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 goal[2], 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 endeavours[5], 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 pitch-blend (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 Erzjebirge 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 Bergkrankheiden"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 mercurlism. 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 exerceant".[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 Bergkrankheid 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 Ühlig[40] (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 cancer [46].

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}uranium 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 x 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 x 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}Bd.[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 (U4+) 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 haemopoeitic 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 Argentine) 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 study[79] 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 $mJ.L.M^3$ (3×10^4 per WLM). 1 $mJ.L.M^3$ is equivalent to an effective dose if 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 connection 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. SO_2 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 - 19µ), mononuclear phagocytic cells formed in the haemopoeitic 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-dinucleutide 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 lisomes also contain peroxides 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, leucotrines, 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 isotope 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 life[125]. 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, SO_2, NO_2, 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 (helmintic in particular), drug reactions, and connective tissue diseases and malignancies.[130,131]

Eosinophils are bone-marrow derived phagocytes with secretary functions, and have membrane receptors for immunoglobulins and complement. They preferentially damage helmintic 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 FEV_1. Horn *et al* [133] (1975) confirmed the association between blood eosinophilia and air flow obstruction, whilst Durham and Kay[132] (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, FEV_1 (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 elasten and changes the elasten-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 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. 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 (FEV_1) 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 x 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 PEFR 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 SO_2 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's[152] 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 CO_2 and particulate matter. Formaldehyde has been linked to respiratory allergies and NO_2 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, SO_2, NO_2, and exhaust particles.[172] The allergenicity of type II pollution was investigated and it was shown that NO_2 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 FEV_1 or PEFR) 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 silicoses 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 FEV_1 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 FEV_1 is still

75% of predicted, the subsequent rate of decline of FEV_1 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 FEV_1 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 anthofhyllit 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 tuberculosis[204]. 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. Baghi[208] 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 spiromatic 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 Abramovich[213] 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]

FEV_1 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-workers[230] 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 Hepplestone[203] 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 carcinogenestic 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 Musk[8] (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 crystaline 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 that 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 Peto[253] "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 females[245]. 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 medium 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 Doll[253] 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 *et al.* [1981] Lundin *et al.* [1971]	821§ (median = 430)	62,556	185	38.4	482
Uranium Czechoslovakia#	Placek *et al.* [1983]# Kunz *et al.* [1978]	289**	56,955	211	42.7	496
Uranium Ontario, Canada	Muller *et al.* [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 *et al.* [1985]	--##	37.730##	104	24.38##	427##
Uranium Saskatchewan, Canada	Howe *et al.* [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 *et al.* [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 *et al.* [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 *et al.* [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 form 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 x 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, Agius[221] 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 1987[267] and again in 1994.[268] Recommendations for standardisation from the European Respiratory Society (ERS)[270] and British Thoracic Society[271] (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 (FEV_1).[261,273]

Measuring FEV_1 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/FEV_1) are 3,5% of reading or 70ml (whichever is greatest) and the mechanical syringe must be accurate within approximately 24ml for FVC and FEV_1.[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 in 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]

FEV_1 is extensively used as an indicator of airflow obstruction. It has a good index of reproducibility. The FEV_1 can be standardised for the VC in the relation $FEV_1x100/FVC=FEV_1\%$. Normally 75% of the FVC is exhaled in one second and expressed as $FEV_1/FVCx100=75\%$. Some researchers and clinicians prefer to express the FEV_1 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%. FEV_1 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 PEFR.[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

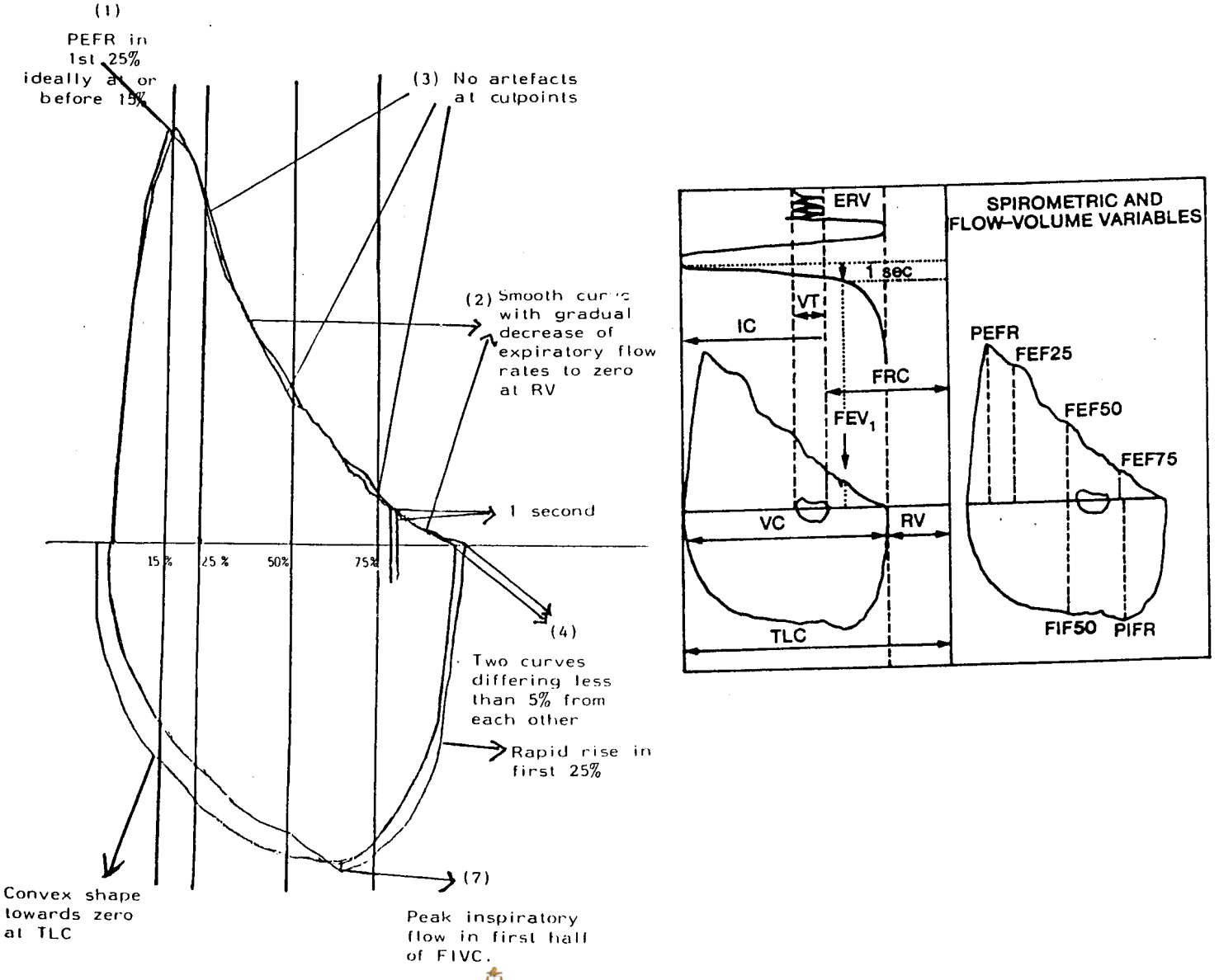
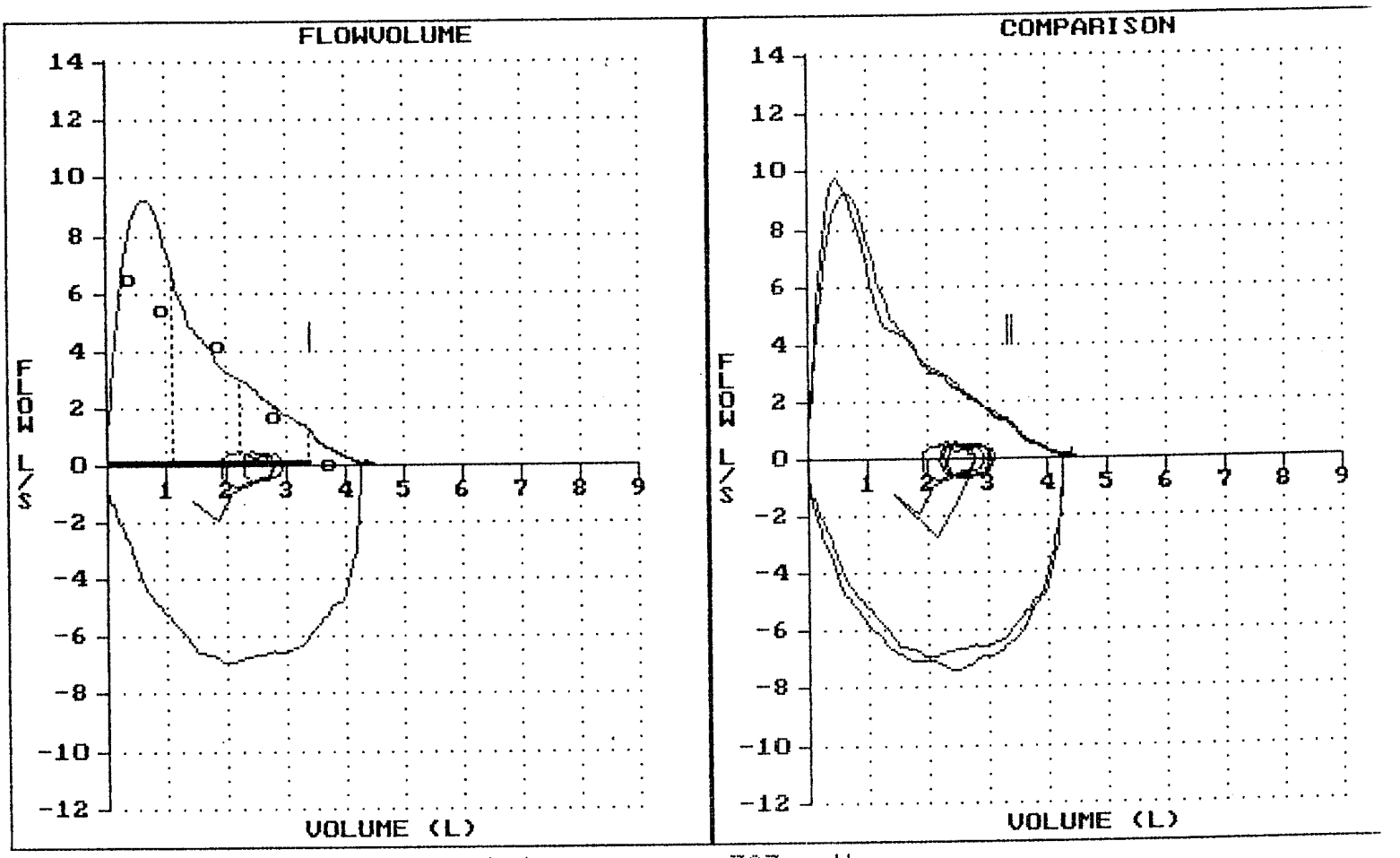


FIGURE 2 – STANDARD RÖSSING LUNG FUNCTION TEST

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 ATTEMP

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 curves[344] 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 (Vmax) 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, FEF_{25}, FEF_{50}, and FEF_{75} 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 (FEF_{50} and FEF_{75}) 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 FEV_1 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 FEV_1, 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 FEV_1, 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 Joubert[313] 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 ATS[272] is not specific in it's recommendation, the official

statement (1993) of the ERS[270] 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 FEV_1 should be multiplied by a factor of 0,87 or to subtract 0,45 liter from FEV_1 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 FEV_1 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, FEV_1 and FEV_1% = 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 FEV_1). 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 FEV_1 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 FEV_1 of more than 50ml per year suggests accelerated progression of disease. The FEV_1 value that is reduced relative to FVC (FEV%) usually points towards an obstructive abnormality. If FEV_1 and FVC are both reduced (with a normal FEV_1%), 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 (SO_2, NOX, CO, O_3, 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 that 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:

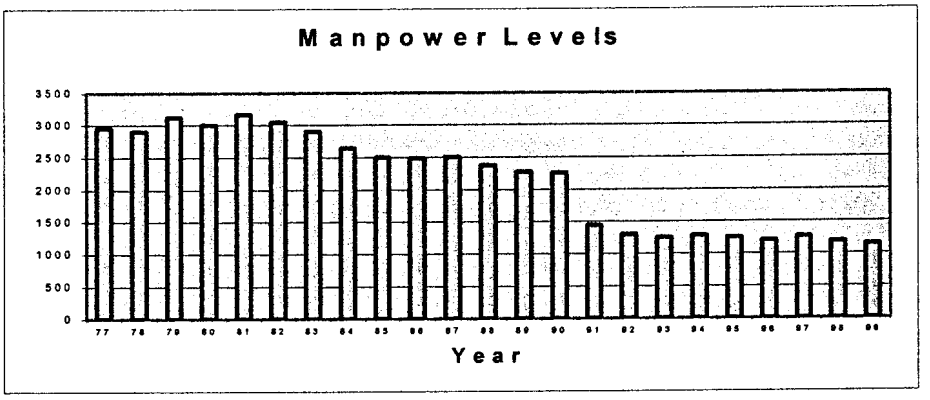
* Aged 35 years and more;
* Twenty-three years of continuous or uninterrupted service;
* Also included were workers who worked for more than 23 years and who had left the employ of the mine.

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

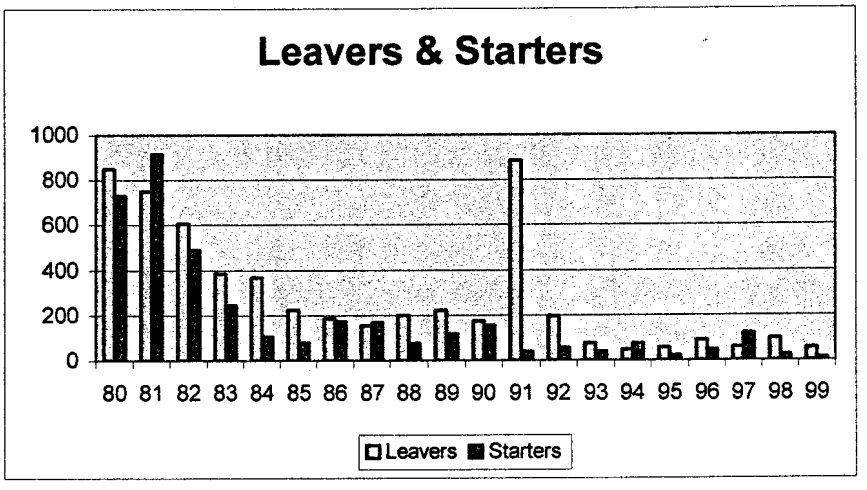
The manning levels at Rössing have varied considerably over the past twenty years. Total manning levels are best reflected by the following graph.

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 H_2O 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 FEV_1. 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 FEV_1 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.
* Brochodilatation 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% FEV_1 from baseline
  - > 10% in FEF_{50} and FEF_{75}

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, FEV_1, peak expiratory flow, FEF_{25-75}, FEF_{25}, FEF_{50}, FEF_{75} 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 FEV_1 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: FVC_1, FEV_1, FEF_{25}, FEF_{50}, FEF_{75}, PEFR, FIVC, and PIFR.
* The manoeuvre with the largest sum of the FVC + FEV_1 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 (spirostat 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 FEF_{50} for the flowscan and the PEFR for the spirostat.

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		**FEF_{50} or FEF_{75} < 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		**FEF_{50} and FEF_{75} < 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		**FEF_{50} and FEF_{75} < 75% of predicted, reduced FVC and/or FEV_1 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. Uranimite is the dominant primary radioactive material and is included in quartz, feldspar and biotite. The average ore grade is 0,035% with uranimite 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.

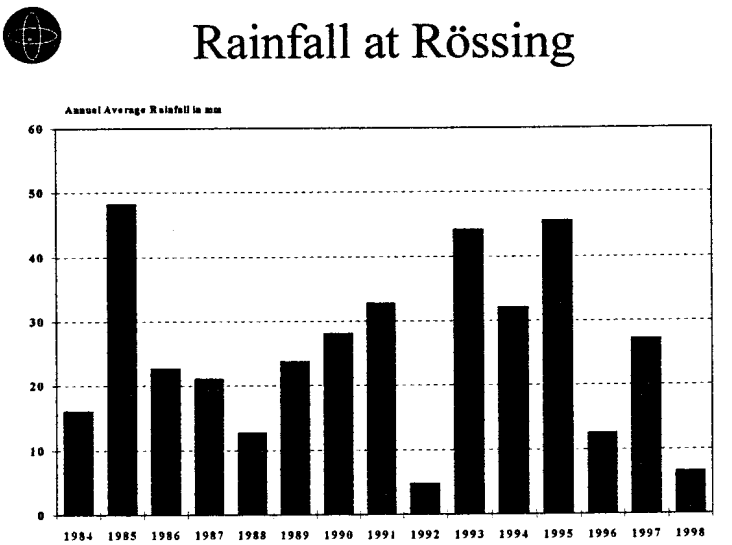
4.1.14 Environmental Characterisation

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.

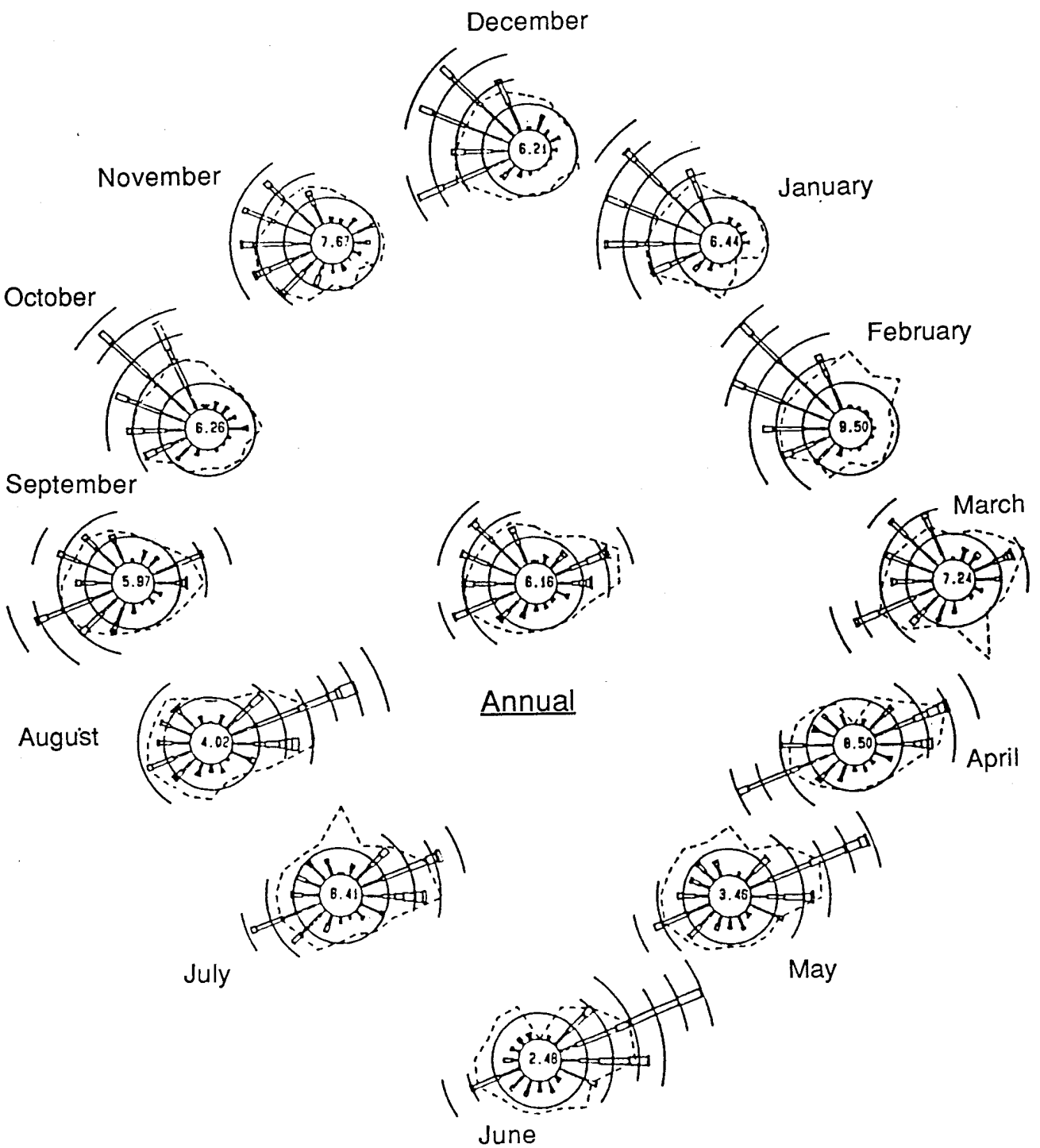
4.1.15 Meteorological Monitoring

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



Annual and Monthly Windroses
Rossing Uranium



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 (terrestial 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	1.65x10^{-2} Sv				
2.48	.052	.0008	.160	1.2x10^{-4}	.0026	7.63
1.39	.250	.0041	.562	5.1x10^{-5}	.0091	3.13
1.52	.334	.0055	.585	4.4x10^{-5}	.0095	2.66
1.39	.028	.0005	.061	5.1x10^{-5}	.0010	3.06
1.41	.640	.0105	1.598	5.8x10^{-5}	.026	3.52
.45	.676	.0112	1.834	2.0x10^{-5}	.030	1.22
Average Individual Dose = 2.00			**Average Individual Risk = 3.2x10^{-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 radionucleid 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/m^3 (MPL = Maximum Permissable Levels – 0.5mg/m^3

	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 arithmatic 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 compulsary 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.