maintenance Boilershop are high, usually above the TWA limits. Monitoring is conducted for SO_2/SO_3 in haul truck cabins, but to date the results have been extremely low.

The US-EPA Industrial Source Complex Short Term Model (ISCST) is used for the modeling of sulphur dioxide (SO_2) emissions from the Acid Plant. The model is run on a routine basis to supplement the monitoring programme and allows a comprehensive concentration characterisation of emissions from the mine in the environment. Additionally, the model is used to make predictions on the influence of varying mine operational parameters as well as design modifications.

4.1.19 Asbestosis Monitoring

The use of asbestos products is limited to only a few workshops and laboratories on the mine. Asbestos is mainly used for thermal insulation in welding and related jobs and also for the handling of hot glassware and utensils in laboratories.

Asbestos products include asbestos cloth, ropes, gloves, paste and plates. The individual fibres are contained in a cement matrix and the relative risk of exposure is therefore minimised.

The users of asbestos products on the mine are:

- * Haul Truck Electrical
- * Mine Maintenance Component Workshop
- * Auxiliary Mechanical Workshop
- * Mine Maintenance Heavy Equipment Workshop
- * Mine Maintenance Boiler Workshop
- * Chemical and Metallurgy Laboratories

The white colour of the asbestos products used on site is indicative of chrysolite asbestos, but this can only be confirmed positively in a laboratory.

The threshold limit values (TLV's) for the various types of asbestos differ. The following TLV's of the American Conference of Governmental Industrial Hygienists (ACGIH) are adhered to:

Table 14 – Asbestos Type and Threshold Limit Value

Asbestos type:		TLV:
Amosite	(brown asbestos)	0,5 fibres/ml of air
Chrysolite	(white asbestos)	2 fibres/ml of air
Crocidolite	(blue asbestos)	0,2 fibres/ml of air

In the event of a mixture of these fibres, the lowest TLV applies.

Other sources of asbestos include dust from brake linings at vehicle service workshops and roof sheeting. Chrysolite asbestos in brake lining changes to antigorite and brucite when heating up, due to friction, and amosite to grunerite and gummintonite. These products so formed are non-carcinogenic and there is virtually no risk to employees cleaning out wheel drums. There is also no evidence that asbestos roof sheeting poses a risk since the asbestos fibres are contained in a cement matrix.

Handling and disposal of all asbestos material on site, despite the comforting assurances by SAAPAC, are treated with utmost care to prevent as far as possible employee exposure to asbestos dust.

4.1.20 Final Product Stack Measurements

Stack measurements are carried out once a year in Final Product Recovery in order to evaluate uranium content and emission parameters. Sampling is carried out on scrubber stacks, combustion stacks, and the baghouse stack. The efficiency of the scrubbers is also evaluated by sampling both inlet and outlet of the scrubbers.

4.1.21 Environmental exposure grading

Determining the effect of an environmental agent requires accurate assessment of the dose received. Dose is characterised by **identity** (uranium containing dust, siliceous dust, radon gas, and criteria

pollutants), **form** (respirable dust, gas) **concentration** (mg/m³/WL) and **time** (years of exposure). It is extremely difficult to determine the dose received (exposure metric). It is complicated by limitations of availability of data, variability in exposure, concentrations as well as a lack of information on time spent in various areas.

The most appropriate system for organising and understanding information for exposure assessment is an exposure data matrix (EDM). The first step is to define the dimensions and scales which, in turn, depends on the availability of data and the importance of each factor in representing exposure. The next step is to define the scale of each of the EDM dimensions, which assists with the degree to which the available information should be grouped.

For the purpose of this study, a two-dimensional EDM was defined by time and exposure type. Each dimension was scaled with time (single years) and area (according to up to 3 levels) of exposure. Several potential matrix cells were formed and arithmetic means (SEM's) were calculated.

Group, and often, individual personal data was available, but since workers move from one environment to another it is extremely difficult to determine their individual exposure levels accurately. It was therefore decided to appoint an "assessment committee" to allocate exposure categories. The committee consisted of environmental control and medical personnel who had detailed knowledge of the working environment, the workers and the type of work done. They assigned exposures categories of high, medium or low. Consensus opinion was required.

4.1.22 Collection Procedures

Data was collected from employees by trained and qualified staff. This took place at the medical centre. Qualified medical practitioners conducted medical examinations. Subjects were intermingled from the different areas to overcome observational bias.

4.1.23 Data Analysis

Data capture and statistical analyses were conducted by Professors D and T Kotze as well as by Dr P Becker of the Medical Research Council, Pretoria. The statistical analysis was done according to the most appropriate statistical techniques.^{318,319} The graphic method of 'box-and-whisker' plots is used to display the essential distributional information of a measurement taken on the members of a sample. The maximum and the minimum are found at the top and at the bottom of the plot; these are shown by an asterisk whenever they are more than a certain distance from the median of the sample distribution. These unusual observations (indicated by an asterisk) are called "outliers" because of their remoteness from the mean and the median, as measured in terms of the spread of the sample distribution. The computer package used - SAS (1985 and updates) - uses well-accepted norms for the identification of univariate outliers or unusual values. For the final data analysis the Stata Software Release 6 (Stata Press, College Station, Texas) was employed and all statistical testing was done at the 0.05 level of significance. Discussions of and references for all the methods employed can be found in the Stata manuals.

The "box" comprises the bottom line that represents the lower quartile (25th percentile), the middle line representing the median (50th percentile) and the top line representing the upper quartile (75th percentile). The mean is indicated by a "+" sign, which is usually inside the box. If the

mean and the median are about the same the distribution is symmetrical. The spread of the distribution can be measured by the distance between the upper and lower quartiles, and this distance is called the inter-quartile distance. The student t-test was used to determine significant statistical differences in the population study and because the value of the standard deviation of the population was unknown. The p-values given are two-tailed.

In the 1999 study 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.

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 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.

Occupational studies are subject to bias from the healthy-worker survivor effect (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”.

4.1.24 Ethical issues

The MRC's ethical guidelines were observed and adhered to. Medical examinations are compulsory and a condition of employment. Routine medical information was collected. If significant clinical abnormalities were detected, the person was advised to seek medical assistance and relevant data was made available to the nominated medical practitioner. Apart from this exception, individual identifiable data was only available to company health personnel and occupational physicians.

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 (standardised 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

FEV₁/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:

FEV₁

FEF₅₀ Forced Expired Flow at 50% of lung capacity

FEF₇₅ 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, FEV₁, FEV₁/FVC, FEF₅₀, FEF₇₅, 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 FEV₁ 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 FEV₁ 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 abnormal (FEF ₅₀ and FEF ₇₅)	288	20%
Total no of abnormal (FEF ₅₀ , FEF ₇₅ and FEV ₁)	140	9%
Total no of abnormal (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 abnormal 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
FEV₁	Mean	95	110	101
	S.D.	11	13	11
	VX	12	12	11
	99% Conf	91	105	97
FEV₁/FVC	Mean	101	98	100
	S.D.	6	11	6
	VX	6	11	6
	99% Conf	99	94	97
FEF₅₀	Mean	92	104	100
	S.D.	22	29	24
	VX	25	28	24
	99% Conf	84	92	94
FEF₇₅	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. Alpha-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 glutamic acid for lysine at position 342. Point mutations in the S protein leads to amino acid substitution glutamic 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 cathepsin G. Elastase has proteolytic activities and also changes the elastin - 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 phagocytes 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 Thio ester group in the Metionine 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 elastin in the alveoli is destroyed through 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 centrilobular type. Panlobular (acinar) 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 uranyl 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 Cofield³²¹ 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 caesium 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 caesium). 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 (TI) 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 ($\pm 50\text{mg U}$) 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:

$$\begin{array}{llll} 90 \text{ keV} & y & = & 2,413x + 3,58,19 - 1 \\ & r & = & 0,852 \end{array}$$

$$\begin{array}{llll} 186 \text{ keV} & y & = & 1,17x + 334,9 - 2 \\ & r & = & 0,83 \end{array}$$

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:

$$\begin{array}{rclclcl} y & = & 2,49 & + & 437,5 & - & 3 \\ r & = & 0,847 & & & & \end{array}$$

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 Saccomanno³³² *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 FEV₁ (**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 FEF₂₅ 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 FEF₅₀ and FEF₇₅ values (**Figs 8 and 9**). The median of the FEF₇₅ 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 FEV₁/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 R^2 (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 R^2 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.

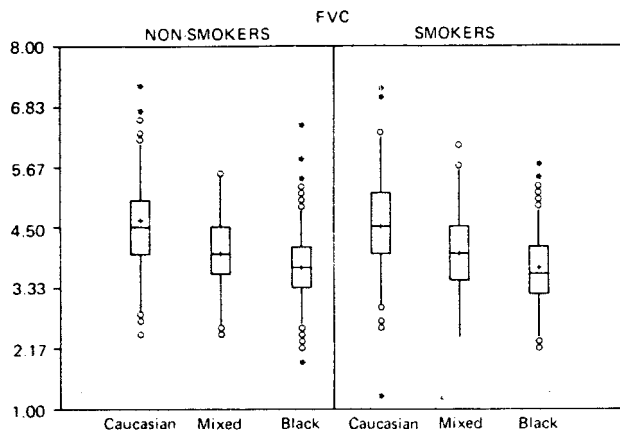


Fig. 3. Box diagram of the observations of FVC separated according to ethnic group and smoking habit.

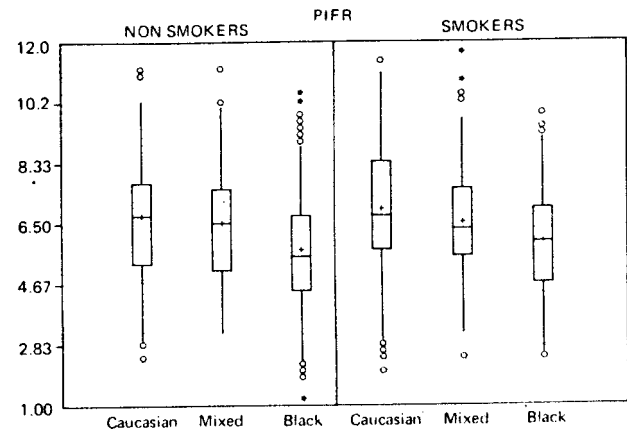


Fig. 6. Box diagram of the observations of PIFR separated according to ethnic group and smoking habit.

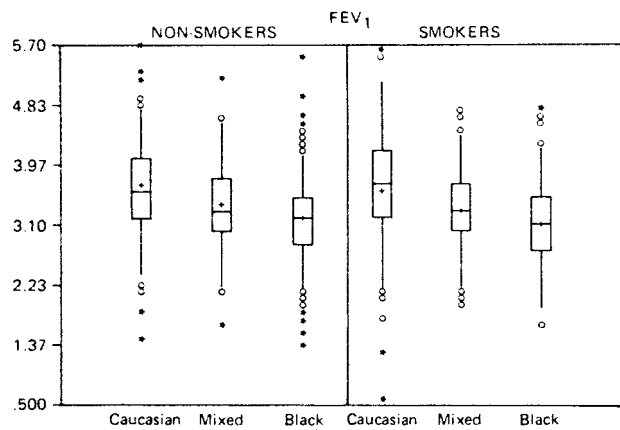


Fig. 4. Box diagram of the observations of FEV₁ separated according to ethnic group and smoking habit.

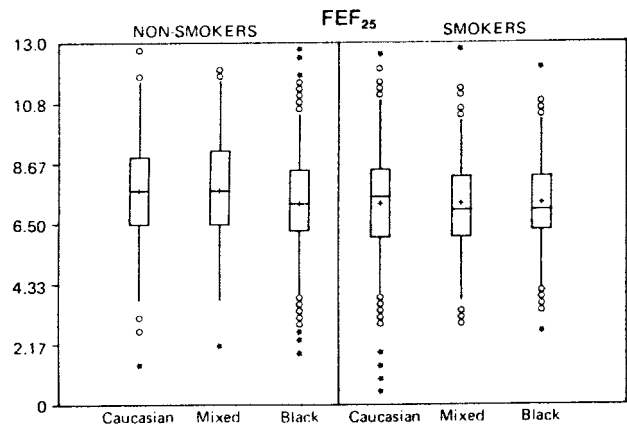


Fig. 7. Box diagram of the observations of FEF₂₅ separated according to ethnic group and smoking habit.

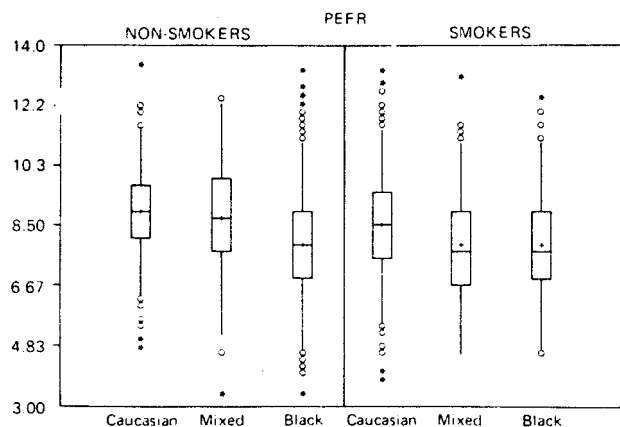


Fig. 5. Box diagram of the observations of PEFR separated according to ethnic group and smoking habit.

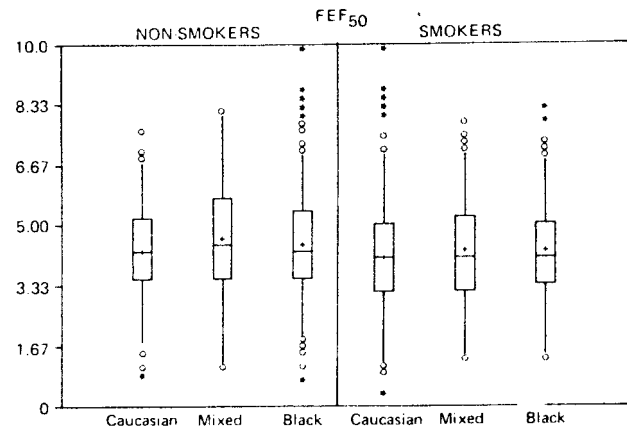


Fig. 8. Box diagram of the observations of FEF₅₀ separated according to ethnic group and smoking habit.



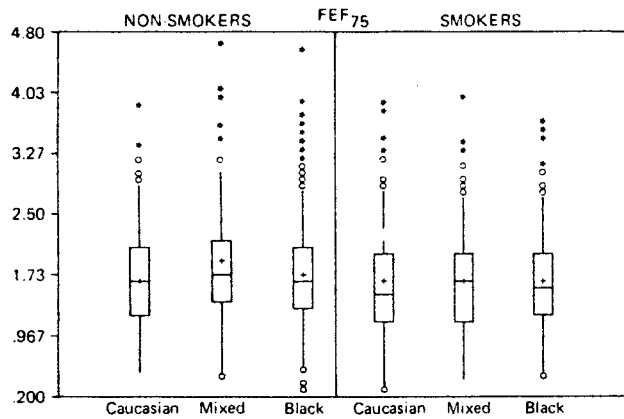


Fig. 9. Box diagram of the observations of FEF_{75} separated according to ethnic group and smoking habit.

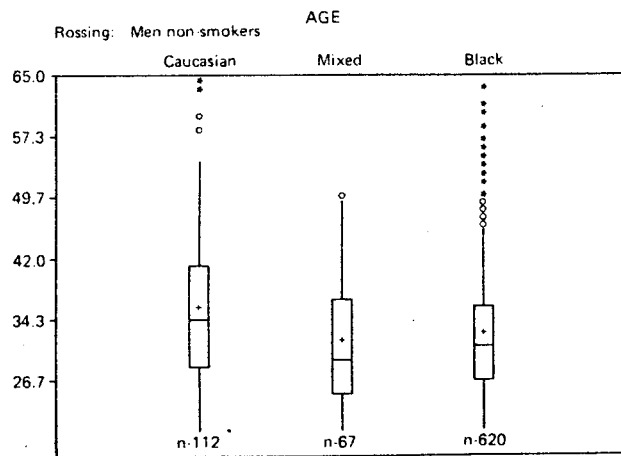


Fig. 11. Box diagram of age for non-smoking males divided into the three ethnic groups.

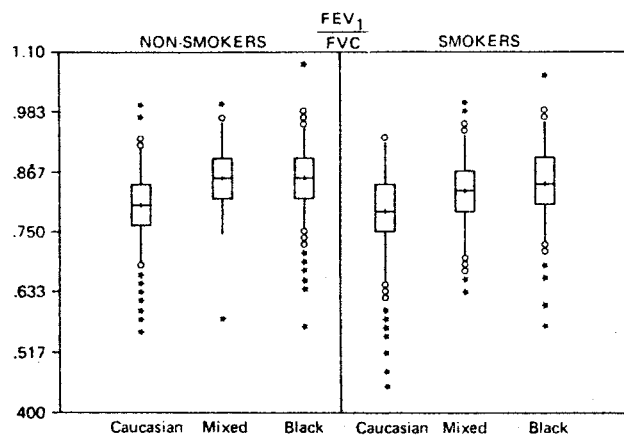


Fig. 10. Box diagram of the observations of FEV_1/FVC ratios separated according to ethnic group and smoking habit. The Caucasian ratios are significantly lower than the ratios of the non-Caucasians ($P < 0.001$).

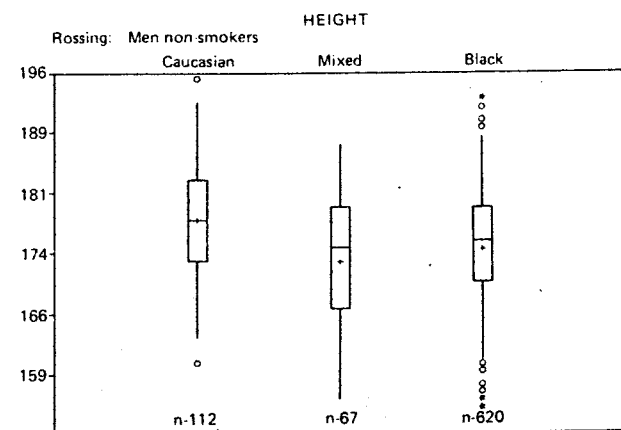


Fig. 12. Box diagram of height for non-smoking males divided into the three ethnic groups.

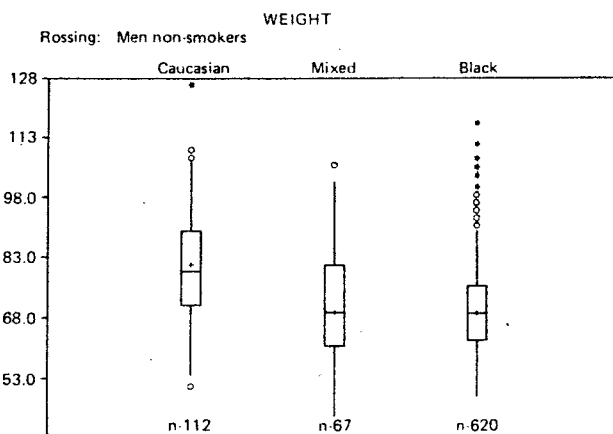


Fig. 13. Box diagram of mass for non-smoking males divided into the three ethnic groups.

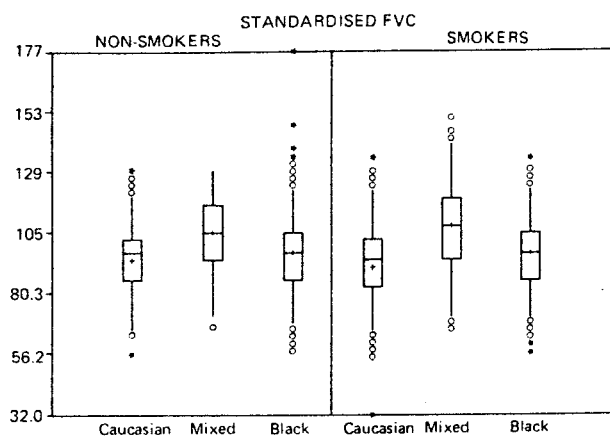


Fig. 14. Box diagram of the observations of standardised FVC according to Schoenberg *et al.*, separated according to ethnic group and smoking habit.



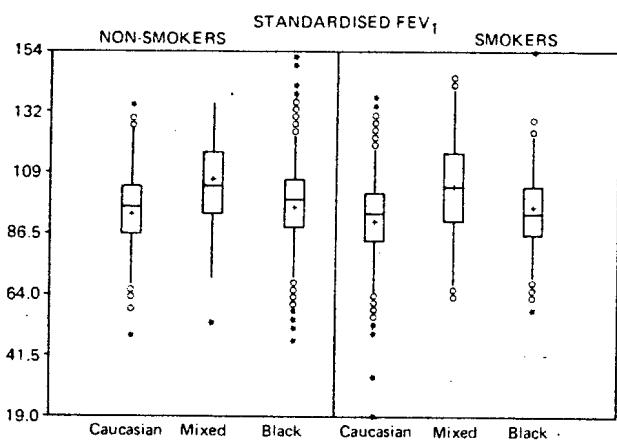


Fig. 15. Box diagram of the observations of standardised FEV₁ according to Schoenberg *et al.*, separated according to ethnic group and smoking habit.

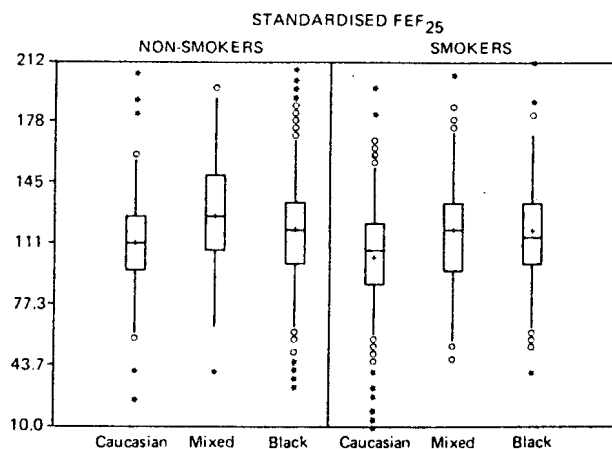


Fig. 18. Box diagram of the observations of standardised FEF₂₅ according to Schoenberg *et al.*, separated according to ethnic group and smoking habit.

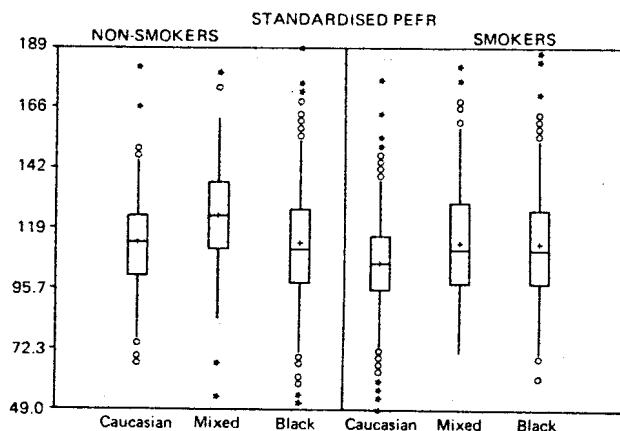


Fig. 16. Box diagram of the observations of standardised PEFR according to Schoenberg *et al.*, separated according to ethnic group and smoking habit.

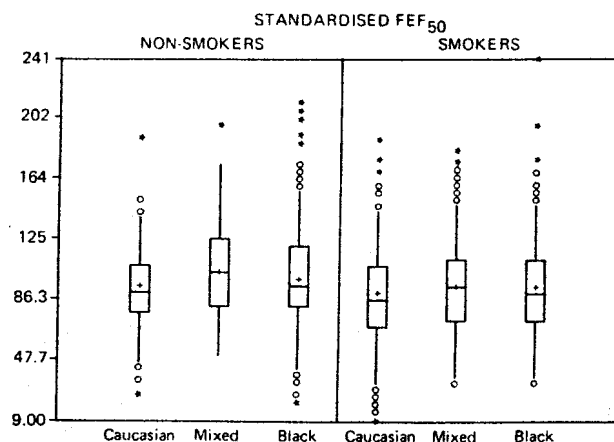


Fig. 19. Box diagram of the observations of standardised FEF₅₀ according to Schoenberg *et al.*, separated according to ethnic group and smoking habit.

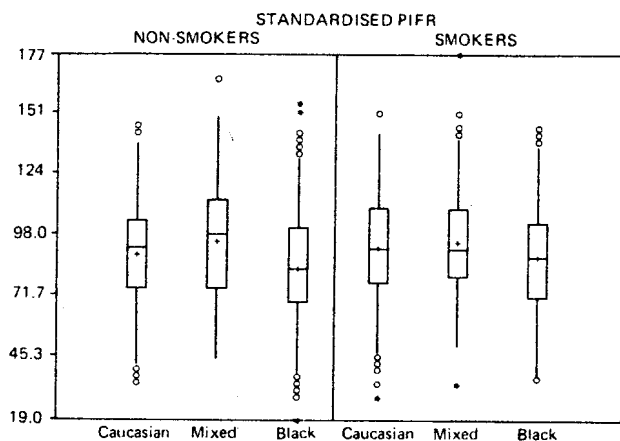


Fig. 17. Box diagram of the observations of standardised PIFR according to Schoenberg *et al.*, separated according to ethnic group and smoking habit.

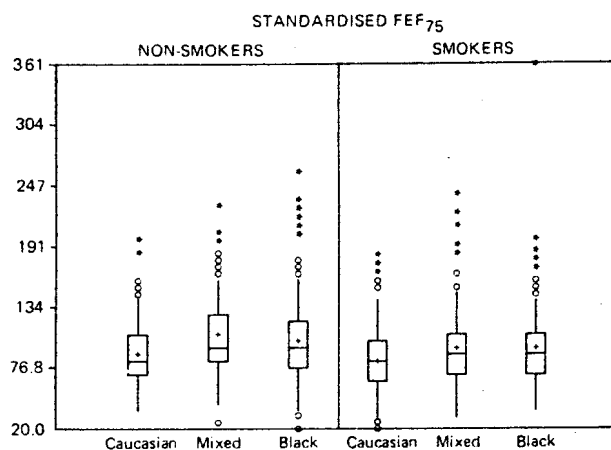


Fig. 20. Box diagram of the observations of standardised FEF₇₅ according to Schoenberg *et al.*, separated according to ethnic group and smoking habit.



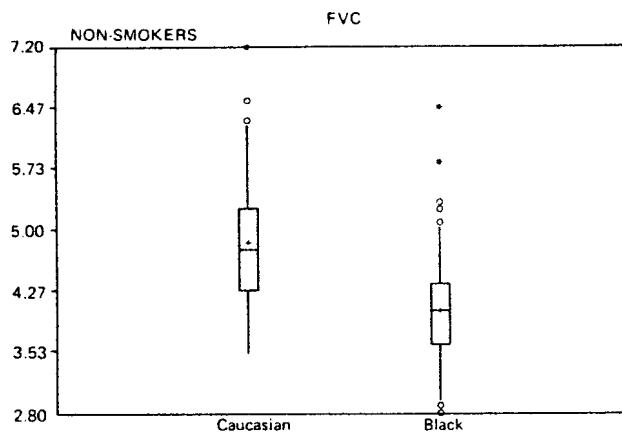


Fig. 21. Box diagram comparing the FVC between comparable groups of Caucasians (62) and blacks (125). FVC in Caucasians is significantly higher than FVC in blacks ($P < 0.0001$).

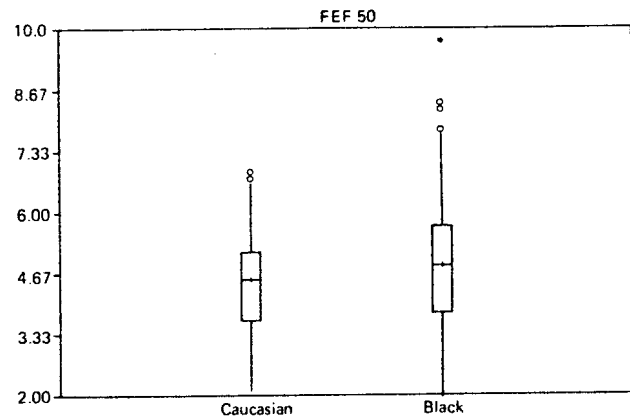


Fig. 24. Box diagram comparing FEF₅₀ between comparable groups of Caucasians (62) and blacks (125). The difference is not statistically significant ($P > 0.05$).

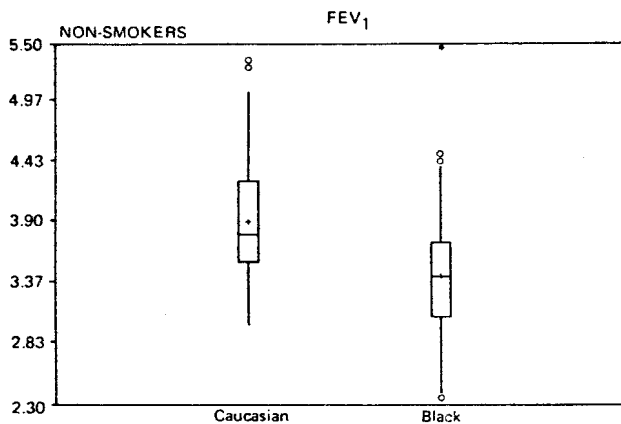


Fig. 22. Box diagram comparing the FEV₁ between comparable groups of Caucasians (62) and blacks (125). FEV₁ in Caucasians is significantly higher than FEV₁ in blacks ($P < 0.0001$).

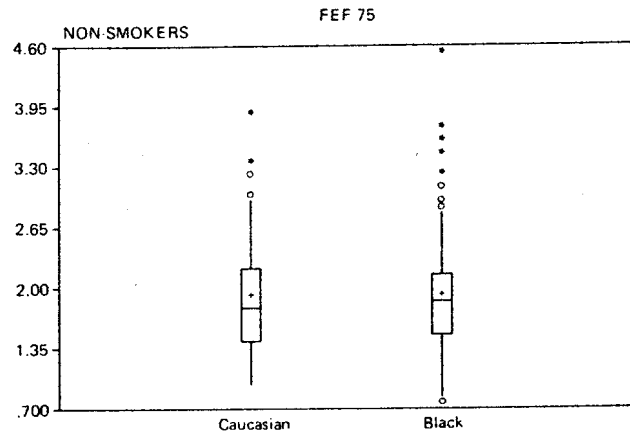


Fig. 25. Box diagram comparing FEF₇₅ between comparable groups of Caucasians (62) and blacks (125). The difference is not statistically significant ($P > 0.05$).

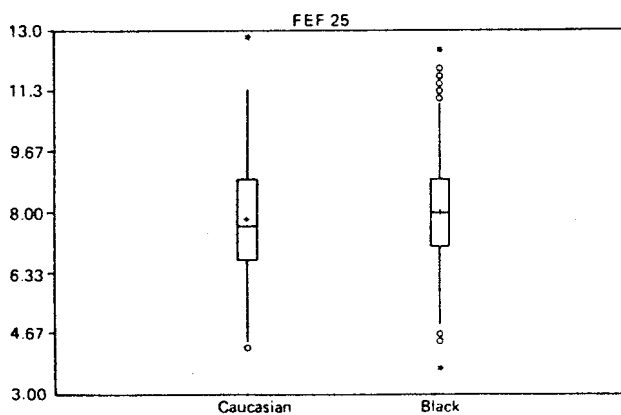


Fig. 23. Box diagram comparing the FEF₂₅ between comparable groups of Caucasians (62) and blacks (125). The difference is not statistically significant ($P > 0.05$).

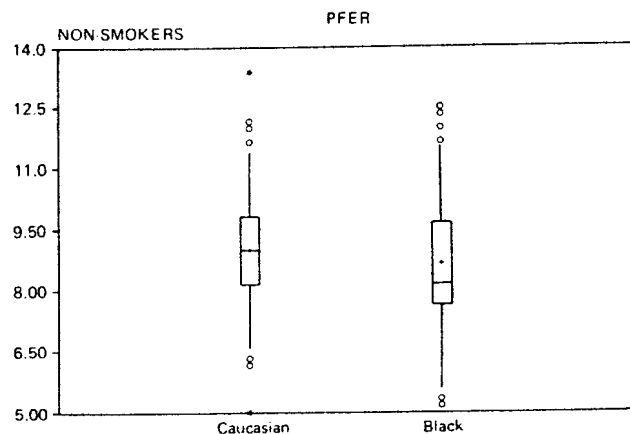


Fig. 26. Box diagram comparing PFER between comparable groups of Caucasians (62) and blacks (125). The difference is not statistically significant ($P > 0.05$).



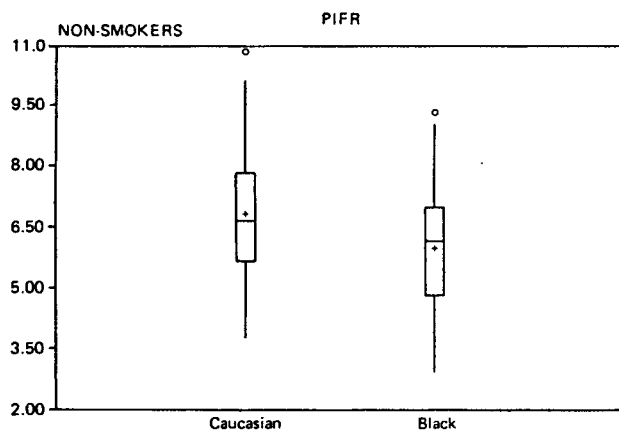


Fig. 27. Box diagram comparing PIFR between comparable groups of Caucasians (62) and blacks (125). PIFR in Caucasians is significantly higher than PIFR in blacks ($P < 0.0002$).

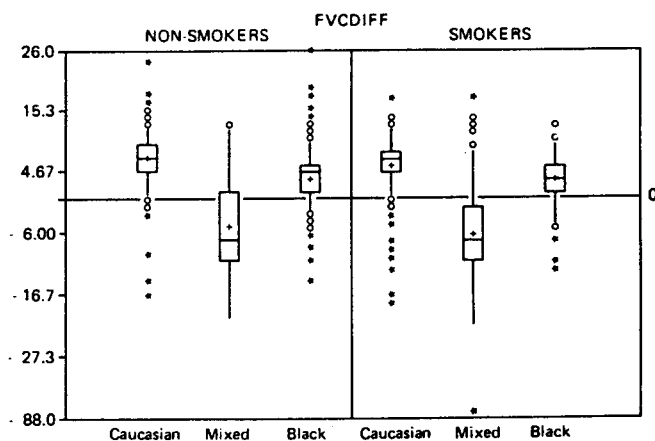


Fig. 28. Box diagram of the difference in the percentage of predicted of the FVC according to the formula described and the formula of Schoenberg *et al.*, separated according to ethnic group and smoking habit.

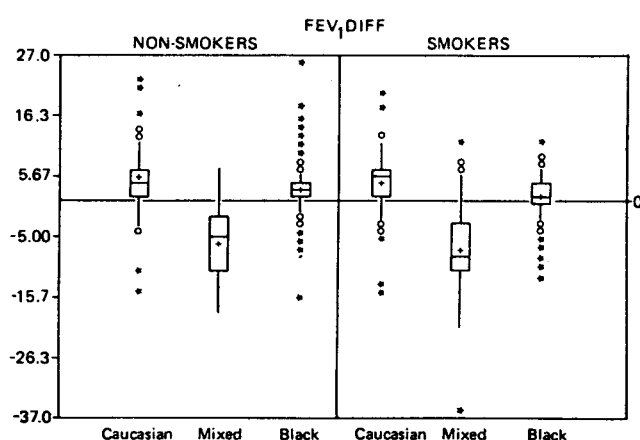


Fig. 29. Box diagram of the difference in the percentage of predicted of the FEV₁ according to the formula described and the formula of Schoenberg *et al.*, separated according to ethnic group and smoking habit.

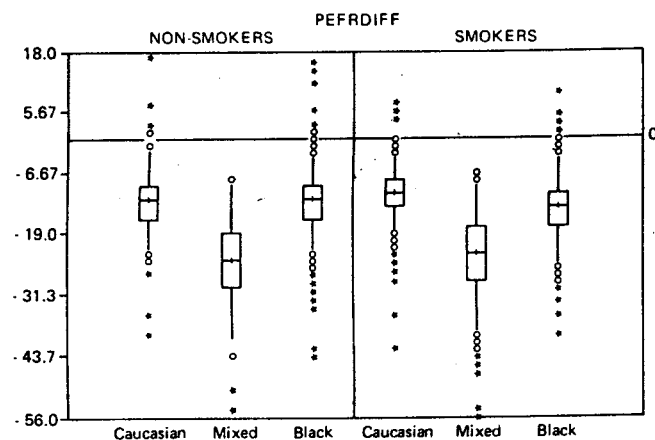


Fig. 30. Box diagram of the difference in the percentage of predicted of the PEFR according to the formula described and the formula of Schoenberg *et al.*, separated according to ethnic group and smoking habit.

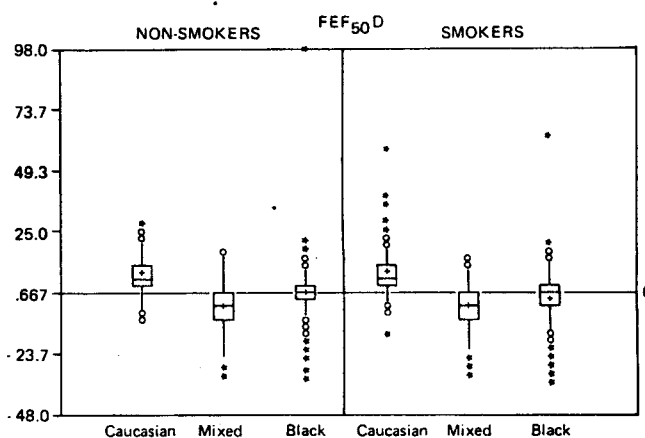


Fig. 32. Box diagram of the difference in the percentage of predicted of the FEF_{50D} according to the formula described and the formula of Schoenberg *et al.*, separated according to ethnic group and smoking habit.

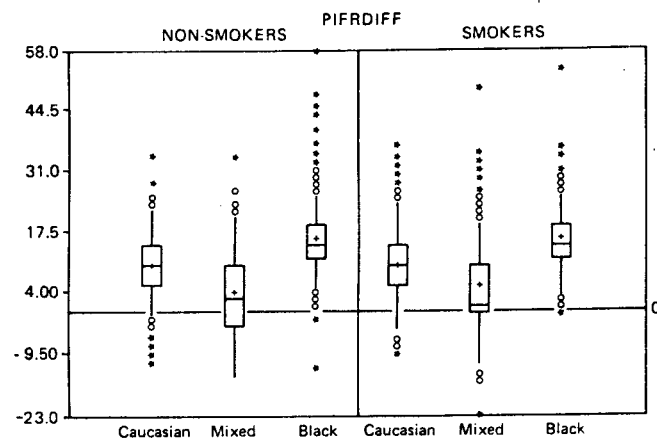


Fig. 31. Box diagram of the difference in the percentage of predicted of the PIFR according to the formula described and the formula of Schoenberg *et al.*, separated according to ethnic group and smoking habit.



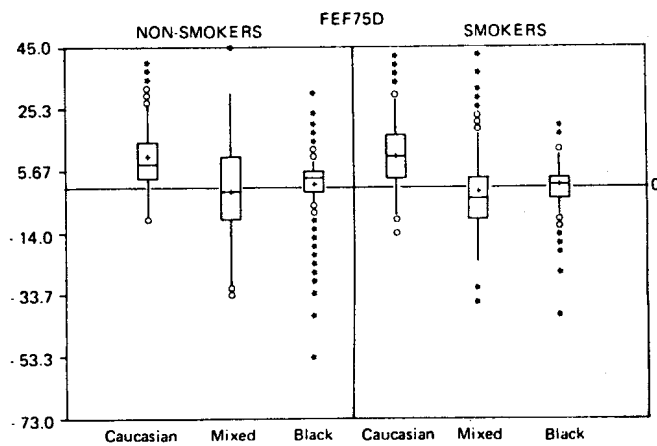


Fig. 33. Box diagram of the difference in the percentage of predicted of the FEF₇₅ according to the formula described and the formula of Schoenberg *et al.*, separated according to ethnic group and smoking habit.

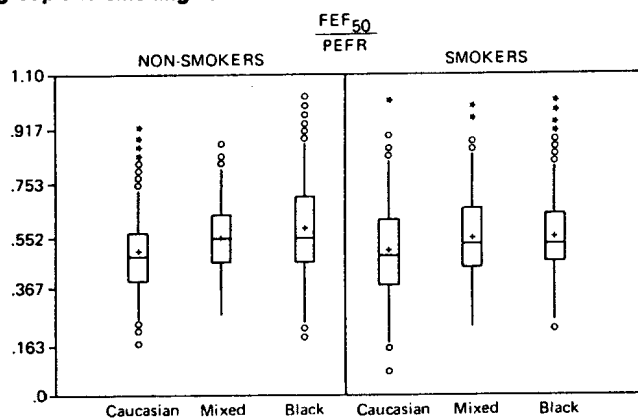


Fig. 35. Box diagram of the observations of FEF₅₀/PEFR ratio separated according to ethnic group and smoking habit. The ratio in blacks is significantly higher than that in Caucasians ($P < 0,001$).

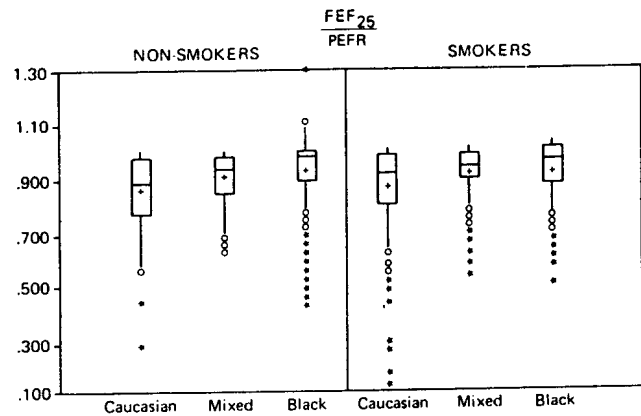


Fig. 34. Box diagram of the observations of FEF₂₅/PEFR ratio separated according to ethnic group and smoking habit. The ratio in blacks is significantly higher than that in Caucasians ($P < 0,001$).

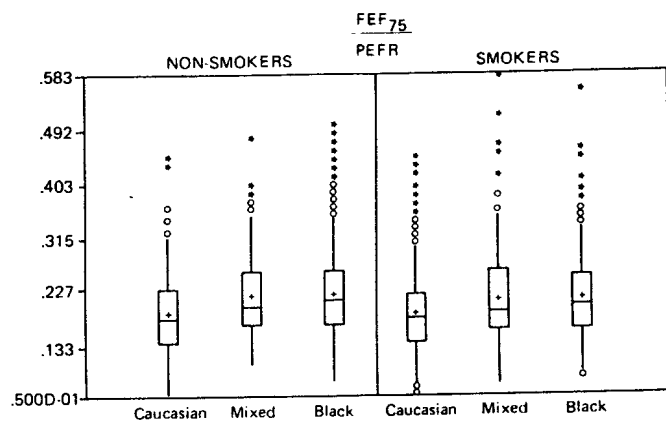


Fig. 36. Box diagram of the observations of FEF₇₅/PEFR ratio separated according to ethnic group and smoking habit. The ratio in blacks is significantly higher than that in Caucasians ($P < 0,001$).



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 (R^2) 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 PEF_R and PIF_R (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 FEF₅₀ 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 FEF₇₅ 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 R^2 (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 R^2 of 0,51 in the complete group of R^2 of 0,64 in the younger group and an R^2 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 R^2 .

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 FEV₁ 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 ($R^2 = 0,61$) was far better than the predictability in the older group ($R^2 = 0,17$). 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 FEV₁ 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 FEV₁ OF NON-SMOKERS IN THREE ETHNIC GROUPS BY MEANS OF HEIGHT, MASS AND AGE						
	INTERCEPT	HEIGHT	MASS	AGE	R ²	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 FEF₅₀ of non-smokers

For the non-smoking black males, predictability of FEF₅₀ 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 FEF₅₀ but the correlation was poor.

TABLE 39						
COEFFICIENTS FROM A STEPWISE REGRESSION TO PREDICT THE FEF₅₀ 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 FEF₇₅ 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 FEF₇₅ 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 FEF₇₅ 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 ($R^2 = 0.31$), 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, FEV₁ 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 FEF₂₅, FEF₅₀ 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

$(O/P \times 100 - O/S \times 100) > 0$;

$O \times 100 (1/P - 1/S) > 0$;

$1/P - 1/S > 0$;

$(1/P > 1/S) \times (P \times S)$:

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 PEF_R 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 FEF₅₀ (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 FEF₇₅ (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, FEV₁, PEFR, FEF₅₀ and FEF₇₅ 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 FEF₅₀ 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 <i>ET AL.</i>								
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			Total
	Black	Caucasian	Mixed Race	
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			Total
	Black	Caucasian	Mixed Race	
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			Total
	Black	Caucasian	Mixed Race	
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

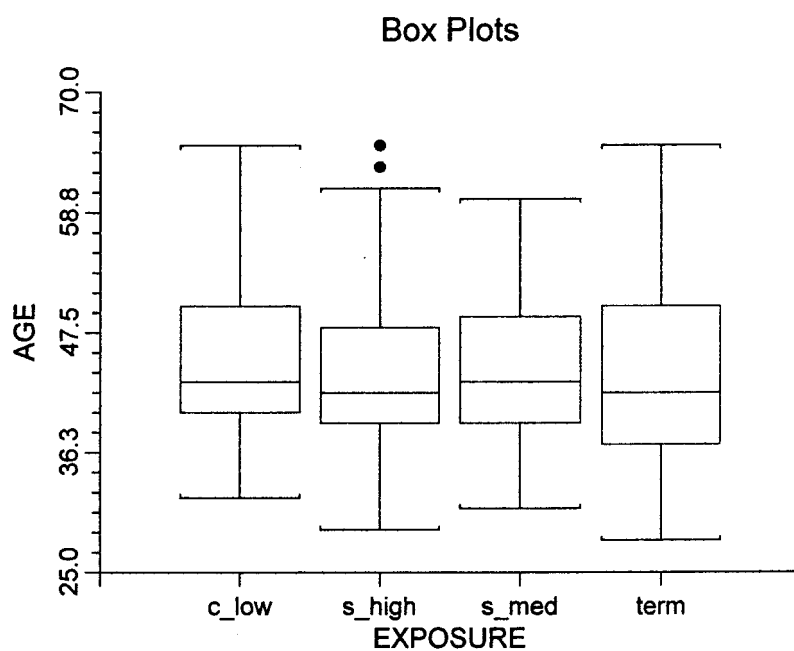
The average age of this group (compared with the results of the previous cross-sectional study) is considerably higher (average age was 32 and is now 42.4). The Caucasians were the tallest and weighed the most with an average height of 178cm and an average weight of 85kg; the average height of the black 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					
	Exposure High – n=398			Exposure Medium – n=174		
	Black	Caucasian	Mixed	Black	Caucasian	Mixed
Study Group n=572						
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

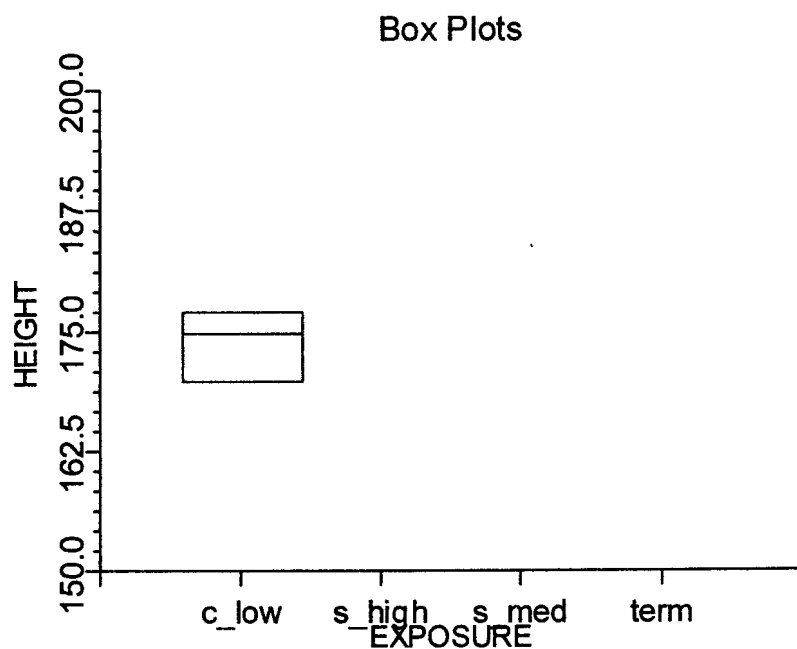
Table 50 Summary of Demographic Data per Exposure Group = Low			
Control Group	Ethnicity		
N=261	Black	Caucasian	Mixed Race
Count of Ethnic	157	69	35
Average Years of Service	16.27	15.93	16.4
Mean Age	44.13	48.55	41.37
Mean Height	172.83	178.00	171.34
Mean Weight	76.90	86.57	79.63

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

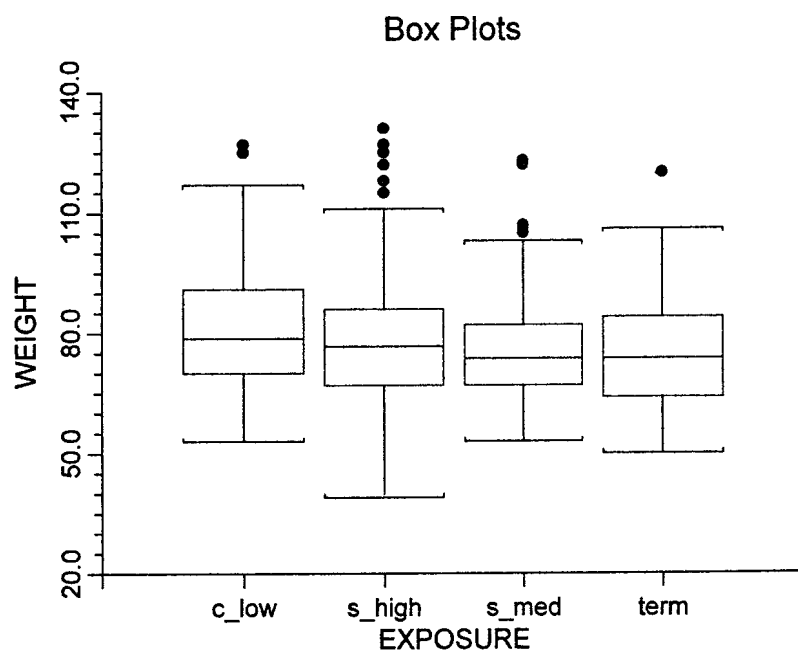
Box plots for age, height and weight for ethnic groups in the various exposure groups were created.

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 Pneumoconiosis³¹⁷ 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, FEV₁, FEF₅₀, FEF₇₅, PEF_R, PIF_R) 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:

$$\text{PREDICTED FVC} = \text{ABSOLUTE FVC} / \text{ADJUSTED FVC}$$

The following predicted results are used:

FVC%
 FEV₁%
 FEV₁/FVC%
 FEF₅₀%
 FEF₇₅%
 PEF_R%
 PIF_R%

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.

FEV₁

The largest **median** value for FEV₁ (adjusted and as a percentage) was in the terminated group. The largest **mean** FEV₁ value was in the control group and the lowest mean and median in the study group with high exposure. The lowest values for FEV₁ adjusted and FEV₁ was found in the study group with median exposure.

FEV₁/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.

FEF₅₀

The lowest **median** value for FEF₅₀ was in the terminated group and the lowest **mean** FEF₅₀ 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.

FEF₇₅

The lowest **mean** and **median** value for FEF₇₅ was in the study group with high exposure. The adjusted FEF₇₅'s lowest values were found in the control group. The **mean** value of FEF₇₅% 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

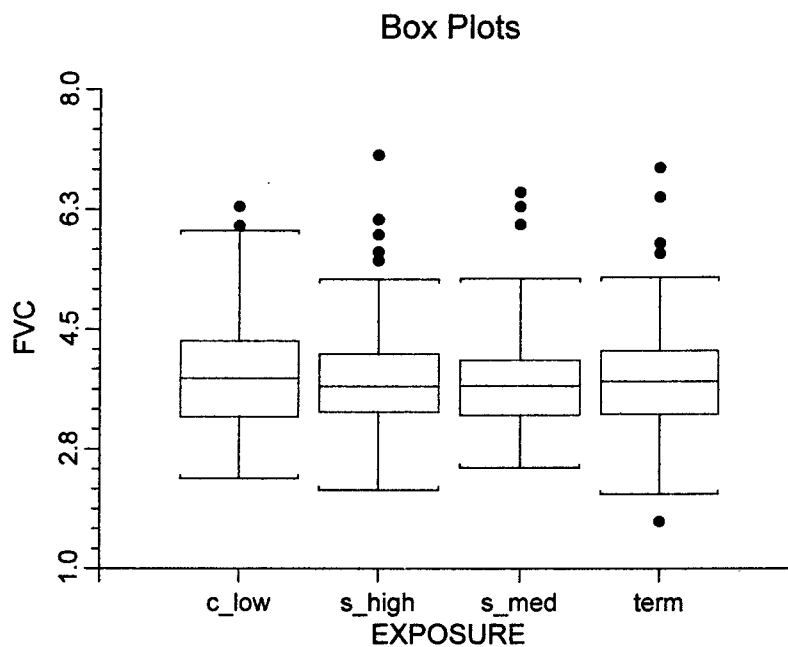
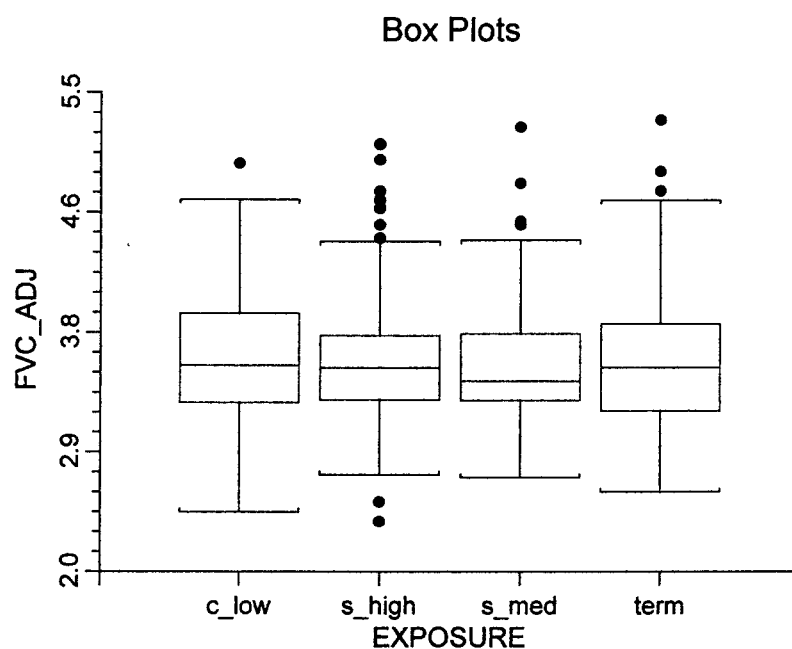


TABLE 58 Descriptive statistics of FVC for EXPOSURE groups

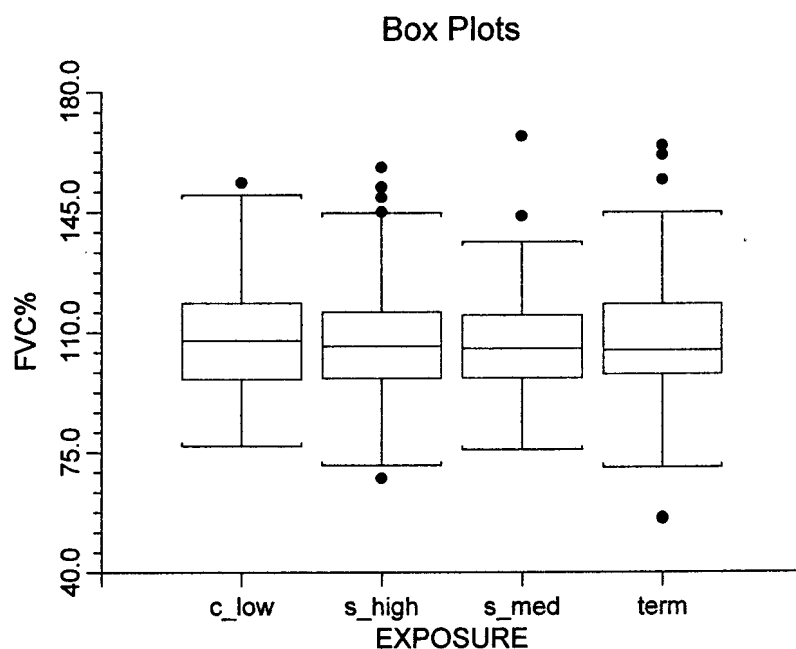
Exposure groups	S_High	C_Low	S_Medium	Terminated
N	302	198	132	133
Mean	3.75	3.86	3.72	3.79
Median	3.69	3.80	3.70	3.76
Std. Dev.	0.69	0.80	0.71	0.82
Range	4.89	3.79	4.02	5.17



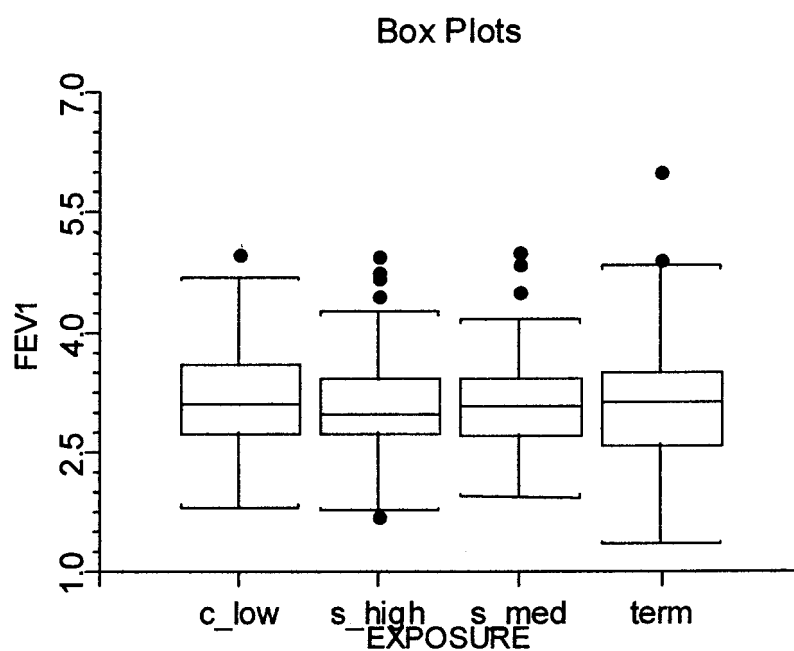
FIGURE 41 Box Plots of FVC_ADJUSTED for Exposure Groups**TABLE 59 Descriptive statistics of FVC_ADJUSTED for EXPOSURE groups**

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

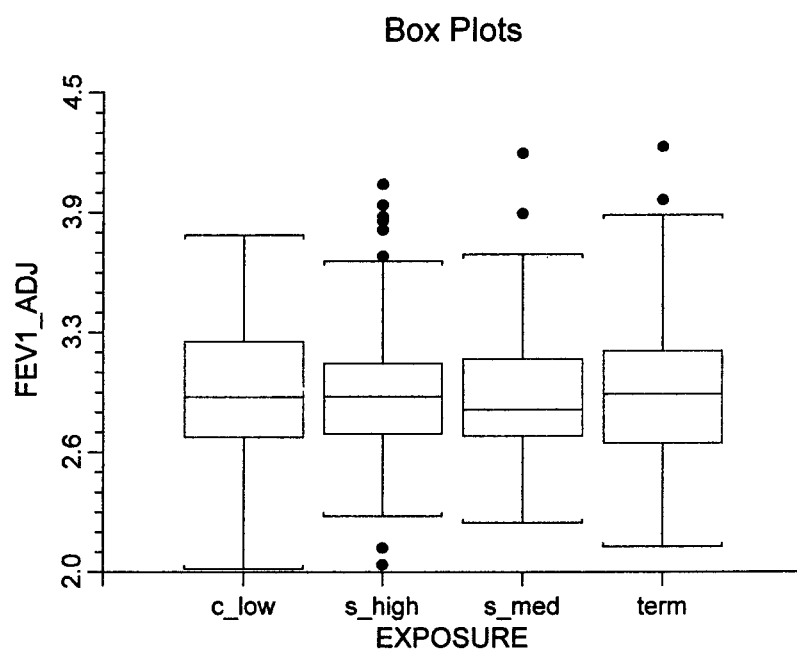


FIGURE 42 Box Plots of FVC% for Exposure Groups**TABLE 60 Descriptive statistics of FVC% for EXPOSURE groups**

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

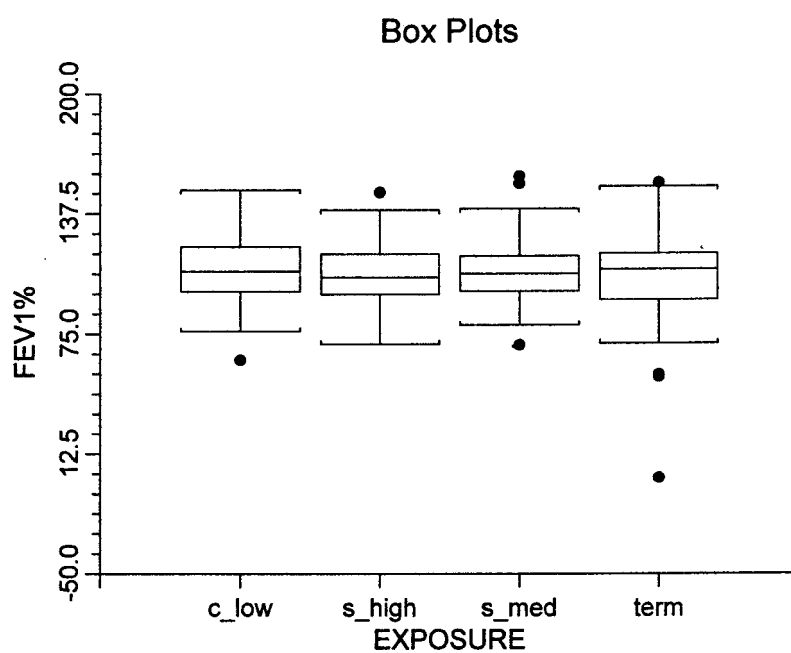
FIGURE 43 Box Plots of FEV₁ for Exposure Groups**TABLE 61 Descriptive statistics of FEV₁ for EXPOSURE groups**

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 FEV₁ ADJUSTED for Exposure Groups**TABLE 62** Descriptive statistics of FEV₁ ADJUSTED for EXPOSURE groups

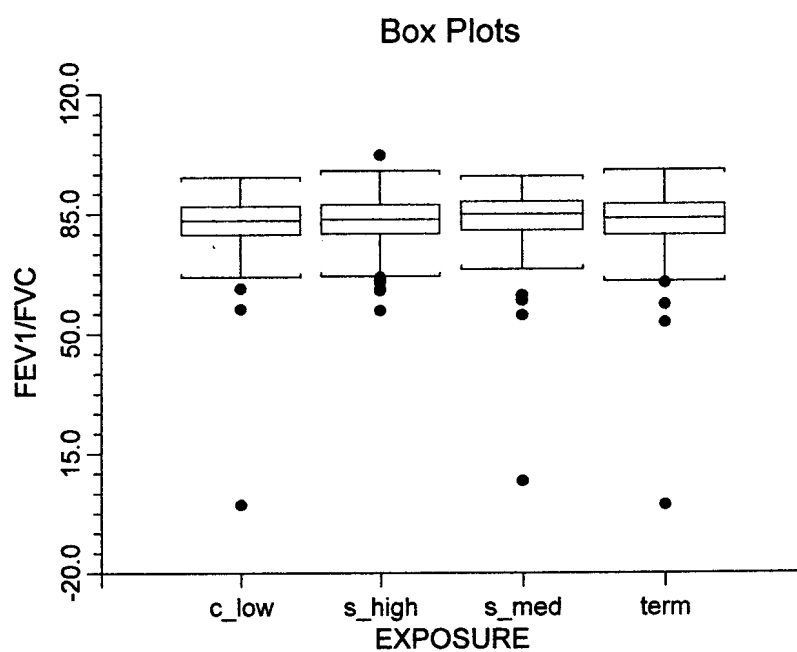
Exposure groups	S High	C Low	S Medium	Terminated
N	302	198	133	133
Mean	2.92	2.93	2.91	2.93
Median	2.92	2.92	2.86	2.94
std. dev.	0.30	0.34	0.32	0.37
Range	1.98	1.74	1.93	2.09



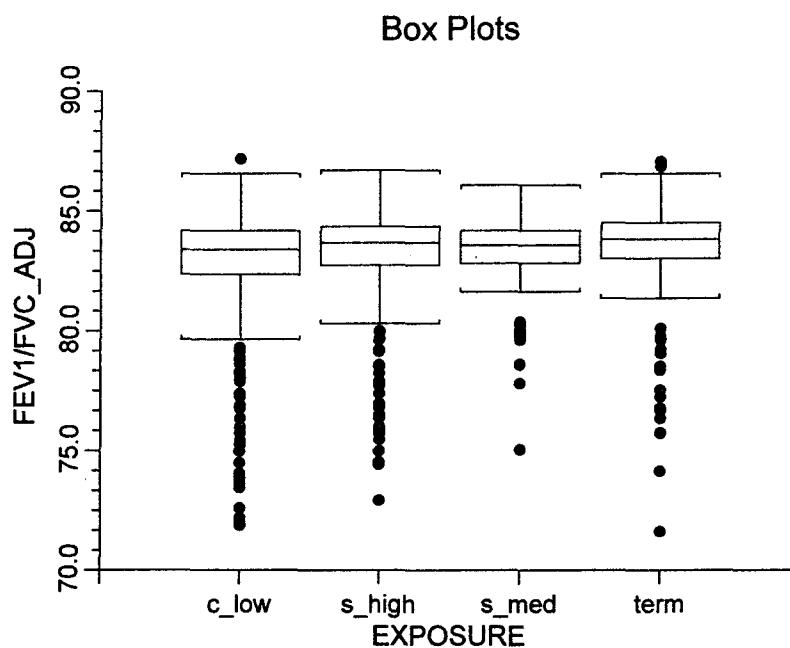
FIGURE 45 Box Plots of FEV₁% for Exposure Groups**TABLE 63** Descriptive statistics of FEV₁% for EXPOSURE groups

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

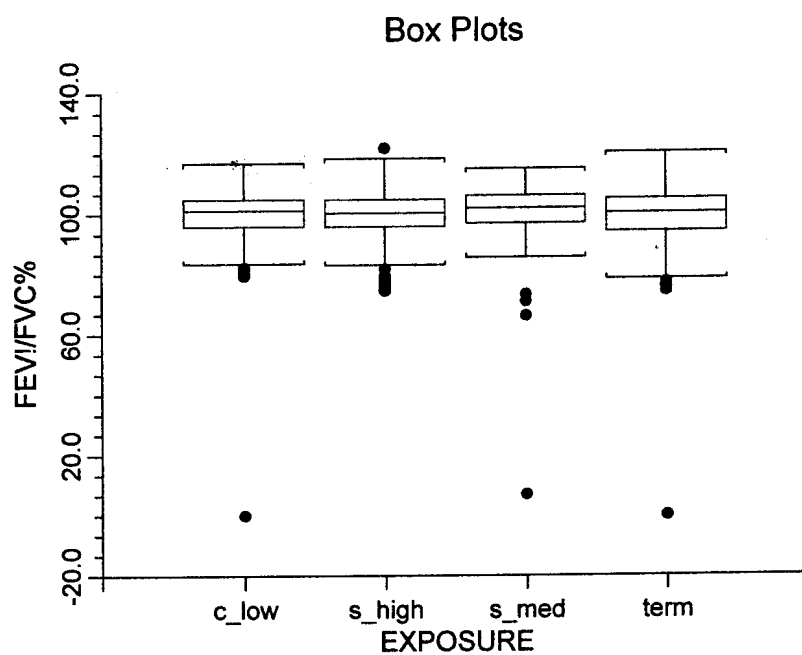


FIGURE 46 Box Plots of FEV₁/FVC for Exposure Groups**TABLE 64 Descriptive statistics of FEV₁/FVC for EXPOSURE groups**

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

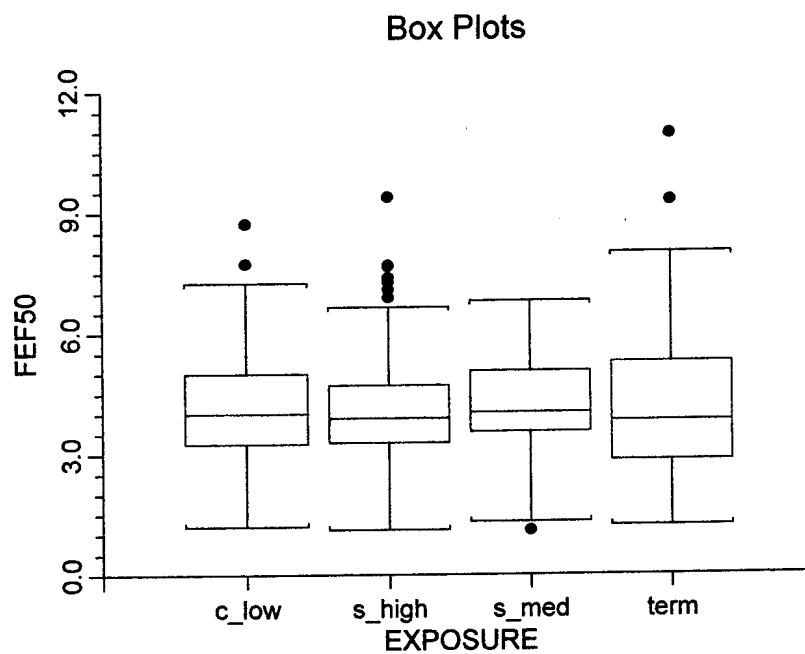
FIGURE 47 Box Plots of FEV₁/FVC ADJUSTED for Exposure Groups**TABLE 65** Descriptive statistics of FEV₁/FVC_ADJUSTED for EXPOSURE groups

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

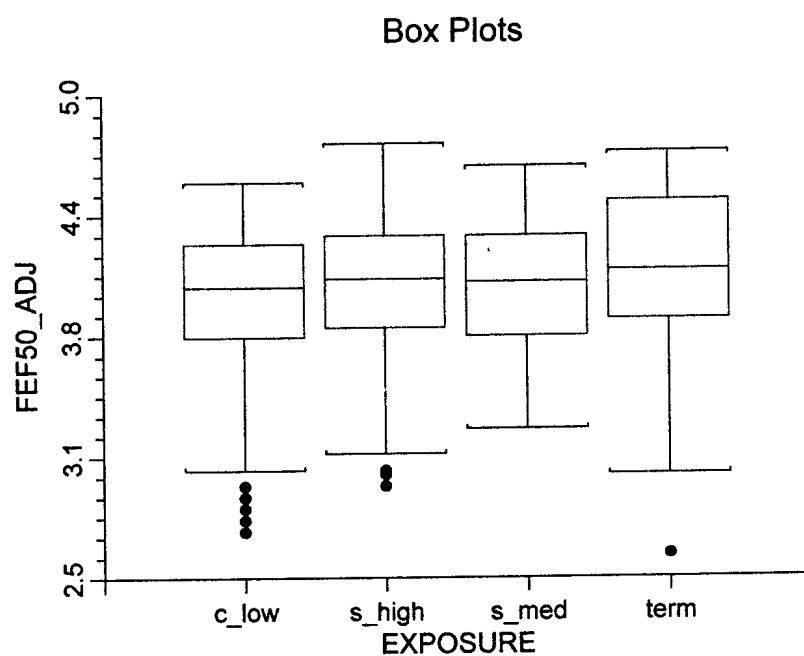
FIGURE 48 Box Plots of FEV₁/FVC% for Exposure Groups**TABLE 66 Descriptive statistics of FEV₁/FVC% for EXPOSURE groups**

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

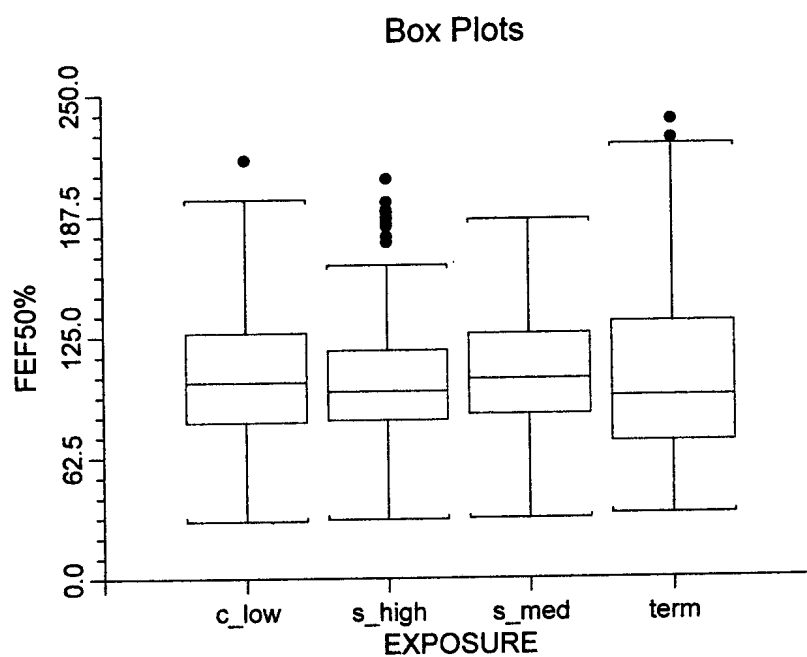


FIGURE 49 Box Plots of FEF₅₀ for Exposure Groups**TABLE 67 Descriptive statistics of FEF₅₀ for EXPOSURE groups**

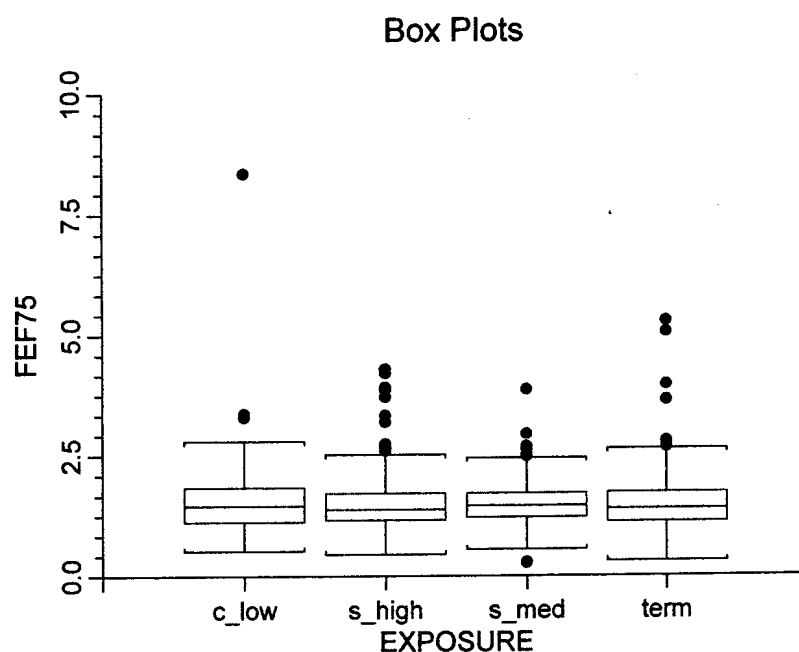
Exposure groups	S_High	C_Low	S_Medium	Terminated
N	302	198	132	133
Mean	4.05	4.07	4.19	4.19
Median	3.93	4.04	4.08	3.86
Std. Dev.	1.23	1.31	1.13	1.77
Range	8.26	7.53	5.69	9.71

FIGURE 50 Box Plots of FEF₅₀ ADJUSTED for Exposure Groups**TABLE 68** Descriptive statistics of FEF₅₀ ADJUSTED for EXPOSURE groups

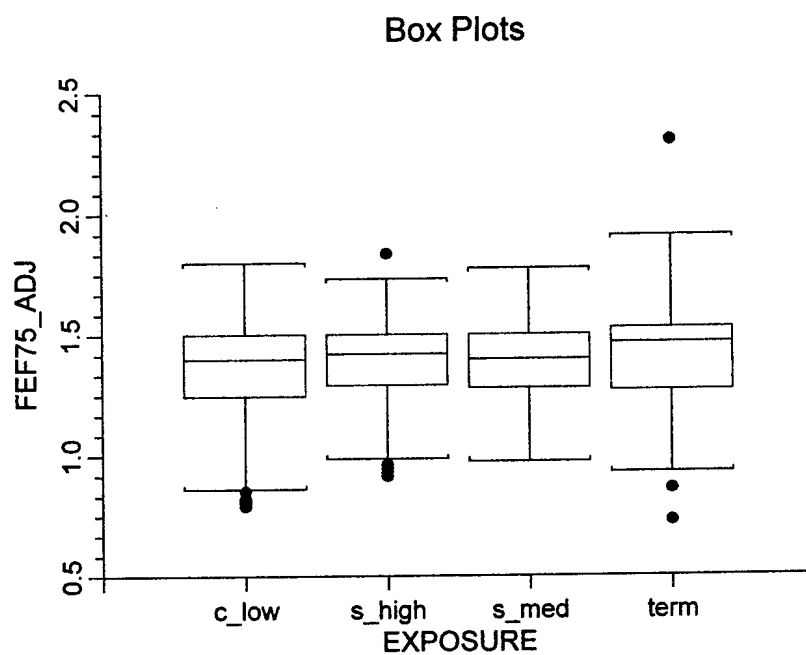
Exposure groups	S_High	C_Low	S_Medium	Terminated
N	302	198	133	133
Mean	4.02	3.94	4.00	4.07
Median	4.05	4.01	4.04	4.10
Std. Dev.	0.36	0.44	0.36	0.43
Range	1.77	1.81	1.36	2.08

FIGURE 51 Box Plots of FEF₅₀% for Exposure Groups**TABLE 69 Descriptive statistics of FEF₅₀% for EXPOSURE groups**

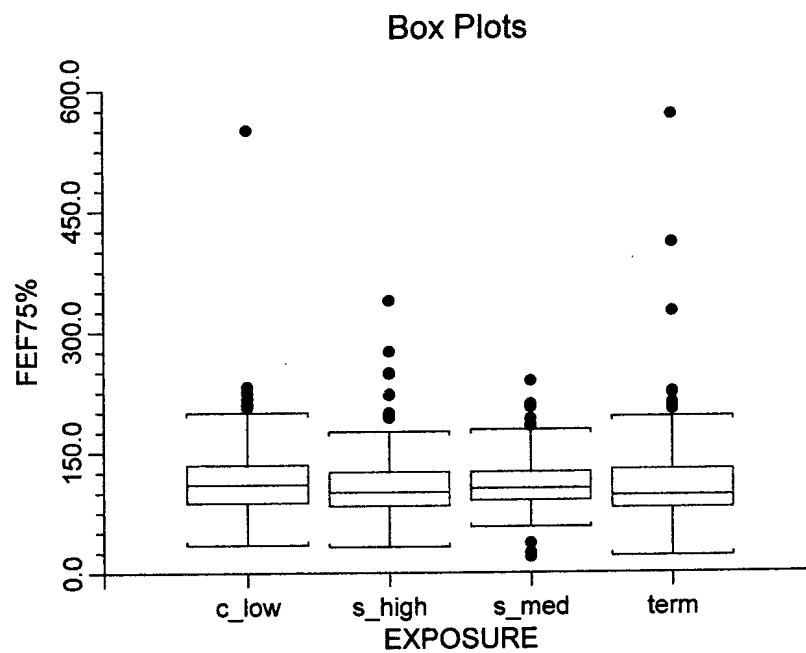
Exposure groups	S_High	C_Low	S_Medium	Terminated
N	302	198	132	133
Mean	101.21	103.98	105.21	103.45
Median	97.41	102.09	103.82	94.69
Std. Dev.	30.48	33.23	29.23	43.64
Range	175.77	186.54	154.31	202.86

FIGURE 52 Box Plots of FEF₇₅ for Exposure Groups**TABLE 70 Descriptive statistics of FEF₇₅ for EXPOSURE groups**

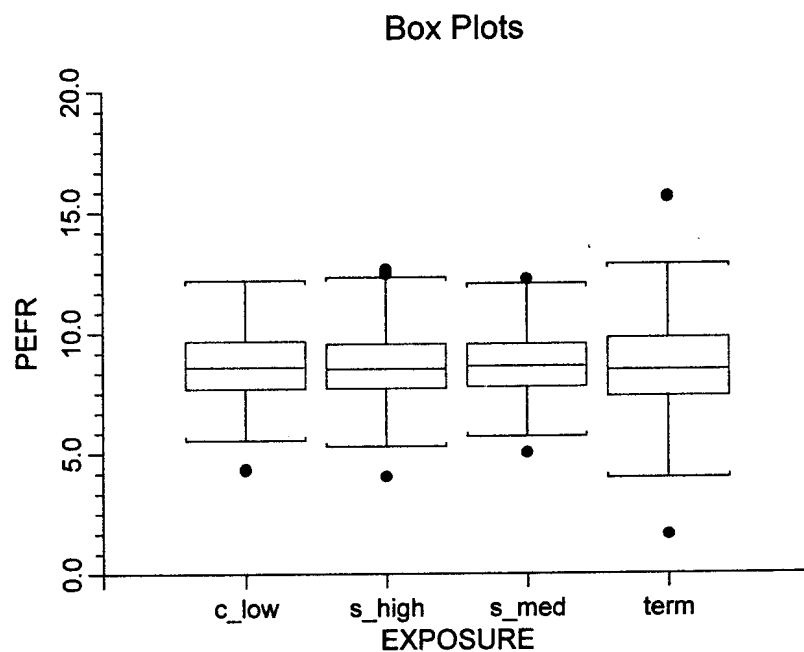
Exposure groups	S High	C Low	S Medium	Terminated
N	302	198	132	132
Mean	1.50	1.56	1.53	1.55
Median	1.41	1.49	1.49	1.42
Std. Dev.	0.57	0.72	0.51	0.77
Range	3.85	7.83	3.6	4.98

FIGURE 53 Box Plots of FEF₇₅ ADJUSTED for Exposure Groups**TABLE 71 Descriptive statistics of FEF₇₅ ADJUSTED for EXPOSURE groups**

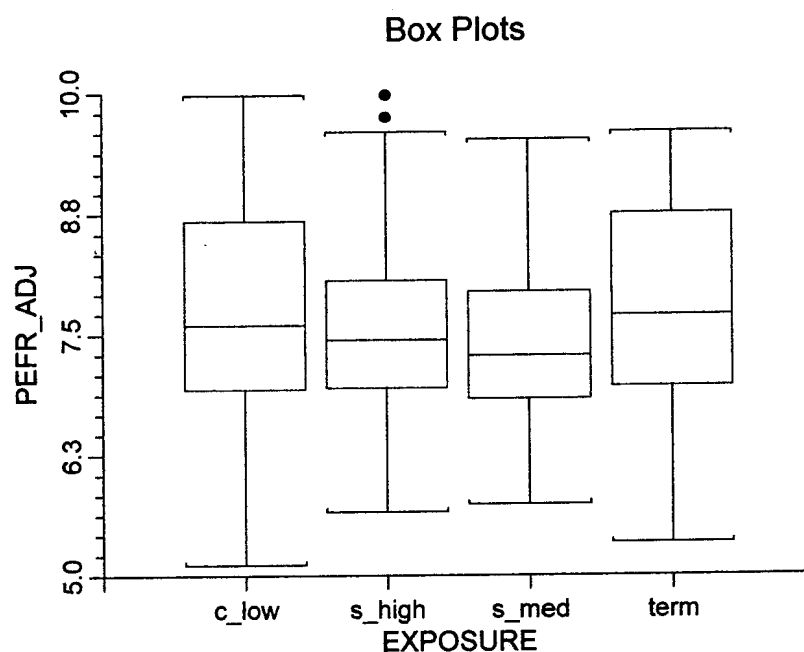
Exposure groups	S_High	C_Low	S_Medium	Terminated
N	302	198	133	133
Mean	1.39	1.35	1.39	1.40
Median	1.43	1.40	1.40	1.47
Std. Dev.	0.17	0.22	0.18	0.22
Range	0.92	1.01	0.80	1.57

FIGURE 54 Box Plots of FEF₇₅% for Exposure Groups**TABLE 72** Descriptive statistics of FEF₇₅% for EXPOSURE groups

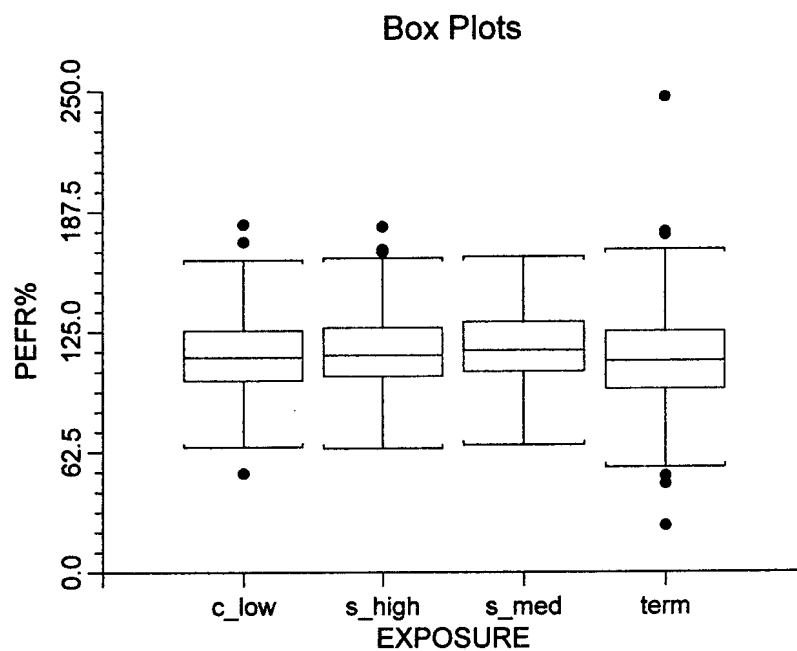
Exposure groups	S_High	C_Low	S_Medium	Terminated
N	302	198	132	132
Mean	108.41	116.33	110.69	112.73
Median	102.41	111.66	106.92	97.97
Std. Dev.	39.27	49.70	35.41	65.66
Range	307.02	516.05	219.18	548.41

FIGURE 55 Box Plots of PEFR for Exposure Groups**TABLE 73 Descriptive statistics of PEFR for EXPOSURE groups**

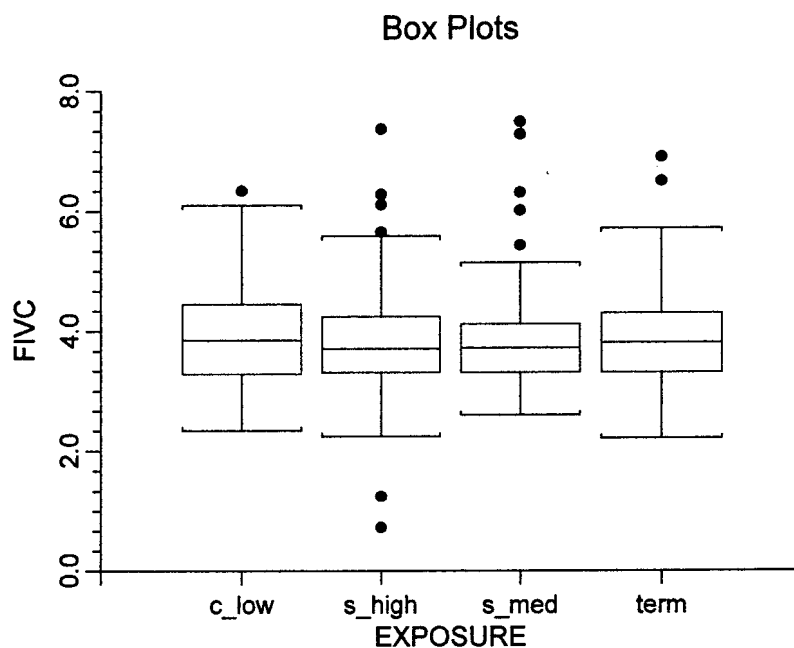
Exposure groups	S_High	C_Low	S_Medium	Terminated
N	302	198	132	133
Mean	8.67	8.60	8.63	8.55
Median	8.56	8.64	8.67	8.50
Std. Dev.	1.39	1.48	1.32	2.10
Range	8.59	7.88	7.2	14.01

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*

FEV₁%

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*

FEV₁/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

FEF₅₀%

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*
FEF₇₅%			

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)

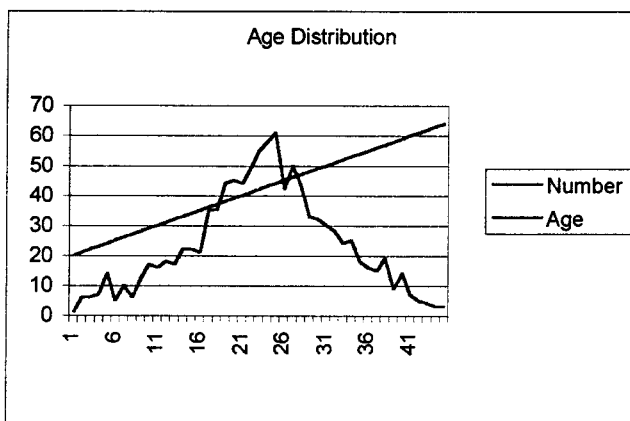
5.4.1 Introduction

Latency is defined as the time from the onset of exposure to measurable outcome. Latency effects are an important factor in 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.

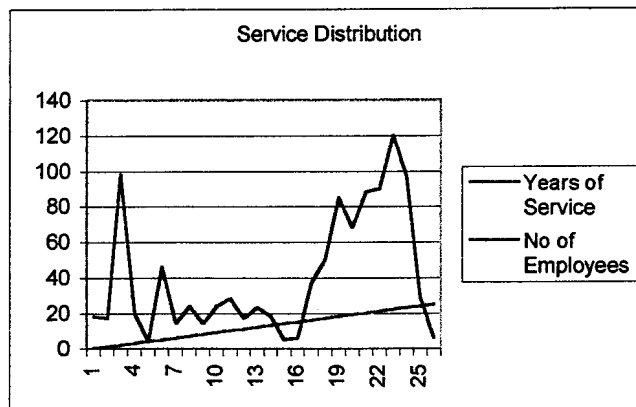
Graph 4 – Age Distribution



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 atopics 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	sarcoidosis	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, FEV₁, FEV₁/FVC, FEF₅₀ 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

FEV₁ $\leq$ 75% of predicted

$FVC \leq 75\%$ of predicted
 $FEV_1 \leq 75\%$ of predicted
 FEV_1 ratio ≤ 0.75 (under 30 years of age)
 ≤ 0.70 (between to and 59 years of age)
 ≤ 0.65 (older than 60 years)
 $FEF_{50} \leq 60\%$ of predicted with a normal FVC
 $FEF_{75} \leq 60\%$ 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 <i>et al</i>	% Abnormal De Kock <i>et al</i>
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 FEV₁ level, a much closer correlation between FEF₅₀ and FEF₇₅ was found. No difference between FEV₁ 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 <i>ET AL</i> AND DE KOCK <i>ET AL</i>)				
Smoking Status	COPD Schoenberg <i>et al</i>	COPD De Kock <i>et al</i>	SAD Schoenberg <i>et al</i>	SAD De Kock <i>et al</i>
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

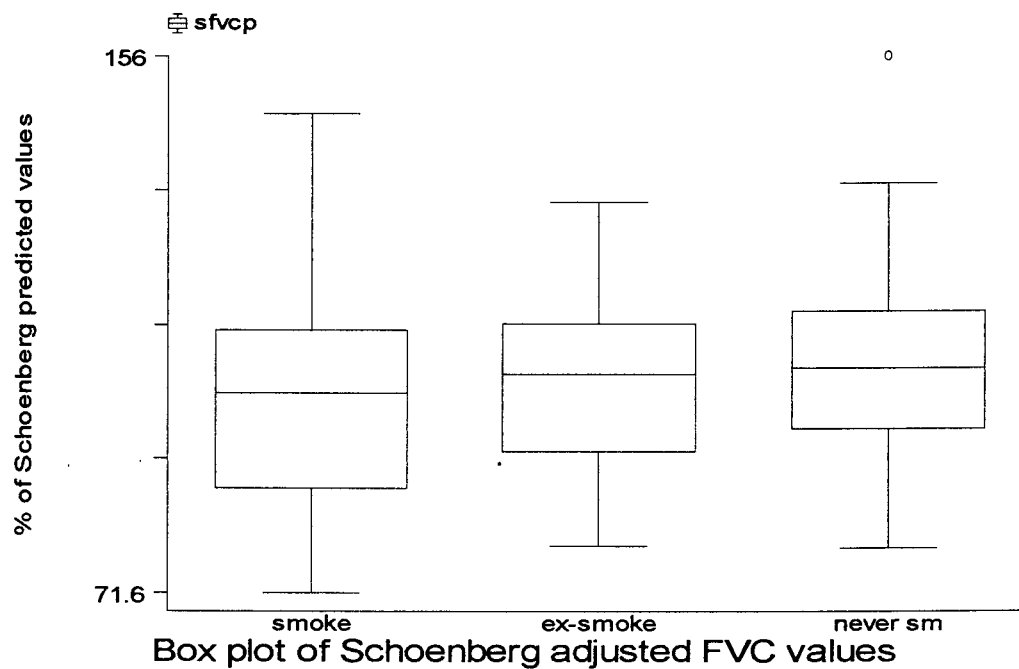


TABLE 98 - SUMMARY OF SCHOENBERG FEV ₁ PREDICTED					
SMOKING	Mean	Std. Dev.	Freq.	P Val	0.0012
Smoke	90.413043	16.434673	23	0.660	
ex-smoke	95.439286	16.951988	28	0.96	
never sm	102.23933	13.086701	89	0.002	
Total	98.936428	15.115014	140		

Figure 60

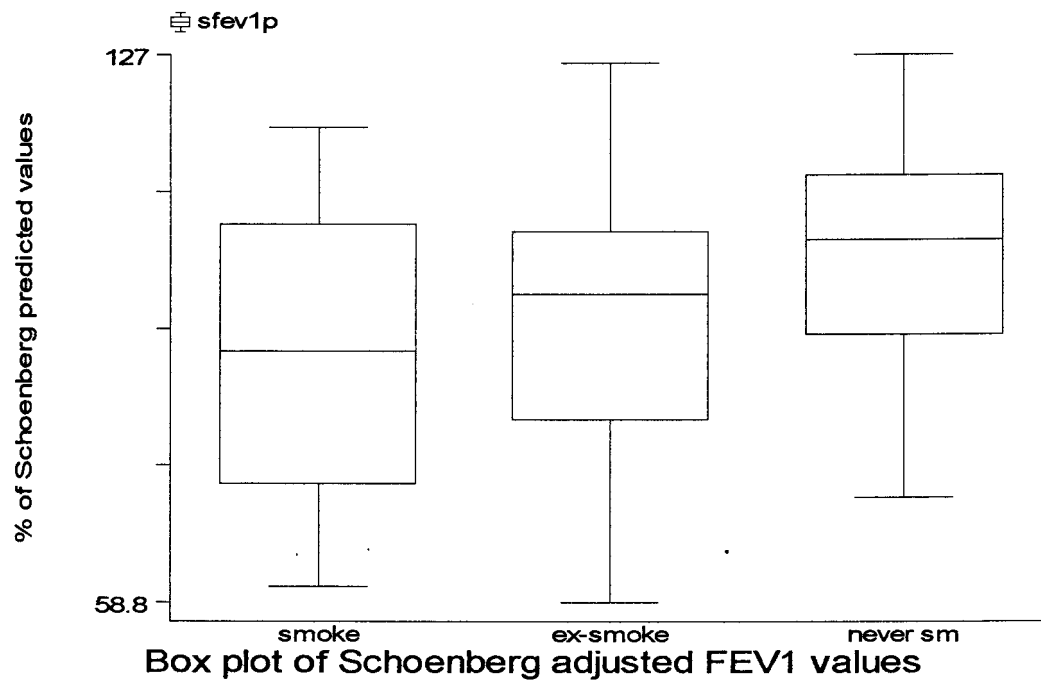


TABLE 99 - SUMMARY OF SCHOENBERG RATIO PREDICTED					
SMOKING	Mean	Std. Dev.	Freq.	P Val	0.0002
Smoke	91.056522	10.961661	23	1.000	
ex-smoke	89.989286	20.171401	28	0.001	
never sm	99.274157	8.1181127	89	0.011	
Total	96.067143	12.568102	140		

Figure 61

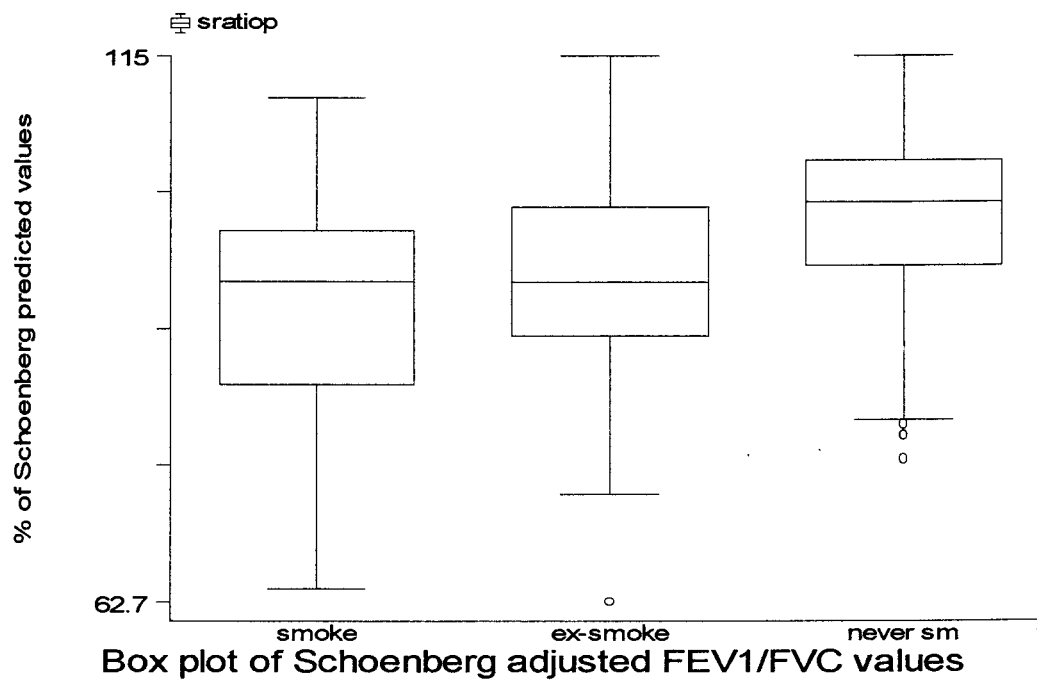


TABLE 100 - SUMMARY OF SCHOENBERG FEF ₅₀ PREDICTED					
SMOKING	Mean	Std. Dev.	Freq.	P Val	<0.0001
Smoke	65.83913	26.963961	23	1.000	
ex-smoke	71.623214	30.946326	28	0.002	
never sm	93.503371	28.52472	89	0.000	
Total	84.5825	30.969922	140		

Figure 62

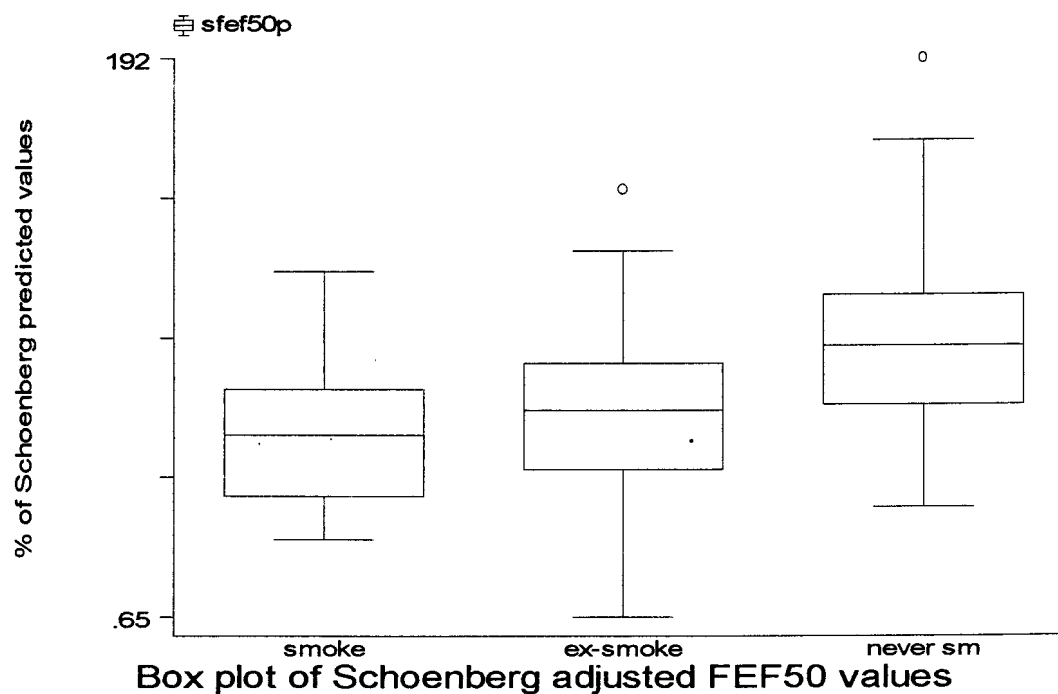


TABLE 101 - SUMMARY OF SCHOENBERG FEF ₇₅ PREDICTED					
SMOKING	Mean	Std. Dev.	Freq.	P Val	0.002
Smoke	58.734783	30.832459	23	1.00	
ex-smoke	64.5425	31.852829	28	.009	
never sm	84.844944	30.759537	89	.001	
Total	76.494929	32.74378	140		

Figure 63

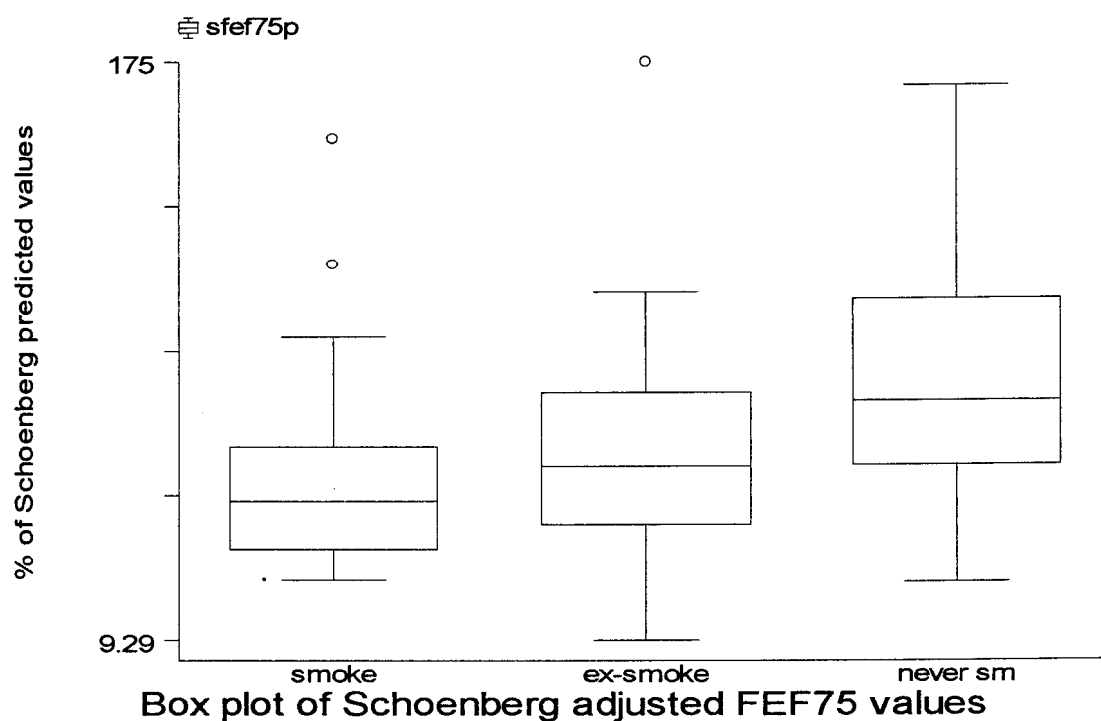


TABLE 102 - SUMMARY OF DE KOCK FVC PREDICTED					
SMOKING	Mean	Std. Dev.	Freq.	P Val	0.4248
smoke	110.19547	21.675968	23	0.951	
ex-smoke	115.0229	18.94357	28	1.000	
never sm	115.37965	15.046152	89	0.590	
Total	114.45661	17.058994	140		

Figure 64

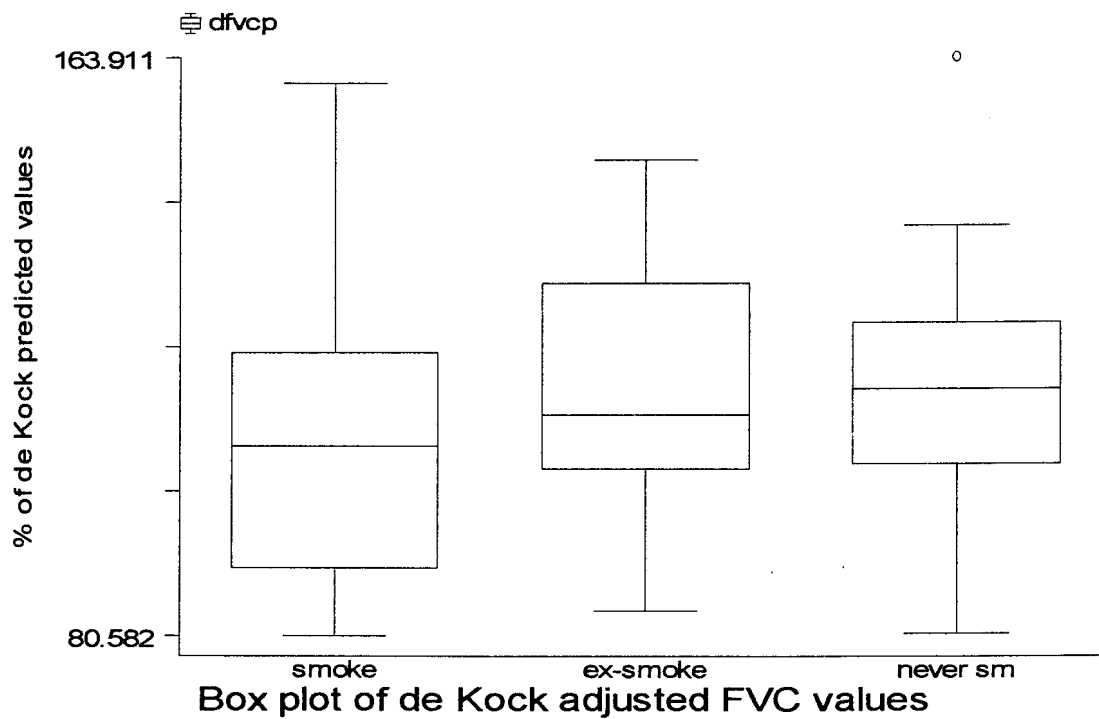


TABLE 103 - SUMMARY OF DE KOCK FEV ₁ PREDICTED					
SMOKING	Mean	Std. Dev.	Freq.	P Val	0.0025
Smoke	96.403833	18.400659	23	0.359	
ex-smoke	103.81108	19.946783	28	0.304	
never sm	109.82116	15.275491	89	0.003	
Total	106.41487	17.434976	140		

Figure 65

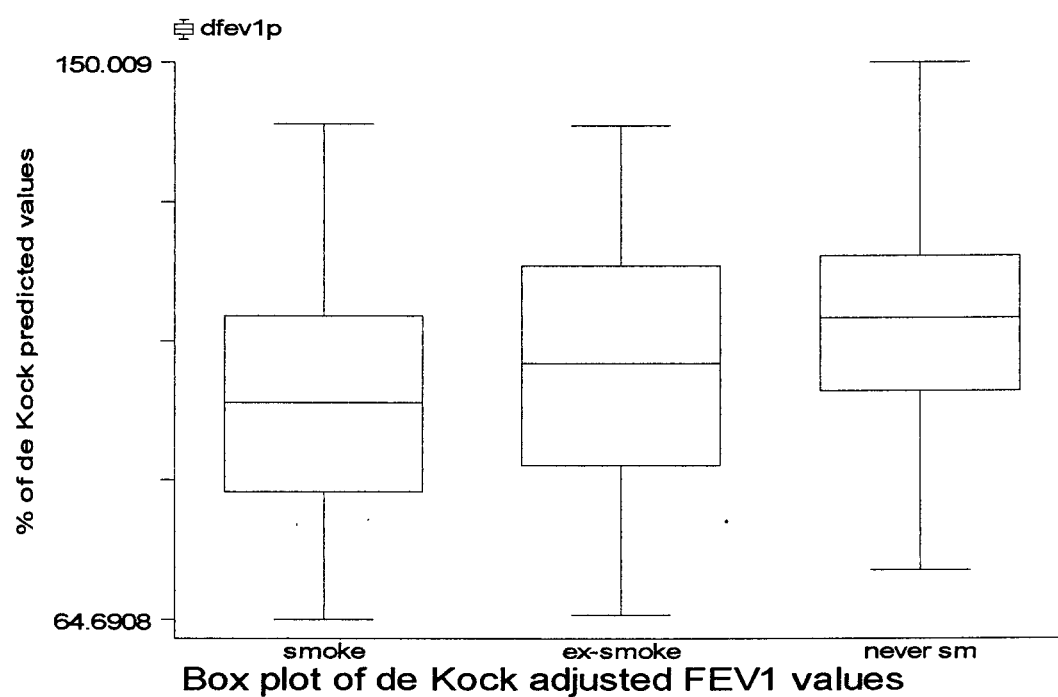


TABLE 104 - SUMMARY OF DE KOCK RATIO PREDICTED					
SMOKING	Mean	Std. Dev.	Freq.	P Val	0.0001
Smoke	88.164035	11.125681	23	1.000	
ex-smoke	89.982488	8.07577	28	0.008	
never sm	95.475328	7.4683897	89	0.001	
Total	93.175619	8.7845005	140		

Figure 66

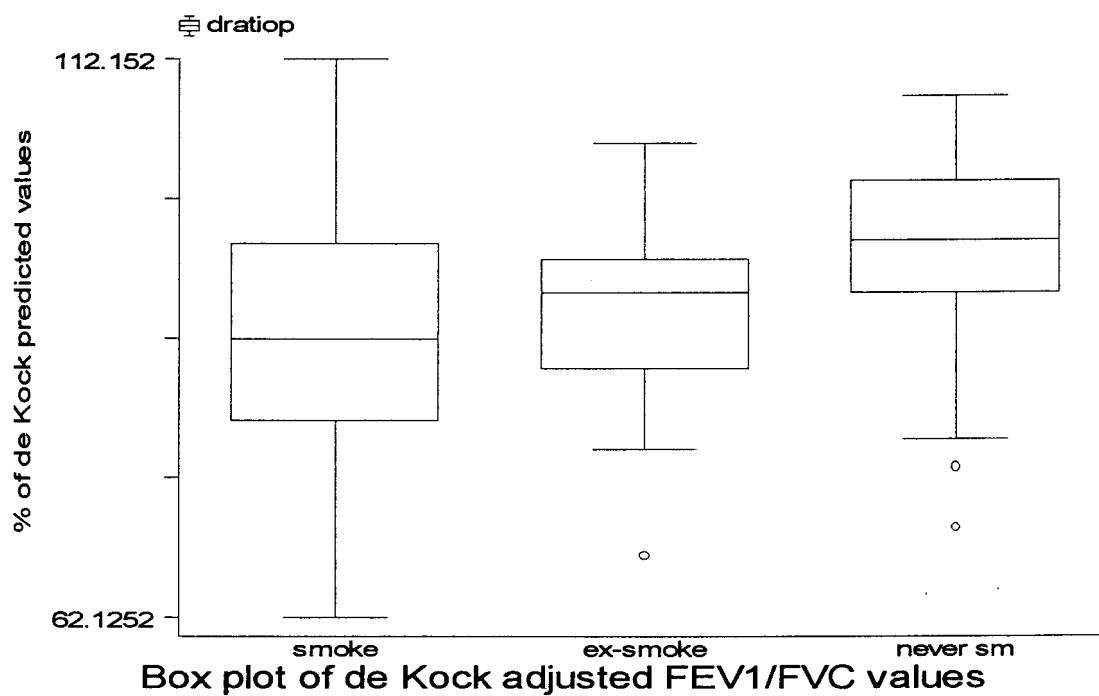


TABLE 105 -SUMMARY OF DE KOCK FEF ₅₀ PREDICTED					
SMOKING	Mean	Std. Dev.	Freq.	P Val	<0.0001
Smoke	67.32048	28.042659	23	0.717	
ex-smoke	76.94382	26.370279	28	0.005	
never sm	97.189661	29.85886	89	0.001	
Total	88.233413	31.199012	140		

Figure 67

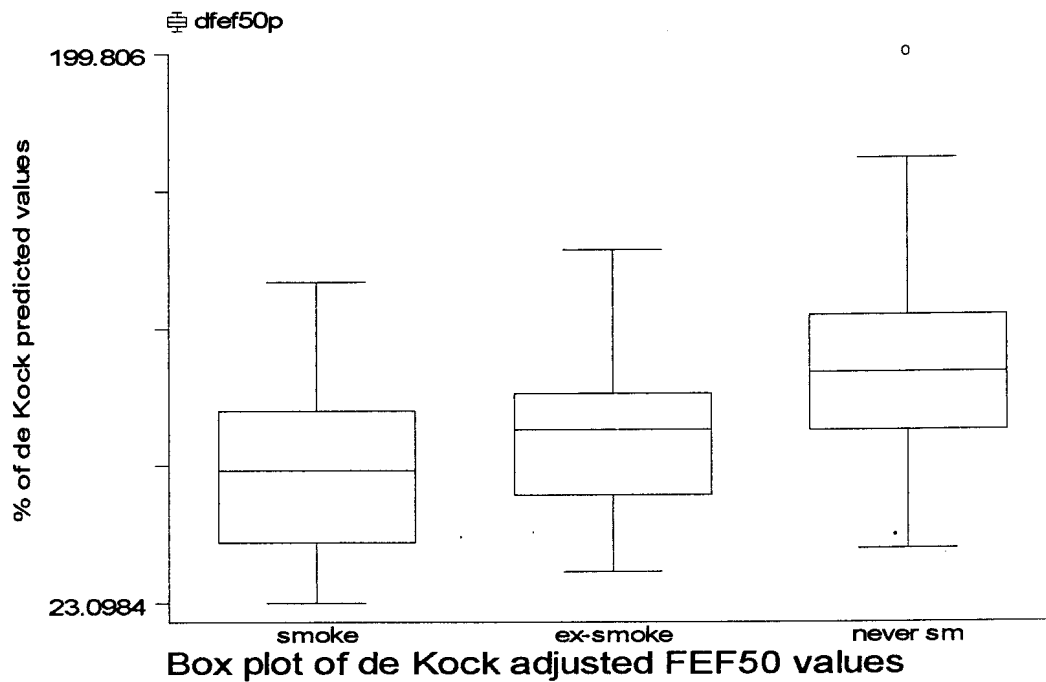
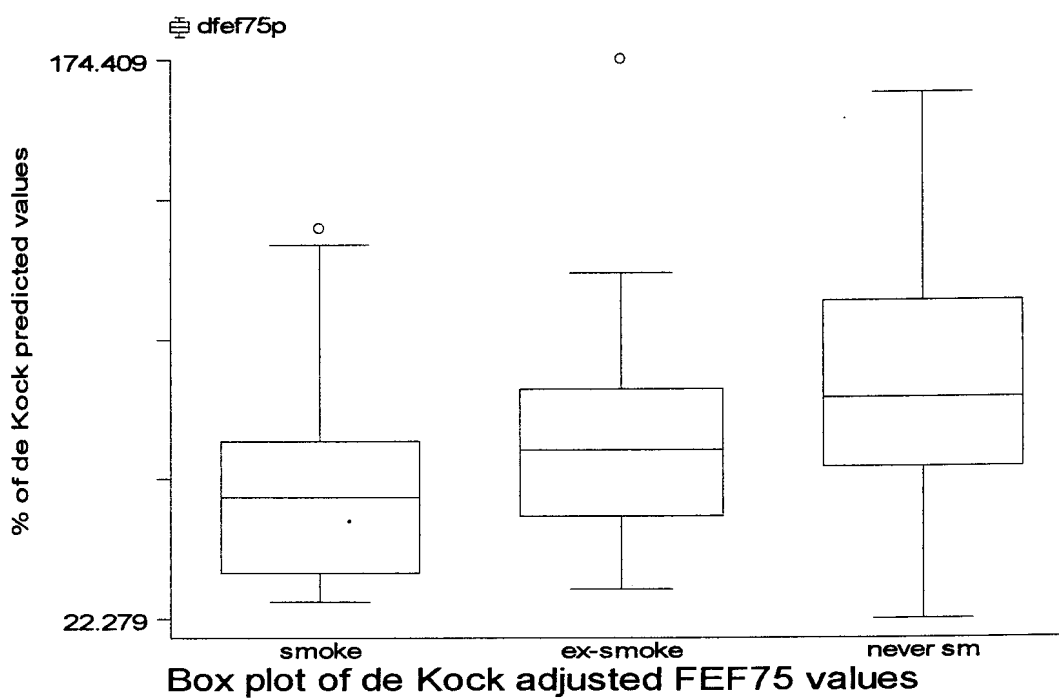


TABLE 106 - SUMMARY OF DE KOCK FEF ₇₅ PREDICTED					
	Mean	Std. Dev.	Freq.	P Val	0.0002
SMOKING	59.104673	29.661998	23	0.541	
ex-smoke	70.787325	29.81401	28	0.048	
never sm	87.062886	31.402245	89	<0.0001	
Total	79.214639	32.509525	140		

Figure 68



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 FEV₁, which is the best repeatable and reliable indicator of airflow obstruction. FEV₁ 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 (FEF₅₀ and FEF₇₅ 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 (FEF₅₀ and FEF₇₅) in the presence of an abnormal FEV₁ (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 FEV₁, FEV ratio, FEF₅₀ and FEF₇₅ 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.³⁶⁵ **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.³⁶³ 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

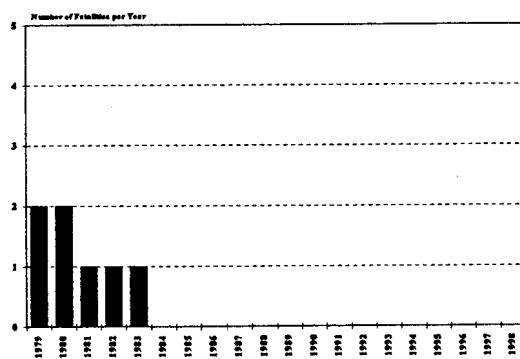
disease to develop as it does in cohort studies. The number of subjects may be small since the study is initiated by the identification of cases which is compared with controls. It is especially important for the etiology of rare diseases and may be the only feasible way to accumulate cases.³⁵⁴

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

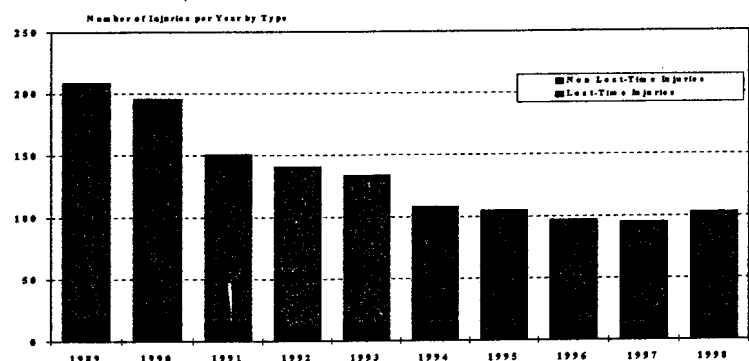
The Rössing mine, by any standards, is a safe mine with an excellent safety record. The following graphs support this statement.

Graph 6



Fatalities 1979 - 1998

Graph 7



Total Injuries

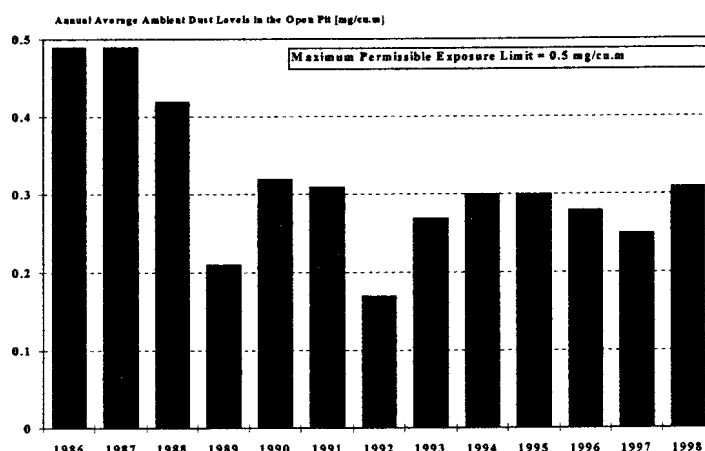


Exposure to **dust**, especially respirable dust, has been a concern, particularly at crushers and in the plant where the average annual respiratory dust levels sometimes exceed the maximum permissible exposure level (MPEL) of $0,5\text{mg}/\text{m}^3$. The crystalline silica content of the respirable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

Graph 8



Open Pit Dust Control



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

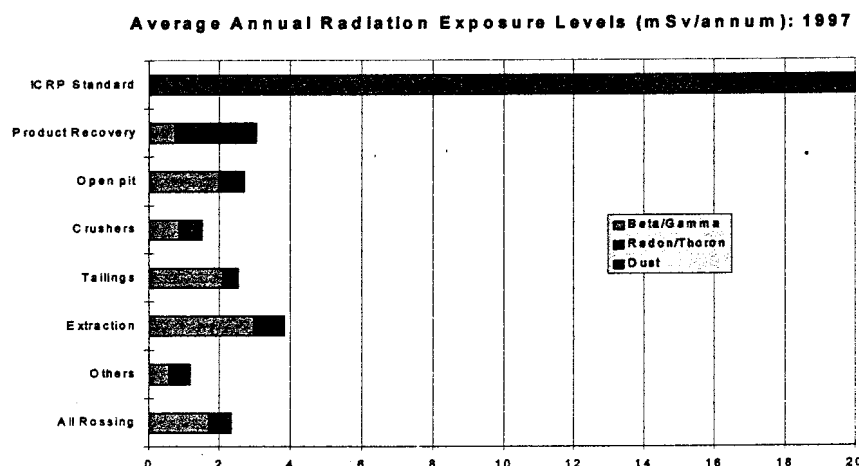
based on the extrapolation of observations obtained at moderate or high doses.³¹⁶

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



Radiation Exposure Levels



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./m³ 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 FEV₁, FEV₁% and FEF₂₅-FEF₇₅. 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. Becklake¹⁸⁷, 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 Abramovich²¹³ found that tobacco-smoking potentiates the effects of silica. The duration of exposure was found to be associated with significant reductions in FEV₁% 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 country 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 ($\pm$ 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.

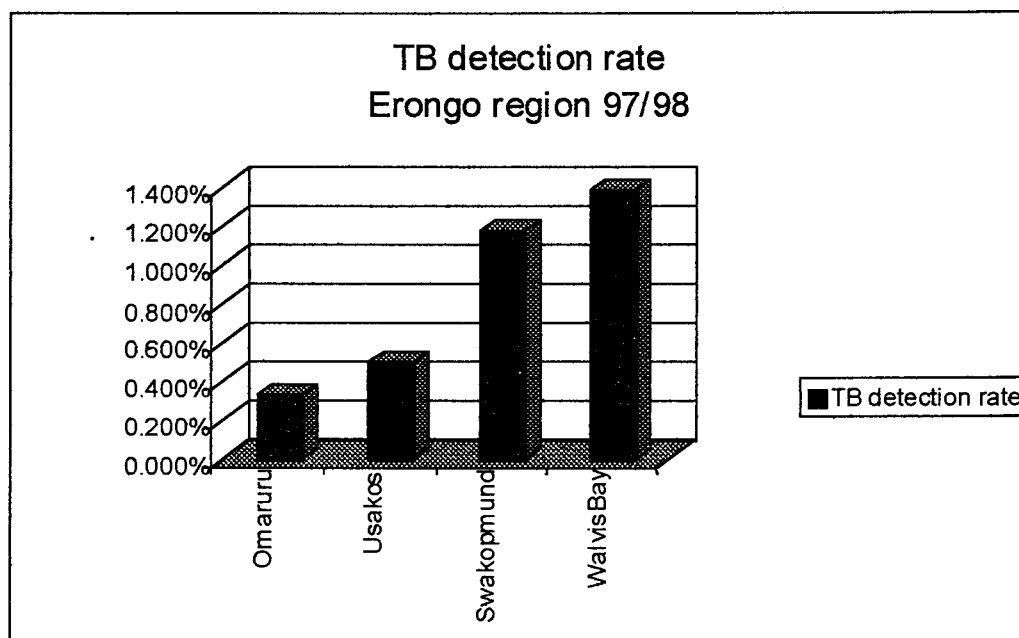
Stewart and Kneale⁸⁶ points out that the sensitivity to carcinogenic effects of radiation increases progressively with age (provided the dose is small). This must be borne in mind by Rössing's strategic planners.

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%

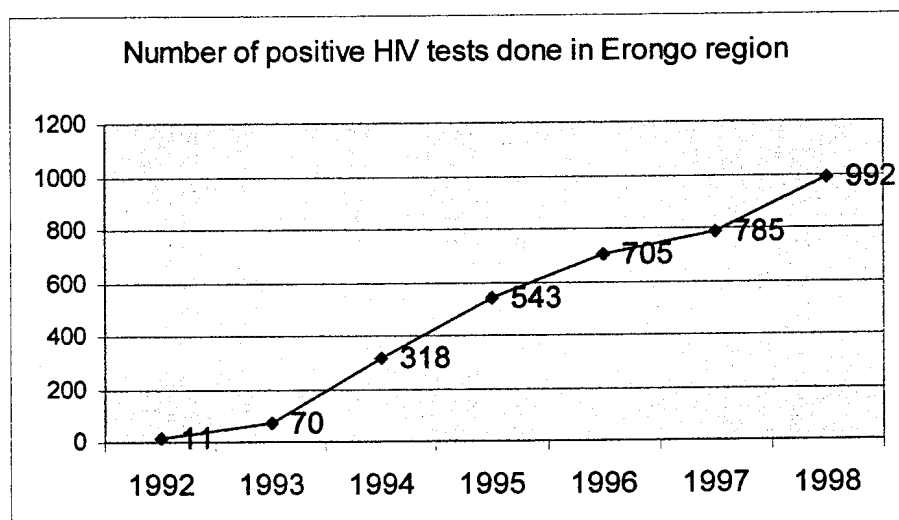
In the 1996 study the cross-sectional survey only revealed two cases of pulmonary tuberculosis being investigated or treated. When the x-rays were retrospectively studied (historical cohorts) a different picture emerged. A total of twenty employees were diagnosed as having definite tuberculosis or strongly 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 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 Balmes²²⁵ 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. Myers³⁰⁶ 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 Becklake³⁰⁹ 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 "FEV₁ 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, FEV₁, FEV₁ ratio, FEF₅₀ and FEF₇₅.^{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, FEV₁ PEFR, and PIFR and to a lesser degree for FEF₅₀ and FEF₇₅. The actual values of FEF₅₀ and FEF₇₅ 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 FEV₁/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.

FEF₇₅ (t=1.9828 p = 0.047) The most commonly reported FEF, is the FEF₇₅. 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 FEV₁, peak flow rate and flow at 25% of forced expiratory vital capacity.^{286,287,288,289,290} Under the above mentioned conditions the FEF₇₅ 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 FEV₁%, FEF₅₀ and FEF₇₅ 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

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APPENDIX A

PAPERS PRESENTED OR PUBLISHED FROM RESEARCH PRESENTED IN THIS THESIS

1. The application of modern methodology to the study of early lung function changes in workers in a uranium mine. MA de Kock, WRS Swiegers, CM Lewis. Poster presentation, International Conference on Occupational Radiation and Safety. Toronto. October 15, 1984.
2. Cross sectional study of uranium mine workers to develop predictive equations for lung functions with reference to chronic obstructive pulmonary disease. MA de Kock, WRS Swiegers, TJvW Kotze, G Joubert. Supplement to the SA Medical Journal. S Afr Med J. 1988; **19** (1): 1-20
3. Flow volume curve as a mass screening test and in epidemiology: emphasis on quality control. MA de Kock, WRS Swiegers, R Wright. S Afr Med J. 1988; **75**: 261 -270

APPENDIX B

OVERVIEW OF RÖSSING

B1 HISTORY OF ROSSING

In 1910 Dr E Reuning first recognised the presence of radioactive materials in the Rössing area. He found a heliodore (golden beryl) in a pegmatite near Rössing Mountain which contained radioactive U_3O_8 (0,02-0,04%) (Berning, 1986). In 1921, Dr P A Wagner postulated that the uranium content of the heliodore indicated that the magmatide solution from which the pegmatite crystallised was also radioactive (Wagner, 1921). In 1928, Captain Peter Louw, a part-time prospector from Swakopmund, and his wife Margery measured radioactive levels on a sample of a heavy black mineral (pitchblende) found 20 kilometres from present day Rössing.

In 1932 (Prof TW Gevers) and in 1948 (CM Schwellnus and GSJ Kuschke) confirmed the presence of radioactive minerals but no economic importance was attached to their discoveries.

The Louw family formed a syndicate in 1953, obtained a prospecting grant and set out to relocate the original discovery. In 1954 they succeeded but were unable to arouse local interest. They approached the Anglo-American Corporation and signed a prospecting and option agreement. After extensive exploration and drilling they concluded that although the area contained several million tons of low-grade uranium, the grade was too low and the mineralisation too erratic to warrant economically viable mining.

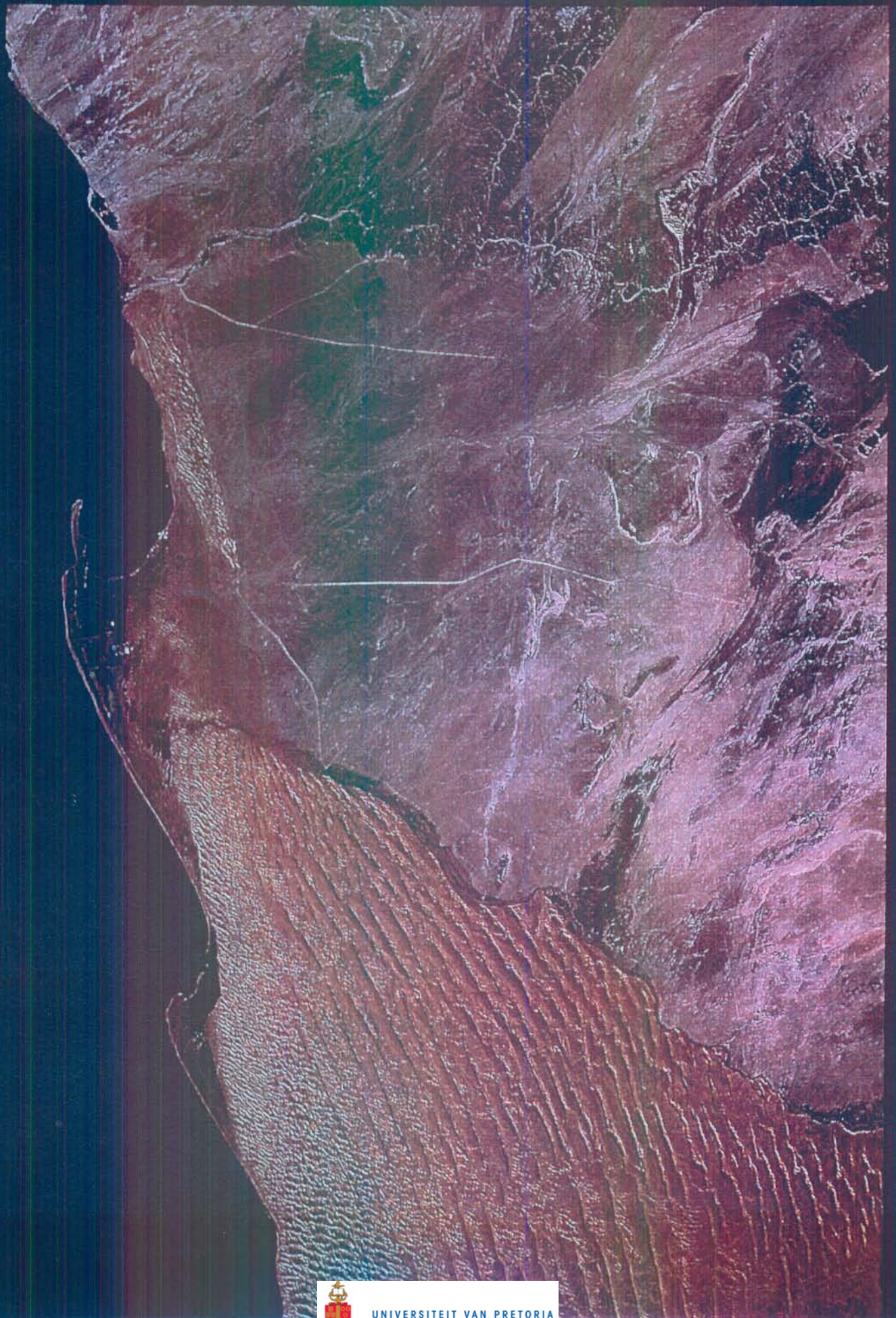
In August 1966, the Rio Tinto Zinc Corporation Ltd (RTZ) acquired the rights to explore this area. Extensive evaluation in a 100 ton per day pilot

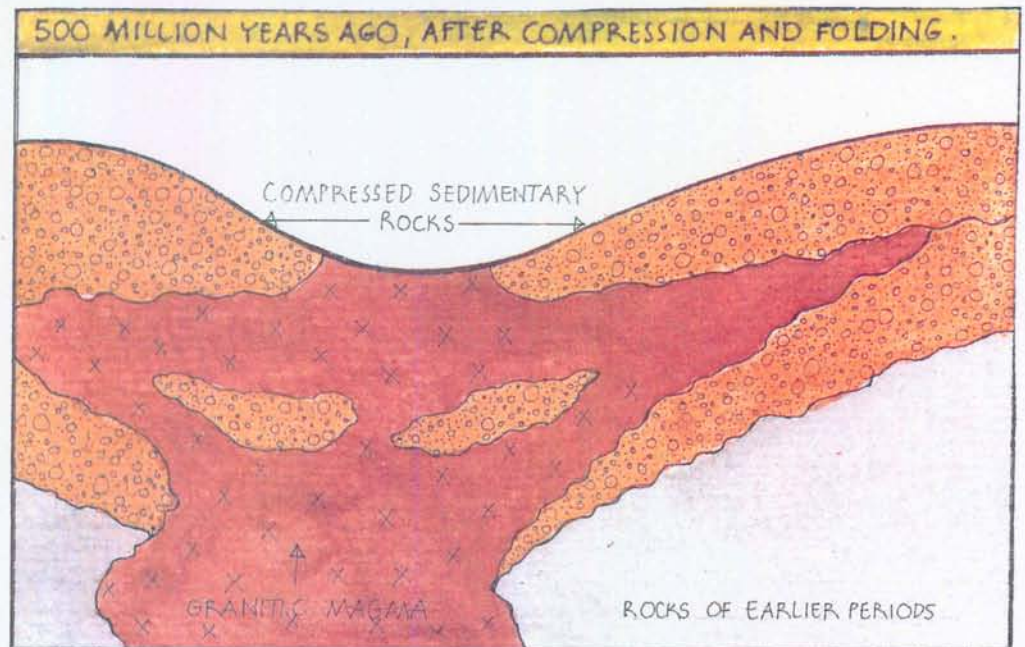
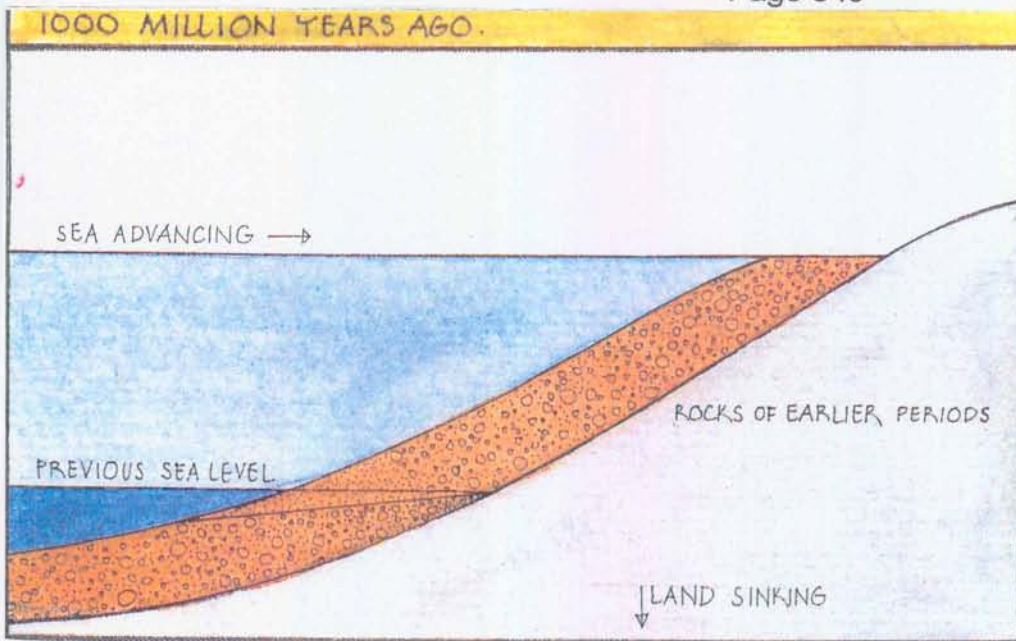
plant confirmed the possibility of establishing a low grade mine, but with a huge deposit and to which the techniques of bulk, low grade open pit mining could be applied. Rössing Uranium Ltd was formed in 1970 and in 1973 the uranium market picked up which enabled commissioning of the mine. The production capacity was set at 5000 annual short tons of oxide.

In mid-1974 the first ground in the open pit was broken and the process plant built producing the first yellow cake. The mine's development was rapid, but the granite Alaskite was highly abrasive resulting in excessive breakdown and maintenance problems.

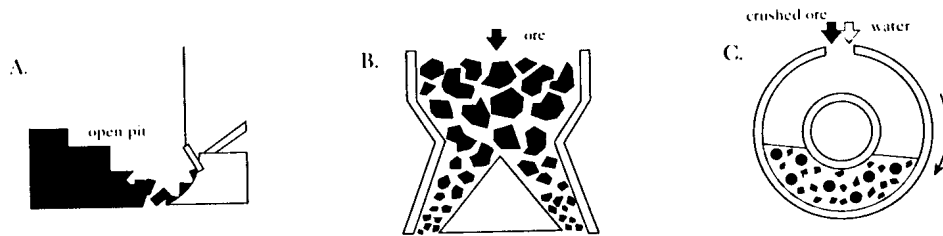
Technical problems with the Rössing start-up necessitated a major modification programme that was implemented in 1978. Unfortunately at midnight on 24 May 1978 a section of the solvent extraction plant burnt down wiping out half the capacity of the biggest uranium solvent extraction plant in the world. However the plant was soon to be operational again.

At times the mine produced up to 5 000 short tons of yellow cake for a number of years. The strategic value of uranium diminished (along with an over-supply) when east/west confrontation politics disappeared during the mid and late 1980's and Rössing retrenched more than half of its work force during the 1989 - 1992 period. It is still producing yellow cake but at a much lower scale (2 000 short tons) and is currently operating with a manpower complement of approximately 1 300 employees. It still produces 7,7 per cent of the Western World's production.





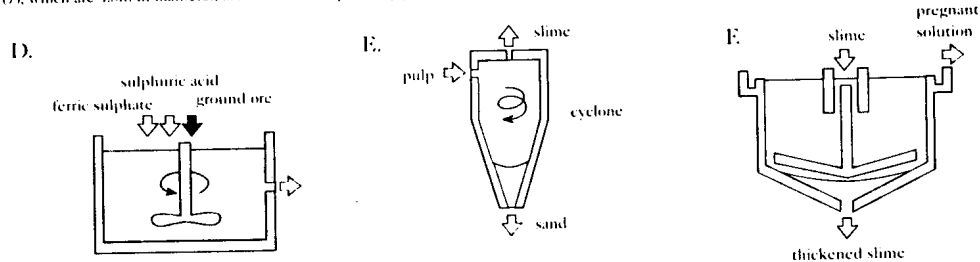
MINING AND METALLURGICAL OPERATIONS



A. MINING: (1) The uranium ore at Rossing is recovered by drilling, blasting, loading and haulage. Due to erratic distribution of minerals in the ground, waste and ore are often mixed together. Radiometric scanners measure the radioactivity level of each truckload (1a). This determines whether the material is sent to the primary crushers (2) or to low-grade stockpile. Waste is transported to a separate dump.

B. CRUSHING: Ore is delivered to the primary crushers (2) by haultruck and then by conveyor to the coarse ore stockpile (3). It passes through a further series of crushers and screens (4) until the particles are smaller than 19mm. After weighing (5) this fine ore is stored on another stockpile (6).

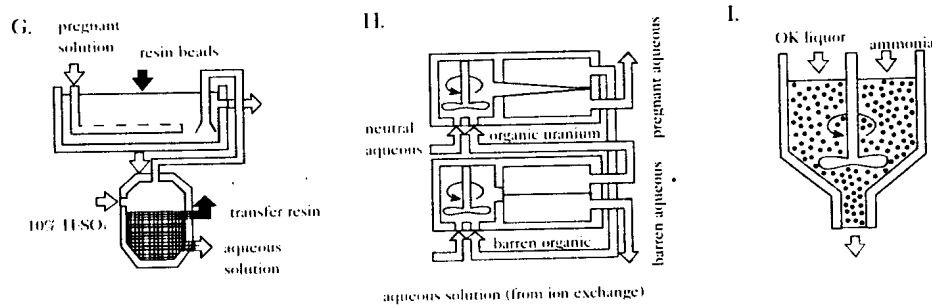
C. GRINDING: Wet grinding of the crushed ore by means of steel rods reduces it further to a slurry with the consistency of mud. The four rod mills (7), which are 4.3m in diameter, are utilised as required by production levels and operate in parallel.



D. LEACHING: A combined leaching and oxidation process takes place in large mechanically agitated tanks (8). The uranium content of the pulped ore is oxidised by ferric sulphate and dissolved in a sulphuric acid solution. Sulphuric acid is produced through a pyrite-roasting process on site (14).

E. SAND/SLIME SEPARATION: The product of leaching is a pulp containing suspended sand and slime. Cyclones separate these components and, after washing in Rotoscops (9) to remove traces of uranium-bearing solution, the sand is pumped through a pipe (9a) to a tailings disposal area.

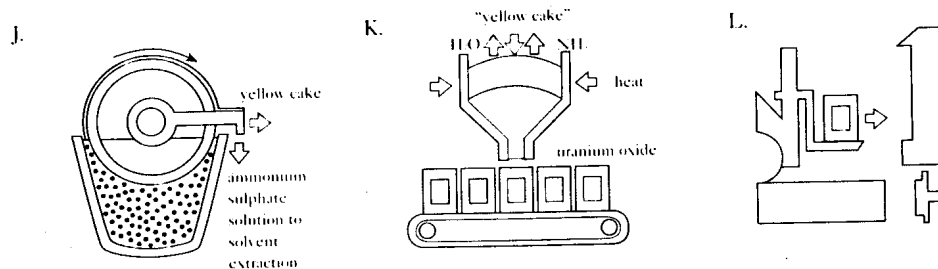
F. THICKENING: Counter-current decantation thickeners (10) wash the slimes from previous stages. A clear uranium-bearing solution (pregnant solution) overflows from No. 1 thickener, while the washed slime is mixed with the sands and pumped to the tailings area (9a).



G. CONTINUOUS ION EXCHANGE: (11) The clear pregnant solution now comes into contact with beads of specially-formulated resin. Uranium ions are absorbed onto the resin and are preferentially extracted from the solution. Beads are removed periodically to elution columns where a strong acid wash removes the uranium from the beads. The resulting eluate is a purified and more concentrated uranium solution.

H. SOLVENT EXTRACTION: (12) The acidic eluate from the ion exchange plant is mixed with an organic solvent which takes up the uranium bearing component. In a second stage, the organic solution is mixed with a neutral aqueous ammonium sulphate solution which takes up the uranium-rich 'OK liquor'. The acidic 'barren aqueous' solution is returned to the elution columns.

I. PRECIPITATION: (13) The addition of gaseous ammonia to the 'OK liquor' raises the solution pH, resulting in precipitation of ammonium diuranate, which is then thickened to a yellow slurry.



J. FILTRATION: (15) The ammonium diuranate is recovered on rotating drum filters as yellow paste: 'yellow cake'.

K. DRYING AND ROASTING: (16) Final calcining drives off the ammonia, leaving uranium oxide. The product is then packed into metal drums. Neither ammonium diuranate nor uranium oxide are explosive substances.

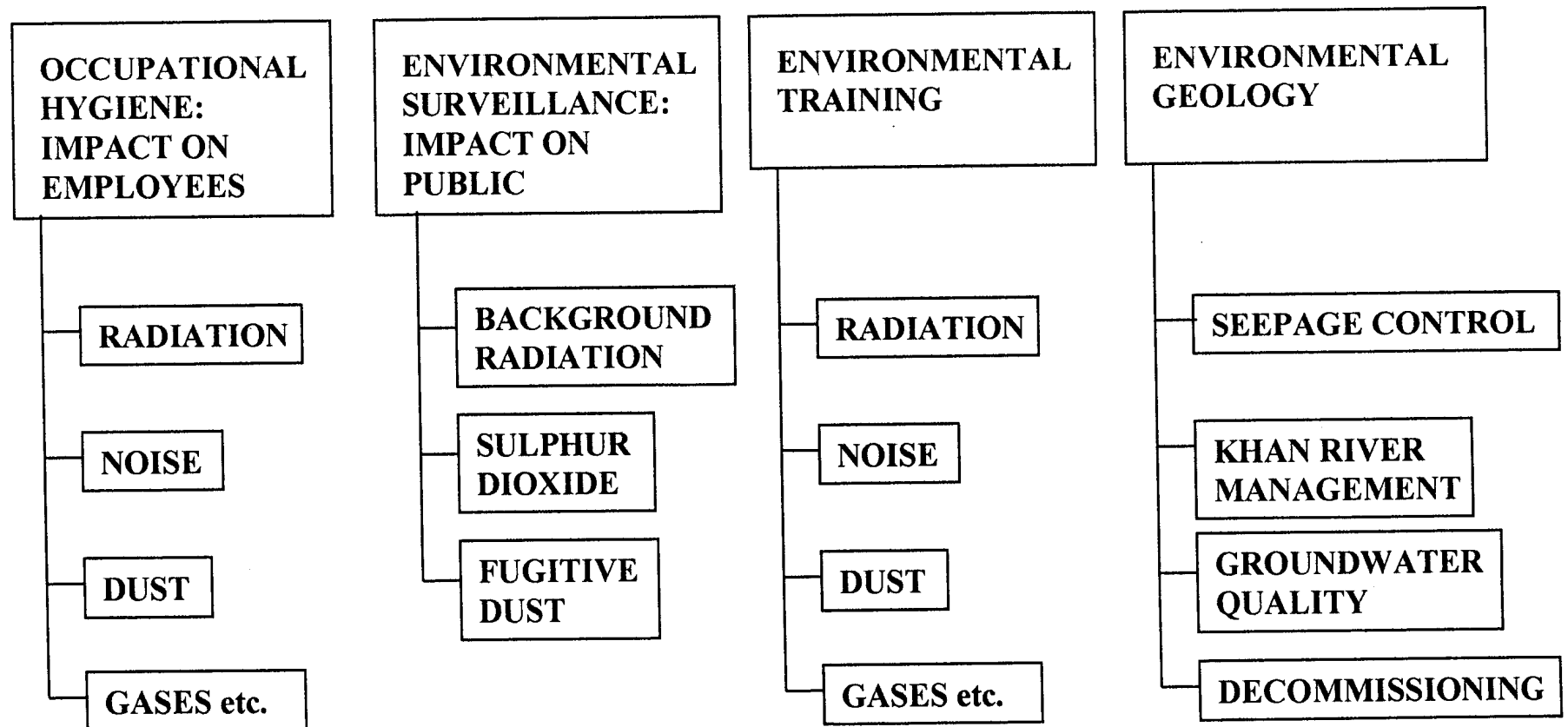
L. LOADING AND DESPATCH: (17) The drums of uranium oxide are loaded and exported to overseas customers for further processing. At full capacity, the plant can produce 5 000 short tons of uranium oxide each year.





Environmental Programme

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B2 ENVIRONMENTAL HEALTH AND SAFETY AT RÖSSING

RTZ is a multi-national mining organisation and required that Rössing Uranium embark on comprehensive preventative programs that conform to standards consistent with world best practices. The best available technology is applied to reduce the impact of the operations on humans and the environment. Conditions potentially hazardous to the health of the inhabitants and/or ecology of the area are carefully monitored.

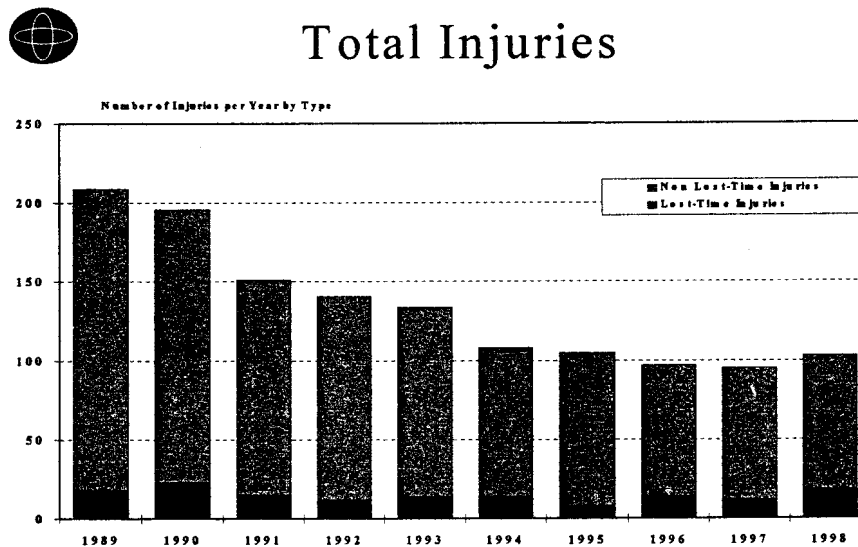
Rössing is generally regarded as a safe mine. The NOSA (National Occupational Safety Association) programme was introduced in 1978 and the first goal was set to achieve the very highest star grading achievable. This grading took place in 1980 and 3 stars were awarded. To complement the NOSA system and to uphold strong motivation amongst employees internal, sectional, departmental and divisional safety competitions were arranged and each divisional manager is responsible for the auditing of sections and departments within his division.

In the following years Rössing's health and safety programme continued, improving successfully and winning major titles in the South African NOSA competitions. In 1981 Rössing was graded a 3-star company and in 1982 it achieved the highest award, namely 5 stars. In 1983, 3 million disabling injury-free man-hours were worked and in 1984 a first place in a National Mining Competition was attained, followed by the first place in 1985 in the National Safety Effort and Efficiency (SEE) open competition. In the same year Rössing bettered the South African record for fatality-free shifts when 3 032 039 shifts were exceeded.

The mine achieved its first NOSCAR award (the highest safety award) in 1986 and joined the ranks of only 36 holders in Southern Africa amongst more than 4 000 participating companies, of which just over 200 are 5-star achievers. The NOSCAR was retained and re-awarded to the mine in 1987 to 1994.

In December 1988, Rössing was acknowledged by the British Safety Council as being one of the 30 safest operations in the world, and presented with the coveted Sword of Honour in recognition of this achievement. The Sword of Honour was retained in 1989 for the second consecutive year, establishing the mine as only one of three companies in the world to maintain this achievement.

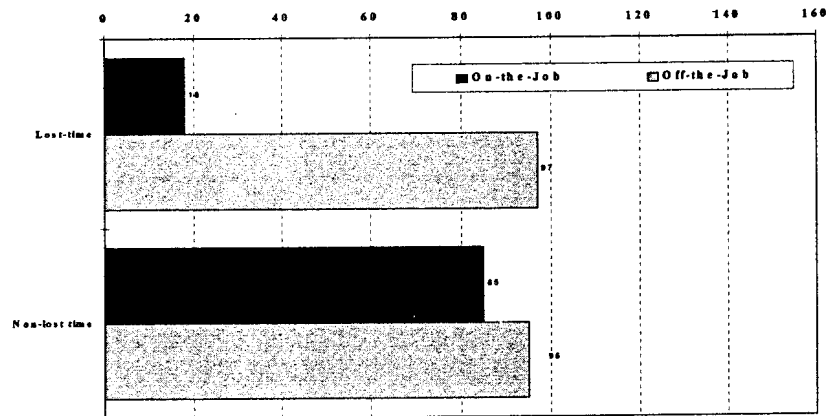
Graph 12



Graph 13



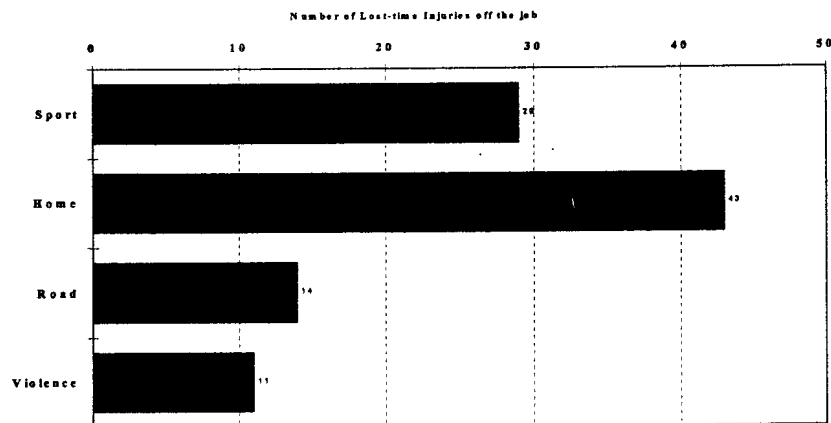
On- and Off-the job Injuries 1998



Graph 14



Off-the-job Injury Profile 1998



B3 GEOLOGY

The Rössing uranium deposit lies within the central zone of the late Pre-Cambrian Damaran Orogenic Belt that occupies much of northern Namibia.

The genesis of the uraniferous deposits commenced in Pre-Cambrian times (one thousand million years ago) during the Damaran sedimentary cycle (Vernon, 1981). The initial deposition took place in a shallow turbulent sea, and consisted of cross-bedded, coarse sediments of the lower Etusis Formation. This was followed by the deposition of silt stones, greywackes and marls that, upon later metamorphism, were converted to the rocks of the upper Etusis Formation. Subsequently, stable conditions prevailed and the fine grained and homogenous sediments of the Khan Formation accumulated. At a later stage (Hakos period) quieter and deeper water conditions developed and more heterogeneous sediments of the Rössing Formation were deposited (marble and corderite gneiss).

Approximately 500 million years ago the great Damaran orogenic movements took place. The mass of sediments began sinking to depths of about 5km and resultant temperatures and pressures caused complex folding and metamorphism of the sediments (Vernon, 1981). At about this time, and again in a later phase, the deeper lying older rocks melted to form a granitic magma that began migrating upwards. This formed the pegmatitic granite known as alaskite that contains the primary uranium. The alaskite intruded into the Hakos and upper Nosob meta sediments, such that the alaskite is now present in a range of intrusive bodies, which vary widely in texture, size and emplacement habit (Vernon, 1981; Berning, 1986; Mouillac *et al*, 1986). Since then, sedimentary rocks and basalts from the Stormberg Series of the Karoo System were deposited and have largely eroded away, leaving thin terrestrial superficial deposits.

Also at this time, numerous dolomite dykes intruded through tensorial fissures in the Pre-Cambrian rocks to the surface (Smith, 1965). These northeast and east-north-east trending dykes are still prominent features of the landscape. During the last 65 million years only superficial deposits have changed the geological landscape and large portions of the central Namib desert are covered by tertiary to recent superficial sands and duricrust deposits, such as gypcrete and calcrete (Jacob *et al*, 1986).

The Rössing orebody is unique in that it is the largest known deposit of uranium occurring in granite. The main deposit is located in the southwesterly flank of a large domal structure. The Rössing ore body is approximately 3km long and 1km wide. The uranium-bearing alaskites at Rössing are medium to coarse-grained and vary from grey to shades of pink and white. All of the primary uranium mineralisation and the majority of the secondary uranium mineralisation occur within the alaskite. The alaskite is not uniformly uraniferous and much of it lies unmineralised or of sub-economic grade (Vernon, 1982). Uraninite is the dominant radioactive mineral present and it occurs as grains ranging in size from a few microns to 0,3mm. It is included in quartz, feldspar, and biotite, but also occurs interstitially to these minerals or along cracks within them (Vernon, 1981; Berning, 1986). The arid climate is an important factor in beneficiating primary ores with secondary minerals released by weathering, and in reducing leaching by rainfall (Mouillac *et al*, 1986). The primary uranium minerals, uraninite and betaphyte give rise to secondary minerals that are usually bright yellow. Of the secondary uranium minerals, beta-uranophane is the most abundant and the mineral is not always confined to alaskite but may also be dispersed into the enveloping country rocks along cracks and fracture lines (Vernon, 1981). The average ore grade at Rössing Uranium is about 0,035% (Dames & Moore, 1984). Uraninite comprises about 53% of the uranium present in the

orebody, betaphyte less than 5% and the secondary minerals account for about 40%.

B4 MINE LOCATION AND ENVIRONMENT

The Rössing Uranium Limited (Rössing) mine and mill complex is located in the Namib Desert some 60 kilometres east-north-east of the town of Swakopmund, Namibia, at approximately 20° 27' south and 15° 02' east. The mine area is situated on the northern bank of the Khan River (a tributary of the Swakop River) 1,4 km from the river. The mine site has a mean altitude of 575m above mean sea level (a.m.s.l.).

Electrical power to the mine and the residential areas is relayed via a 220kW line. Water is pumped from sand wells in the Kuseb River delta near Walvis Bay and from the Omaruru River delta to the north. Wells in the Khan River bed provide brackish water for dust suppression in the pit. Rössing uses between 17 000 to 27 000 cubic metres of fresh water (mostly for the process plant) and 12 000 cubic metres daily from the Khan. This water is supplemented by brackish water from the bottom of the open pit.

B5 THE CLIMATE

The Namib Desert area is dry and sometimes dusty with large variations in temperature and humidity. Precipitation is infrequent and averages less than 30mm per annum, but extremely heavy rainfalls of short duration may occur. The main elevation above sea level is 573 metres. The temperature ranges between 4,5°C and 40°C and humidity between 5% and 80%. Fog occurs on about 60 days during the night and on about 30 days during the day per annum. The precipitation from this fog is not measured.

B5.1 Winds

Surface winds tend to be from a southwesterly direction most of the year with strong easterly berg wind conditions developing in winter.

Meteorological conditions combined with the effects caused by terrain features cause complex particulate and gas dispersion patterns (Earth Science Services, 1987). During the winter months (April to September) a cool down-valley wind sets in after midnight and prevails until 10:00 to 12:00. Between 11:00 and 14:00 general winds are strong and unmodified by local conditions. By 14:00 the local thermal and pressure gradients have reversed and a southwesterly up-valley wind prevails. From 15:00 to 18:00, the wind speed increases under the influence of the sea breeze. By 19:00 the sea influences precipitate, with another transition period between 22:00 and 24:00, after which the cycle is repeated. During the summer months (October to March) those parts of the cycle which are dependent on the cool air drainage are absent and the parts dependent on the heating process are more pronounced. Down-valley north easterlies are weak whilst the terminal north-westerlies prevail during the day from 08:00 to 14:00. These are interrupted by the inland penetration of afternoon sea breezes until approximately 20:00 when they are replaced by north/north westerly winds. These are relatively weak during the night but strengthen during the day and veer to become north westerly.

B5.2 Temperature

Air temperatures at Rössing vary greatly on a day-to-day basis, although seasonal variations are less marked. The mean diurnal temperatures range from 28,8°C in late autumn (May) to 15,4°C in spring (October), an annual range of 8,4°. This is very similar to the 9° range reported for Swakopmund (Goudie, 1972). Minimum temperatures are recorded in the

early morning and range from 2°C in August to 12°C in March (Earth Science Services, 1987). In contrast, the range of maximum diurnal temperatures show very little month-to-month variation, ranging from 31,8°C in July to 39°C in January, due to the occurrence of hot berg winds during the winter months. On very hot days, air temperatures measured in the Khan River gorge near Rössing may reach 44°C and some 5° higher than those measured at the mine (OJ Ashton, unpublished data). Monthly temperature ranges vary from 28° in summer to 32,9° in winter (Earth Science Services, 1987).

Whenever air temperatures are high, soil and rock temperatures reach even higher levels, particularly when they are dark. Temperatures of 60 - 70°C were recorded at the soil surface of the gravel plains of the central Namib and are similar to temperatures at Rössing.

B5.3 Humidity

Atmospheric humidity levels at Rössing are very variable on both an hour-to-hour and day-to-day basis (Earth Science Services, 1987). The lowest values (5 - 8%) are recorded at midday, whilst the highest values (up to 84%) are usually recorded during the early morning. Humidity levels rise rapidly immediately after one of the infrequent rainfalls and the afternoon sea breeze also contains appreciable humidity levels. However, these high humidity levels are usually of short duration and the diurnal average humidity level is usually below 15%.

B5.4 Radioactivity

The irregular distribution of the uraniferous material gives rise to a highly irregular radioactivity pattern for the area. It is complicated by the fact that two major radiochemical parameters affect the actual measurement of the radiation.

- B5.4.1 Secular disequilibrium where the relative loss or gain of radioactive components in the ^{238}U decay chain leads to incorrect measurements;
- B5.4.2 Mineralogical characteristics, in particular variations in the uranium thorium ratio and the uranium potassium ratios that affect estimates of the uranium grade, present.

The degree of disequilibrium is generally not constant within a uranium deposit and is usually higher both where secondary minerals predominate and within the zone of fluctuation of, or above, the water-table. While Rössing falls into this category, it is buffered by the arid climate prevailing in the Namib Desert. An intermediate nucleate radon 222, the noble gas daughter product of radon 226, is particularly mobile in open environs such as fracture zones or weathered rock. Background environmental radon concentrations in areas away from the uraniferous Rössing deposit (example Swakopmund) vary between 25 to 50 becquerels per m^3 (Grundlingh *et al*, 1988).

The shales in the vicinity of the Rössing mine are generally very shallow (less than 25cm) and grey-ochre in colour, with a large proportion of coarse fragments and occasional calcium carbonate concretions.

B6 THE OPERATION

The orebody is contained in granite rock known as alaskite. This ore is recovered by open pit mining and involves the removal of a series of 15 metre high benches in the pit that is 3km long and 1km wide, to a depth of 450m. Rössing is a high tonnage, low-grade mine with a stripping ratio of 2,5:1. The mining sequence is conventional drill, blast and load operation using Gardner Denver 120 drills, P & H 2100 and Marian shovels and a fleet of Wabco and Euclid 170 ST haul trucks. The material is sent to the primary crushers or to a low-grade stockpile whilst waste goes to a separate dump. Ore is delivered to the primary crushers and then by conveyor to the coarse ore stockpile.

It passes through a series of crushers and screens until the particles are 14mm in diameter. This is referred to as fine ore and, after weighing, is stored in another stockpile. The grinding process involves the wet grinding of the crushed orebody by means of steel rods and reduces it further to slurry with the consistency of mud. The four-rod mills (4,3 metres in diameter) operate in parallel.

The metallurgical process is conventional acid leach with ion exchange solution concentration and solvent extraction purification followed by precipitation of ammonium diuranate and roasting to uranium oxide. The metallurgical plant also has a pyrite burning sulphuric acid producing plant.

B6.1 Leaching

A combined leach and oxidation process takes place in large mechanically agitated tanks. The uranium content of the pulped ore is oxidised by

manganese dioxide and dissolved by the action of sulphuric acid at elevated temperatures.

B6.2 Sand/Slime Separation

The product of leaching is a solution containing suspended sand and slime. Cyclones separate these components and the sand, after washing in rotoscopes to remove traces of solution, is pumped through pipes to a tailings disposal area.

B6.3 Thickening

Counter-current decantation thickeners wash the slimes from the previous stages. The clear uranium bearing solution (pregnant solution) overflows from the No.1 thickener while the washed slime is mixed with the sands and pumped to the tailings area.

B6.4 Continuous ion exchange (CIX)

The clear pregnant solution now comes into contact with beads of specially formulated resin. Ions containing uranium are absorbed onto the resin and are preferentially extracted from the solution. Beads are removed periodically to elution columns where a strong acid wash removes the uranium from the beads. The resulting eluate contains uranium solution.

B6.5 Solvent Extraction (SX)

The acidic eluate from the ion exchange plant is mixed with an organic solvent which takes up the uranium-bearing component. In a second stage the organic solution is mixed with a neutral aqueous ammonium