Recommendation of a classification system and occupational exposure limits for chemical carcinogens

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Preface

This mini-dissertation is submitted in partial fulfilment of the requirements for the degree *Magister Scientiae in Occupational Hygiene* at the Potchefstroom Campus of the North-West University. The same reference style will be used throughout the mini dissertation to ensure uniformity. The accredited journal chosen to use as guideline for referencing was the *Annals of Occupational Hygiene*. The journal requires text referencing to be in the form of Jones (1995), or Jones and Brown (1995), or Jones *et al.* (1995) if the number of authors of a publication is more than two. The list of references should be in alphabetical order by the name of the first author, whilst the abbreviation and punctuation should be according to the Vancouver Style.

It was decided to use the article format for the purpose of this study. Chapter one is the introductory chapter with the aims and objectives for the study. Chapter two is the literature study giving a detailed discussion of all the aspects that may play a role in influencing the study's outcomes as well describing the theory behind chemical carcinogens and the acquisition of data for the study. Chapter three is the article written according to the format required by the *Annals of Occupational Hygiene*. Chapter Four is the concluding chapter containing a summary and conclusion as well as recommendations for future studies.

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Author's Contribution

This study was planned and executed by a team of co-authors. The contribution of each co-author is listed in the table below:

Name	**Contribution**
Ms. S Blake	• Protocol and planning of the study; • Literature searches, interpretation of data and writing of article.
Prof. JL du Plessis (Supervisor)	• Supervisor • Assisted with approval of protocol, interpretation of results and documentation of the study; • Gave guidance with regard to scientific aspects of the study.
Mr. SJL Linde (Co-supervisor)	• Co-supervisor • Assisted with designing and planning of the study, approval of protocol, interpretation of results and documentation of the study.

The following is a statement from the co-authors confirming their role in this study:

I declare that I have approved this mini-dissertation and that my role in the study, as indicated in the table above, is representative of my actual contribution. I hereby give my consent that it may be published as part of S Blake's *Magister Scientiae in Occupational Hygiene* mini-dissertation.

Ms. S Blake	Prof. JL du Plessis (Supervisor)	Mr. SJL Linde (Co-supervisor)

Abstract

Title: Recommendation of a classification system and occupational exposure limits for chemical carcinogens

Introduction: An increased number of occupational cancers reported annually can be attributed to workers being exposed to hazardous chemical substances (HCSs) in their workplace. Carcinogen classification systems such as the International Agency for Research on Cancer (IARC), the American Conference of Governmental Industrial Hygienists (ACGIH), Environmental Protection Agency (EPA), National Toxicology Programme (NTP) and the European Union (EU) help to identify the carcinogenic risk associated with certain HCSs with the help of data collected from scientific research programmes. Incorporation of such a system into South African legislation may reduce the number of occupational cancers developed by the South African workforce.

Aim and objectives: The Aims and objectives are as follows: (1) to evaluate existing carcinogen classification systems of developed countries in order to establish which system or combination of systems is the best option to use for establishing a carcinogen classification system to be recommended for incorporation into South African occupational health legislation; (2) To identify hazardous chemical substances (HCSs) listed in the carcinogen classification systems of developed countries and to compare them with the HCSs listed in the Regulations for Hazardous Chemical Substances (RHCS) and the Mine Health and Safety Regulations (MHSR) that should be classified as carcinogenic; and (3) to compare the occupational exposure limits (OELs) of above mentioned carcinogens as listed by developed countries or organisations with the OELs listed in the RHCS and the MHSR.

Methods: A carcinogen classification system was identified by making use of set criteria points. Thereafter, the HCSs that were considered human carcinogens were identified in the RHCS and the MHSR using the selected carcinogen classification's notations. The OELs listed in the RHCS and MHSR for these HCSs were then compared to the OELs listed for the same HCS's OELs within ten developed countries/jurisdictions with the help of the geometric means method. In addition the interval method was used for the comparison of the number of MHSR OELs that are similar, lower or higher than that of the RHCS.

Results: The carcinogen classification system with the highest score was the IARC. Therefore, this study used the HCSs classified as human carcinogens by the IARC. The RHCS contains two tables that list OELs for HCSs namely Table I and Table II. The total

number of HCSs listed in the RHCS (Table I = 22 HCS and Table II = 55 HCS) was 77. It was found that the country/jurisdiction with the lowest geometric mean when Tables I and II were combined was Finland with a geometric mean of 0.300. It was found that there is no statistical significant difference (p = 0.138) between the geometric means of the RHCS's Table I and II. The database for the MHSR only contained 76 substances listed as carcinogenic by the IARC. Finland also had the lowest geometric mean with a value of 0.475. Since the geometric mean for Finland in both the analysis for the RHCS and MHSR was far below 1, it indicated that the OELs contained in this list was the lowest of all the developed countries included in this study. When the interval method was used to determine the number of MHSR OELs for carcinogens that are similar, lower or higher than the RHCS OELs it was found that 64.5% of the RHCS OELs are similar to the MHSR and 34.2% of the MHSR OELs were lower than the RHCS OELs.

Conclusion: The carcinogen classification reasonably practicable for use within South African occupational health legislation is the IARC's carcinogen classification, which classified a total of 481 substances of which the RHCS contained 77 substances and the MHSR contained 76 substances classified as carcinogenic to humans (Group 1, Group 2A and Group 2B). It was found that South African OELs are at a higher level than the OELs listed by some developed countries. The geometric mean values calculated for most developed countries were below 1 with the exception of OSHA in the RHCS. In the MHSR it was found that OSHA, Australia and the United Kingdom had a geometric mean >1. When the RHCS's OELs were compared to the MHSR a geometric mean of 0.651 was calculated that confirmed the overall level at which OELs of the MHSR are set were at a lower level. Using the lowest available OEL from all countries/jurisdictions will provide protection to the workforce in South Africa against the development of occupational cancer.

Key words: Carcinogen, Classification, South African occupational health legislation, Occupational exposure limits, Geometric means method, Interval method.

Opsomming

Titel: Aanbeveling van ‘n klassifikasiestelsel en beroepsblootstellingsdrempels vir chemiese karsinogene

Inleiding: ‘n Toename in die aantal beroepskankers wat jaarliks gerapporteer word kan toegeskryf word aan werkers wat blootgestel word aan gevaarlike chemise substanse (GCS) in die werksplek. Karsinogeen klassifikasiestelsels soos die Internasionale Agentskap vir Navorsing op Kanker (IANK), die Amerikaanse Konferensie van Regerings Industriële Higiëniste (AKRIH), Omgewing Beskermings Agentskap (OBA), Nasionale Toksikologie Program (NTP) en die Europese Unie (EU) help met die identifisering van die kanker risiko wat deur sekere GCSe ingehou word met behulp van die insameling van data deur wetenskaplike navorsingsprogramme. Inkorporering van ‘n soortgelyke sisteem kan die aantal beroepskankers verlaag wat deur die Suid Aftikaanse werksmag ontwikkel word.

Doelstelling en doelwitte: Die doel van die studie was as volg: (1) Om bestaande karsinogeen klassifikasie stelsels van ontwikkelde lande te evalueer en om te bevestig watter stelsel of kombinasie van stelsels aanbeveel kan word vir inkorperering in Suid Afrikaanse beroepswetgewing; (2) Om die GCS wat as karsinogene in karsinogeen klassifikasie stelsels van ontwikkelde lande gelys is te vergelyk met die GCS wat in die Regulasies vir Gevaarlike Chemiese Substans (RGCS) en Die Myn Gesondheid en Veiligheids Wet Regulasie 22.9 (MGVR) gelys is en as karsinogenies geklassifiseer moet word; en (3) om die beroepsblootstellingsdrempel (BBD) van bogenoemde karsinogene gelys in ontwikkelde lande of organisasies te vergelyk met die BBDs gelys in die RCSR en MGVR.

Metodes: ‘n Karsinogeen klassifikasie stelsel is geïdentifiseer deur gebruik te maak van vasgestelde kriteria punte. Die GCS wat as menslike karsinogene geag was is in die RCSR en MGVR deur die geselekteerde karsinogeen klassifikasie se notasies geïdentifiseer. Die BBD wat in die RCSR en MGVR gelys is vir hierdie GCS was met tien ontwikkelde lande se BBD’s vir dieselfde GCS’e vergelyk met behulp van die meetkundige gemiddeld metode. Bykomend is daar gebruik gemaak van die intervalmetode om die hoeveelheid GCS in die MGVR wat dieselfde, laer of hoër BBD’s as die RCSR gehad het te vergelyk.

Resultate: Die karsinogeen klassifikasiestelsel met die hoogste telling was die IANK en is gebruik om GCS geklassifiseer as menslike karsinogene deur die IANK te identifiseer. Die RCSR bevat twee tabelle met BBD waardes naamlik Tabel I en Tabel II. Die totale aantal

GCS in die RCSR gelys as karsinogene (Tabel I = 22 en Tabel II = 55) was 77. Daar was bevind dat die land/jurisdiksie met die laagste meetkundige gemiddeld wanneer Tabel I en II gekombineer was, Finland is met ‘n meetkundige gemiddeld van 0.300. Daar is bevind dat daar geen statisties betekenisvolle verskil (p = 0.138) tussen Tabel I en Tabel II van die RCSR is nie. Die databasis van die MGVR het 74 GCS bevat wat gelys is as karsinogenies deur die IANK. Finland het weereens die laagste meetkundige gemiddeld gehad met ‘n waarde van 0.475. Aangesien die meetkundige gemiddeld vir Finland in beide die analise vir die RCSR en MGVR ver onder 1 was, het dit aangetoon dat die BBDs vervat in die lys die laagste was van all die ontwikkelde lande ingesluit in die studie. Toe die intervalmetode gebruik was om te bepaal hoeveel van die MCVR BBD waardes dieselfde, laer of hoër as die RCSR BBD waardes, is bevind dat 64.5% van die RCSR se BBD waardes dieselfde was as die MGCR en 34.2% van die MGVR BBD waardes was laer as die RCSR BBD waardes.

Samevatting: Die karsinogeen klassifikasiestelsel wat redelikerwys uitvoerbaar is vir gebruik in Suid Afrikaanse beroepsgesondheid wetgewing is die IANK se karsinogeen klassifikasie stelsel wat ‘n total van 481 substanse as karsinogenies klassifiseer waarvan die RCSR 77 substanse en die MGVR 76 substanse bevat wat as karsinogenies vir die mens geklassifiseer is (Groep 1, Groep 2A en Groep 2B). Dis dit was bevind dat meeste van die lande ingesluit in hierdie studie ‘n meetkundige gemiddeld <1 gehad het met die uitsondering van die Beroepsveiligheid en Gesondheids Administrasie (BGA) in die RCSR. In die MGVR was bevind dat BGA, Australië and the Verenigde Koninkryk ‘n meetkundige gemiddeld van >1 gehad het. ‘n Vergelyking tussen die RCSR en MGVR het n meetkundige gemiddeld van 0.651 opgelewer wat bevestig dat die BBD waardes gelys in die MGVR teen ‘n laer vlak as die RCSR opgestel is. Die gebruik van die laagste beskikbare BBD uit alle ontwikkelde lande/jurisdiksies sal die nodige beskerming aan die arbeidsmag in Suid Afrika bied teen die ontwikkeling van beroepskankers.

Sleutelterme: Karsinogeen, Klassifikasie, Suid Afrikaanse beroepsgesondheid wetgewing, Beroepsblootstellingsdempel, Meetkundige gemiddeld metode, Intervalmetode.

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Symbols and units

%	Percentage
^{o} C	Degrees Celsius
mg/m^3	Milligrams per cubic meter
ppm	Parts per million

Abbreviations

ACGIH	American Conference of Governmental Industrial Hygienists
CL or C	Ceiling Limit
DNEL	Derived no-effect level
EPA	Environmental Protection Agency
EU	European Union
GHS	Global Harmonized System of classification and labelling of chemicals
HCS	Hazardous Chemical Substance
RHCS	Hazardous Chemical Substance Regulations
IARC	International Agency for Research on Cancer
MHS Act	Mine Health and Safety Act
MHSR	Mine Health and Safety Regulations
NCGIH	National Conference of Governmental Industrial Hygienists
NIOSH	National Institute for Occupational Safety and Health
NOAEL	No Observed Adverse Effect Level
NOEL	No Observed Effect Level
NTP	National Toxicology Programme
OEL	Occupational Exposure Limit
OEL-CL	Occupational Exposure Limit-Control limit
OEL-RL	Occupational Exposure Limit-Recommended limit
OHS Act	Occupational Health and Safety Act
OSHA	Occupational Safety and Health Administration

REACH	Regulation on Registration, Evaluation, Authorisation and Restriction of Chemicals
RoC	Report on Carcinogens
SCOEL	Scientific Committee on Occupational Exposure Limits
STEL	Short Term Exposure Limit
Table I	Table 1 of the Hazardous Chemical Substance Regulations
Table II	Table 2 of the Hazardous Chemical Substance Regulations
TLV	Threshold Limit Value
TWA	Time Weighted Average
UF	Uncertainty Factor
UR	Unit Risk
USA	United States of America
WHO	World Health Organisation

Chapter 1

Introduction

1.1 Introduction

South Africa is an economically developing country and one of the major problems faced by developing countries is an increase in cancer cases reported (Creamer, 2010; Jemal *et al.*, 2011). This increase can be attributed to a variety of factors, the most important being the adoption of a more westernised lifestyle. However, the types of occupations followed may also be an important factor. The nature of the occupations available in the industrial and mining sector causes exposure to carcinogens which can cause disability or even death (Jemal *et al.*, 2011; Ding *et al.*, 2014). A recent study conducted in Canada found that occupational cancers are one of the leading causes of work-related deaths but that the cause of these deaths often goes unreported and, therefore, is not always attributed to occupational exposure (Bianco and Demers, 2013). The type of cancer developed by a worker depends on the frequency and level of exposure to a certain carcinogen. The development of cancer cannot only be attributed to the inheritability of the cancers concerned, but some of the cancers developed are avoidable when considering epidemiologic evidence (Brawley, 2011). During a study conducted by Jemal *et al.* (2011), it was found that 56% of reported cancer cases and 64% of deaths from cancer were all from economically developing countries, but that these percentages were significantly higher in economically developed countries. Worldwide 2.3 million deaths occur annually due to occupational injuries and work-related diseases, with 32% of these deaths being attributed to work-related cancers (Takala *et al.*, 2014). Worldwide 10% of reported lung cancers are as a result of exposure to carcinogens in the work environment with 70% of all occupational cancers accounted for by lung cancer. Leukaemia and lung cancer represent the occupational cancers that are considered a global burden (Yang, 2011). The list of hazardous chemical substances (HCSs) every country considers having the potential of causing occupational cancer differs since the legislation and industries in each country differ (Carey *et al*., 2013).

A classification system for HCSs used in the workplace that may lead to the development of cancer was established and incorporated into environmental and occupational health regulations (Paustenbach *et al.*, 2011). Currently there are several agencies with a system for classifying the carcinogenic potential of HCSs in developed countries, namely the International Agency for Research on Cancer (IARC), the National Toxicology Programme (NTP) and the Environmental Protection Agency (EPA) (which are both based in the USA) to only name a few, but none in South Africa (ACS, 2013).

The data gathered from international sources is used as a basis for classification of a HCS as a confirmed or known human carcinogen in IARC and EU systems. While classification systems such as the American Conference of Governmental Industrial Hygienists (ACGIH), EPA and NTP mainly focus their classifications of confirmed human carcinogen or known human carcinogen on data gathered from their own research programmes. In all systems sufficient evidence needs to suggest that a HCS has the potential to cause cancer in humans and be backed by quantitative exposure data (Bolt and Huici-Montagud, 2008; Paustenbach *et al.*, 2011).

To control the exposure of a worker to a HCS (which may also be considered to be carcinogenic) an Occupational Exposure Limit (OEL) is specified. An OEL can be defined as the maximum concentration to which a worker can be exposed to a HCS without experiencing adverse health effects (Ding *et al*., 2011; Paustenbach, 2011; Ding *et al*., 2014).

Two Acts govern South African occupational health, namely the Occupational Health and Safety (OHS) Act (No. 85 of 1993) and its Regulations applicable to general industries and the Mine Health and Safety (MHS) Act (No. 29 of 1996) applicable to the mining industry. The Regulations for Hazardous Chemical Substances (RHCS) of the OHS Act state OELs in Tables 1 and 2. Section 22.9 of the MHS Act's Regulations (MHSR) contain OELs applicable to the mining industry (South African Department of Labour, 1995; South African Department of Minerals and Resources, 1996). Henceforth the acronym RHCS will refer to the Regulations for Hazardous Chemical Substances of the OHS Act and the acronym MHSR will refer to Section 22.9 of the MHS Act's Regulations.

In the RHCS and MHSR there is no notation to indicate if a HCS is a carcinogen or not. This makes the task of protecting workers against exposure to carcinogens more challenging. Currently there is no system for classifying a HCS as carcinogenic in South Africa. These shortcomings need to be addressed. The importance of assessing existing systems for the classification of carcinogens being used by developed countries is pivotal in deciding whether to implement one of these existing systems or to use a combination of these systems in South African legislation. The implementation of such a carcinogen system must be reasonably practicable to adopt and use within the mining and industrial sectors in South Africa. Furthermore, since the RHCS is 20 years old and the OELs in MHSR last updated in 2006, it would be of interest to compare OELs for substances that must be classified as carcinogenic to those of developed countries. A previous study found that as OELs are

revised, these exposure limits tend to decrease which may also be a reason for the OELs being used in South Africa to be outdated and higher than those of other developing countries (Viljoen, 2012).

Cancer has a latency period after which it develops which means it only develops years after initial exposure to a carcinogenic HCS and the data collected surrounding exposure and cancer development, therefore, also takes years (Blair *et al.*, 2011). This causes insufficient data surrounding some carcinogenic HCSs and the models used to determine the carcinogenic risk of HCSs (Bolt and Huici-Montagud, 2008). Agencies such as the ACGIH apply a practical threshold to carcinogens since the exact dose which will trigger cancer development is not known (Paustenbach, 2011), but this concept factors in the mechanisms humans naturally have in place to combat naturally occurring carcinogens in our diets and the assumption that these mechanisms may play the same role for industrial chemicals. Whether there truly is a safe level for exposure to carcinogenic HCSs is still unclear.

In conclusion, evaluating existing carcinogen classification systems to identify a carcinogen classification system that will be applicable for use within the RHCS and MHSR will improve South African legislation and facilitate better control of worker exposure to carcinogens in the working environment. Comparing the overall level at which South African OELs for these carcinogens are set compared to developed countries' OELs will also help to guide the setting of future OELs for carcinogenic HCSs in the RHCS and MHSR. This comparison is done with the help of the geometric means method which was first applied by Hansson (1998) and is regarded as the best indicator of the difference between the OELs. A geometric mean equal to 1 indicates that there is no difference in the OELs for a substance on both lists. A geometric mean below 1 indicates that an overall lower level of OELs is present on the list being compared whilst a geometric mean higher than 1 indicates an overall higher level of OELs (Schenk *et al*., 2008; Viljoen, 2012).

1.2 Aims and objectives

The aims of this study are:

1. To evaluate existing carcinogen classification systems of developed countries in order to establish which system or combination of the systems is the best option to use for establishing a carcinogen classification system to be recommended for incorporation into South African occupational health legislation.

2. To identify HCSs listed in the carcinogen classification systems of developed countries and to compare them with the HCSs listed in the RHCS and the MHSR that should be classified as carcinogenic.
3. To compare the OELs of above mentioned carcinogens as listed by developed countries or organisations with the OELs listed in the RHCS and the MHSR.

The specific objectives of this study are:

1. To compare systematically the carcinogen classification systems used by the ACGIH, IARC, EU, NTP and US EPA with the help of criteria points to establish which system or combination of systems will be reasonably practicable to incorporate in developing a carcinogen classification system for the RHCS and the MHSR.
2. To assign a notation to indicate the carcinogenic risk of HCSs identified through comparison of the above mentioned carcinogen classification system's listed HCSs with those substances listed in the RHCS and the MHSR.
3. To establish whether the levels at which OELs set by the RHCS and the MHSR for HCSs differ significantly from the OELs set by developed countries and/or organisations for HCSs classified as carcinogens in the RHCS and the MHSR by using the geometric means method.

1.3 Hypothesis

The OELs set by developed countries and/or organisations for carcinogenic HCSs are at a lower level with geometric mean values <1 than the OELs set at present in both the RHCS and MHSR.

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Chapter 2

Literature Study

2.1 Introduction

During the course of an adult's life most of their waking hours will be spent at work. In the working population many hazards are faced on a daily basis including exposure to chemicals, biological agents and physical factors that may lead to injury. In addition to injuries, more than a 100 occupational diseases have been identified which include respiratory diseases, cardiovascular diseases, neurotoxic diseases, skin diseases and cancer (Concha-Barrientos *et al.*, 2004). Exposure to chemicals is a major concern since some hazardous chemical substances (HCSs) can lead to the development of occupational cancer and are known as chemical carcinogens. Cancer is a multistage process with estimates suggesting that 70-90% of all cancers developed by humans can be linked to environmental factors, diet and behavioural factors (McCormack and Schüz, 2012; Klaunig, 2013). Since Africa has shown the fastest growth in population and urbanisation compared to developed countries, along with this growth, the number of preventable diseases which includes cancer has also increased. Environmental and occupational exposures has caused the cancer burden in Africa to increase since the conditions in African countries allow unnecessarily high exposures to carcinogenic HCSs (McCormack and Schüz, 2012). In South Africa the most common cancer developed is lung cancer and this can be linked with the industrial and mining activities found in the country. There are control measures and exposure prevention strategies in the workplace but since the legislation has not been updated in the past few years, a risk for workers to develop occupational diseases, such as cancer arises (McCormack and Schüz, 2012).

This literature study will focus on cancer as disease, cancer developed as a result of occupational exposure to carcinogenic HCSs, agencies that strive to identify and classify the HCSs in the occupational setting responsible for cancer development, how OELs are established for carcinogens and what provisions are made for carcinogens in South African occupational health and safety legislation.

2.2 Cancer as disease

The term cancer is used for a large group of diseases that affect any part of the body and cause abnormal cell growth which can also spread to an adjoining part of the body or even other organs (WHO, 2015). This abnormal growth of cells is referred to as a neoplastic lesion and when a lesion is visible as a result of swelling the term tumour is used. When the cell

growth spreads beyond cellular growth limits or to other organs in the body this process is referred to as metastasis (Klaunig, 2013).

When neoplastic lesions progress to the tumour phase, two distinct types can be distinguished namely, malignant tumours and benign tumours. Malignant tumours refer to tumours that have an invasive growth pattern which is capable of metastasis to other organs of tissues. Benign tumours show expansive growth at slow rates without invading other tissues or organs (Klaunig, 2013).

Globally the most common cancers reported in 2000 were lung cancer (12.3%), breast cancer (10.4%) and colon and rectal cancers (9.4%). The cancer deaths reported globally state that 17.8% of the total cancer deaths was as a result of lung cancer, 10.4% were from stomach cancers and 8.8% were from liver cancers (Parkin, 2001).

Cancer can be caused by multiple factors that are usually a combination of genetic and external factors (Stewart, 2008; Environmental Chemistry, Toxicology and Ecotoxicology Resources, 2010). Cancer can be characterised by modified gene expression, mutation, irregular cell growth and cell proliferation (Klaunig, 2013). Only a small fraction of cells that mutate result in cancer formation. This can be explained by physiological systems that regulate cell growth and the body's immune system which recognises mutated cells and destroys them. Several different activated oncogenes are simultaneously required to cause cancer since cancer cells have less survival capacity than normal cells and die easily. Oncogenes are abnormal genes that control cell growth and mitosis (Hall, 2011). Cancer cells are considered immortal since they can reproduce indefinitely when not opposed by physiological systems and this may be as a result of the presence of an enzyme called telomerase. Telomerase is the enzyme that adds the telomere to the end of chromosomal DNA to protect the DNA against rearrangement and degradation. Normal somatic cells lack telomerase activity. Therefore, as a normal somatic cell reproduces the telomere shortens by 50-nucleotide segments and this shortening causes chromosomes instability which leads to cell death (Garrett and Grisham, 2010). This does not happen in cancer cells and the telomere stays intact avoiding cell death.

Carcinogenesis is a process with multiple definable stages which includes an initiation stage, promotion stage and progression stage. Initiation is the first stage and is a process that is caused by chemical or physical agents which cause genetic changes such as mutation and deletions in cellular DNA (Environmental Chemistry, Toxicology and Ecotoxicology Resources, 2010). These substances are also referred to as initiators or initiating agents.

This stage is non-reversible. In order for mutations and deletions to occur indirect-acting genotoxic compounds need to be activated metabolically so that these carcinogens can bind to the nuclear DNA of the cell. If these inappropriate base pairings and mutations are not repaired they are replicated in the new cells during DNA synthesis in the cell cycle and lead to the development of cancer. Only one replication of this mutated cell is enough to ensure the mutations are passed on to the next generation of cells. Genotoxic substances interact with nuclear DNA and cause damage to the nuclear DNA (Klaunig, 2013). Complete carcinogens have genotoxic properties and can induce all three stages of the carcinogenesis process (Greim and Snyder, 2009; Klaunig, 2013). Genotoxic carcinogens can become complete carcinogens at high doses and/or repeated exposures which means they progress through all the stages of the cancer process (Klaunig, 2013).

Promotion is the second stage in the carcinogenesis process and is caused by endogenous and exogenous cell growth stimulation. This is achieved through several mechanisms that cause changes in gene expression which result in sustained cell proliferation (Klaunig, 2013). This can be attributed to wounding and inflammation present at the site where the neoplastic lesion is forming, the blood flow to this area increases which promotes growth of the neoplastic lesion (Vincent and Gatenby, 2008; Venkatesh *et al.*, 2015). Chemical agents that function at this stage of carcinogenesis are referred to as tumour promotors. Sustained cell proliferation can be as a result of increases in cell proliferation and/or inhibition of apoptosis. Modulation of gene expression occurs through receptor or non-receptor-mediated processes (Greim and Snyder, 2009). Non-genotoxic carcinogens are substances that do not cause cancer as a result of damage or binding directly to the nuclear DNA but follow other mechanisms that lead to cancer formation (Klaunig, 2013). These substances function in the promotion stage and the exposure needs to be continued above a certain dose to induce cell proliferation. Promotion is a reversible process which means that as soon as the carcinogen causing agent is removed, the cell will return to the normal state. Carcinogens of the promotion stage have been shown to have organ specific effects, which means if the tumour promotor is for skin, it will not be a tumour promoter for other tissues (Klaunig, 2013).

Progression is the final stage in carcinogenesis where benign cell growth is converted into malignant or cancerous cell growth. Increased DNA synthesis in cell proliferation causes added genotoxic events which in turn causes extra DNA damage including chromosomal damage such as translocations and other abnormalities. These cells outgrow the normal surrounding cells and use more nutrients than normal cells which leads to the starvation of

normal cells. Carcinogenic substances in this final stage tend to be genotoxic and the progression stage is also irreversible (Klaunig, 2013).

2.3 Occupational cancer

Occupational cancers are cancers that develop as a direct result of exposure to carcinogenic substances or chemicals in the completion of a normal work day. A HCS is defined as a chemical carcinogen when it is capable of inducing either or both malignant and benign tumours (Klaunig, 2013). The occupational settings where these carcinogens are most frequently released include the manufacturing process and the products produced from of these processes (Coggon, 1999). These cancers are, however, avoidable in principle with the implementation of appropriate exposure control strategies (Brawley, 2011). Although most countries have implemented control strategies for carcinogenic exposure and the number of occupational cancers developed worldwide have been reduced, the overall impact has not been well documented (Blair *et al.*, 2011). The focus of this study is not to discuss all occupational cancers in detail but rather to focus attention on the challenges faced by legislation to protect the work force against preventable exposure to carcinogens.

There are two types of HCS that can cause cancer to develop after exposure, namely genotoxic substances and non-genotoxic substances. Genotoxic substances, e.g. vinyl acetate, interact with the nuclear DNA of a cell and cause unrepaired DNA damage that is transferred to the next generation of cells. These substances can be further divided into two categories namely: direct-acting carcinogens (do not require metabolic activation) and indirect-acting carcinogens (requires metabolic activation) (Klaunig, 2013). For some genotoxic carcinogens a practical threshold for exposure can be determined whilst others have insufficient evidence to determine a safe threshold for exposure which will be discussed further in Section 2.6.2 of this chapter. Non-genotoxic substances, e.g. 1,4-dioxane, cause cancer through mechanisms that do not include direct binding, damage and interaction with the nuclear DNA of cells (not even the metabolites of these substances). For these substances a dose-response relationship can be used to determine a No-Observed-Adverse-Effect-Level (NOAEL) (Bolt and Huici-Montagud, 2008; Klaunig, 2013). This study, however, not only focuses on one type of chemical carcinogen but on all HCS currently classified as carcinogens to humans.

The major cause of death in the workplace worldwide is cancer developed as a result exposure in the work environment. According to the latest numbers on cancer cases reported the International Agency for Research on Cancer (IARC) estimated that 14 million new cancer cases are reported each year (Takala, 2015). The occupational cancer burden in Sub-Saharan Africa is greatly underestimated since a lack of cancer data systems exist compared to the systems found in developed countries (Morhason-Bello *et al.*, 2013). South Africa is a mineral rich country and mining of these minerals leads to the exposure of workers to HCSs including many carcinogenic HCSs. Since it is estimated that 6% of the South African are employed in the mining sector, better monitoring of exposure to carcinogenic HCS should be put in place (McCormick and Schüz, 2012). Two well documented HCSs that can be linked to the development of lung cancer are the mining of asbestos and the exposure to quartz/crystalline silica dust during mining practices since silica can be found in most rock types, especially sandstone and granite (McCormick and Schüz, 2012). Asbestosis and silicosis are chronic lung disease that can progress even after exposure is ceased and sufferers of these lung diseases have an increased risk of developing lung cancer (Wagner, 1997). Lung cancer as a result of asbestos exposure amounts to 47 000 deaths in the European Union (EU) alone. The quantity of asbestos used by a country or region also plays a role in the number of cancer cases developed as a result of asbestos exposure (Takala, 2015). Silicosis accounts for 18% of the occupational diseases reported in South African among gold-miners (McCormick and Schüz, 2012). Despite the knowledge surrounding asbestos and crystalline exposure, the number of cases reported as a result of workplace exposure persists.

2.4 Agencies with carcinogen classification systems

There are five agencies with a carcinogen classification system that are important to this study. Carcinogen classification systems use data acquired from scientific studies to classify the risk associated with a HCS and the role they play in the development of cancer. They will be discussed according to their origin as well as the notations they use to distinguish between the carcinogenic risk assigned to a chemical substance. These agencies are: the International Agency for Research in Cancer (IARC), the Environmental Protection Agency (EPA), the National Toxicology Programme (NTP), the American Conference of Governmental Industrial Hygienists (ACGIH) and the European Union (EU).

2.4.1 International Agency for Research on Cancer (IARC)

The IARC is the most prominent organisation in the collection of information, toxicological data and scientific data that play an important role in the classification and regulation of chemical carcinogens, occupational exposure and lifestyle factors. It was established in 1965 and is part of the World Health Organisation (WHO) (Stewart, 2008; Environmental Chemistry, Toxicology and Ecotoxicology resources, 2010; IARC, 2015).

The substances (specific chemicals, groups of related chemicals, complex mixtures, occupational and environmental exposures, cultural of behavioural practices, biological organisms and physical agents) that are included in the monographs undergo critical reviews and evaluations to establish the evidence of carcinogenicity for human exposure. Epidemiological studies such as cohort studies, case-control studies, correlation or ecological studies and intervention studies are all used to collect data on the carcinogenicity of a substance with relation to humans. The classification of a substance is then based on the results obtained from these studies. If additional research needs to be conducted on these substances it will also be included in the monographs which also include the assessments and results for each substance. International authorities use the monographs to compile risk assessments, establish preventative measures and implement control measures important for public health. Since public health options vary from country to country, the monographs do not make recommendations on regulations or legislation since this is the responsibility of individual governments and other international organisations (IARC, 2015).

The notations given to a substance (chemical or biological) to indicate its carcinogenic risk are as follows (IARC, 2015):

- *Group 1* – Carcinogenic to humans

- *Group 2A* – Probably carcinogenic to humans. Certainty with regards to their ability to cause cancer in humans exists

- *Group 2B* – Possibly carcinogenic to humans. Uncertainty exists with regards to their ability to cause cancer in humans

- *Group 3* – Not classifiable as to its carcinogenicity to humans.

- *Group 4* – Probably not carcinogenic to humans

For Group 1 sufficient evidence on its carcinogenicity exists from epidemiological evidence, occupational exposure as well as animal studies that showed the relevant mechanisms of carcinogenicity to humans. According to the IARC's website there are 118 agents that were assigned this notation according to the monographs published by the IARC. Agents in group 2A had limited evidence of carcinogenicity in humans and sufficient evidence from animal studies. The evidence also showed that carcinogenesis is mediated by the same mechanisms as in humans. There are 75 agents with this notation. Agents in group 2B had limited evidence in humans and sufficient or limited evidence in animals and there are 288 agents with this notation. Agents in group 3 had inadequate evidence for humans and the evidence for animals was inadequate or limited. The carcinogenesis found in animals is not applicable to humans. There are 502 agents with this notation. There was only one agent with the notation of Group 4 namely, Caprolactam. Group 4 is not used since it shows negative evidence of carcinogenicity (Cancer Council Australia, 2015).

2.4.2 Environmental Protection Agency (EPA)

The United States Environmental Protection Agency (US EPA) also has a carcinogen classification system of which the first carcinogen risk assessment was published in 1986. The most recent updated version was published in 2005 in which provisions are made for any scientific advances that may occur. The notations given to chemicals according to the 1986 guidelines started at A (Human carcinogen) through to E (Evidence of noncarcinogenicity for humans), this was a six-category alphanumeric classification system including A, B1, B2, C, D and E. However, this classification system was replaced in 2005. The latest classification of carcinogens was published in the 2005 Guidelines for Carcinogenic Risk Assessment and the classification is as follows (EPA, 2015):

- *Carcinogenic to humans* – Strong evidence of human carcinogenicity. There is convincing evidence of causal association between human exposure and cancer development.

- *Likely to be carcinogenic to humans* – The weight of evidence is adequate to demonstrate carcinogenic potential to humans but does not reach the weight of evidence for the "Carcinogenic to humans" category.

- *Suggestive evidence of carcinogenic potential* – The weight of evidence is suggestive of carcinogenicity; a concern for potential carcinogenic effects in humans is raised but the data are judged not sufficient for a stronger conclusion.

- *Inadequate information to assess carcinogenic potential* – The available data are judged inadequate for applying one of the other categories.

- *Not likely to be carcinogenic to humans* – The available data are considered robust for deciding that there is no basis for human hazard concern. Positive results in animal case studies but the mode of action in experimental animals does not operate in humans.

The US EPA classifies mainly the carcinogenic hazard of pesticides and the hazards that may result from the exposure to children during the preconception and prenatal or postnatal development to sexual maturity. The epidemiological evidence of 550 pesticides can be viewed on the Integrated Risk Information System (IRIS) internet accessible database which is the EPA's human health assessment programme. On this website all the data evaluated for each chemical substance are listed either by name or by date revised (EPA, 2015).

2.4.3 National Toxicology Programme (NTP)

The NTP was established in 1978 by Joseph A. Califano Jr., with the mission of evaluating agents which may be of concern to public health by developing and applying methods of toxicology and molecular biology. Since many human diseases can be linked to direct or indirect exposure to certain chemicals, the NTP wanted to prevent these diseases by eliminating or decreasing human exposure to chemicals and was granted permanent status as an authority in October 1981. The NTP has a carcinogen classification system called the Report on Carcinogens (RoC) which is a congressionally mandated, science-based public health report that identifies substances that pose a risk to residents of the US. The 13th edition of the RoC was released on the 2nd of October 2014 (NTP, 2015). The carcinogen notations assigned to substances in the RoC are as follows (NTP, 2014):

- *Known to be a human carcinogen* – There is sufficient evidence of carcinogenicity from studies in humans which indicates a causal relationship between exposure to the agent, substance or mixture and human cancer.

- *Reasonably anticipated to be a human carcinogen* – There can be three reasons for assigning this notation to a substance. Firstly, there is limited evidence of carcinogenicity from studies in humans, which indicates that causal interpretation is credible, but that alternative explanations, such as chance, bias or confounding factors could not be excluded. Secondly, there is sufficient evidence of carcinogenicity from studies in experimental animals which indicates there is an increased incidence of malignant and/or a combination of malignant or benign tumours. Thirdly, there is less than sufficient evidence of carcinogenicity in humans or laboratory animals, however; the agent, substance or mixture belongs to a well-defined, structurally-related class of substances whose members are listed in a previous Report on Carcinogens as either a known to be a human carcinogen or reasonably anticipated to be human carcinogen, or there is convincing relevant information that the agent acts through mechanisms indicating it would likely cause cancer in humans.

The 13th RoC lists 243 substances which include a complete profile for each substance which includes the carcinogenicity, properties, use and production exposure. The complete RoC can be downloaded from the NTP's website.

2.4.4 American Conference of Governmental Industrial Hygienists (ACGIH)

It was established in 1938 but the organisation was first known as the independent National Conference of Governmental Industrial Hygienists (NCGIH) and officially changed its name to the ACGIH in 1946. The ACGIH has been a well-respected organisation in industrial hygiene, occupational and environmental health and safety industry for over 75 years. Its most well-known work is the publication of the Threshold Limit Values (TLVs) booklet which was first published in 1941 with the most recent publication being published in 2015 (ACGIH, 2015). The classification system used by the ACGIH to identify a carcinogen assigns notations to carcinogens as follows (ACGIH, 2014):

- *A1* – Confirmed human carcinogen. “This agent is carcinogenic to humans based on the weight of evidence from epidemiologic studies”

- *A2* – Suspected human carcinogen. ”Human data are accepted as adequate in quality but are conflicting or insufficient to classify the agent as a confirmed human carcinogen; OR, the agent is carcinogenic in experimental animals at dose(s), by route(s) of exposure, at site(s), of histologic type(s), or by mechanism(s) considered relevant to worker exposure. Primarily used when there is limited evidence of carcinogenicity in humans and sufficient evidence of carcinogenicity in experimental animals with relevance to humans”

- *A3* – Confirmed animal carcinogen with unknown relevance to humans. “The agent is carcinogenic in experimental animals at a relatively high dose, by route(s) of administration, at site(s), of histologic type(s), or by mechanism(s) that may not be relevant to worker exposure. Available epidemiologic studies do not confirm an increased risk of cancer in exposed humans. Available evidence does not suggest that the agent is likely to cause cancer in humans except under uncommon or unlikely routes or levels of exposure”

- *A4* – Not classifiable as a human carcinogen. “Agents which cause concern that they could be carcinogenic for humans but which cannot be assessed conclusively because of lack of data. *In vitro* or animal studies do not provide indications of carcinogenicity which are sufficient to classify the agent not one of the other categories”

- *A5* –Not suspected as a human carcinogen. “The agent is not suspected to be a human carcinogen on the basis of properly conducted epidemiologic studies in humans. These studies have sufficiently long follow-up, reliable exposure histories, sufficiently high dose, and adequate statistical power to conclude that exposure to the agent does not convey a significant risk of cancer to humans; OR, the evidence suggesting a lack of carcinogenicity in experimental animals is supported by mechanistic data”

The exact number of chemical substances classified as carcinogens by the ACGIH is not documented. If substances do not have human of experimental animal data regarding their

carcinogenicity the ACGIH does not assign a carcinogen notation to the substances (ACGIH, 2014). The carcinogen notations can be found in the Threshold Limit Values (TLVs) booklet along with the occupational exposure limit (OEL) for each substance.

2.4.5 European Union (EU)

The EU is a political system founded in 1945 that consists of European countries and various agencies and bodies. The Regulation on Registration, Evaluation, Authorisation and Restriction of chemicals (REACH) falls under the EU and is in control of the legislative framework on chemicals of the EU. The REACH aims to protect human health and the environment. Under REACH manufacturers and importers are obligated to provide derived no-effects levels (DNELs) for HCSs that are produced or imported when these amounts exceed 10 tonnes per year (Tynkkynen *et al*., 2015). It holds the industry responsible for assessing and managing chemical risks by providing safety information to their users. The Global Harmonized System of Classification and Labelling of Chemicals (GHS) identifies hazardous chemicals and uses symbols to inform users of the hazards associated with the use of these chemicals (UNECE, 2015). The first version of the GHS was published in 2003 with the latest version being published in 2015. In the section describing how carcinogenic chemicals should be indicated and labelled, it assigns the following notations to carcinogens:

- *Category 1A* – Known to have carcinogenic potential for humans; the placing of a substance is largely based on human evidence.

- *Category 1B* – Presumed to have carcinogenic potential for humans; the placing of a substance is largely based on animal evidence.

- *Category 2* – Suspected human carcinogen. Based on strength of evidence from human and/or animal studies with limited evidence of carcinogenicity in human studies or from limited evidence of carcinogenicity in animal studies.

The number of substances that was assigned a category 1A notation was 189, category 1B was 826 and a category 2 was 188. The total number of substances assigned carcinogenic notation in the GHS was 1 203 (Lißner *et al*., 2014).

2.5 Occupational exposure limits (OELs)

To ensure that a worker does not suffer any adverse health effects from being exposed to a HCS an Occupational Exposure Limit (OEL) is specified. An OEL can be defined as the maximum level, given in a numerical concentration, to which a worker can be exposed to a HCS without experiencing adverse health effects (Ding *et al*., 2011; Paustenbach, 2011; Ding *et al*., 2014). These OELs are incorporated into legislation for each country and aim to protect the health of the working population.

2.5.1 Types and uses

OELs are widely used in the work environment as a risk management tool against exposure to HCSs in the workplace (Ding *et al.*, 2011). Setting of OELs are a very complex process which factors in science, law and policies. The use of OELs goes beyond the limits of national interests and international borders and, therefore, the definitions for the three types of OELs that can be specified is the same in all legislation (Howard, 2005). These three types of OELs used for airborne exposure to HCSs are: Time-Weighted Average Occupational Exposure Limits (TWA-OEL), Short-term Exposure Limits (STELs) and Ceiling Limits (CL) or (C). The definitions for these OELs are as follows (South Africa Department of Labour, 1995; South African Department of Minerals and Resource, 1996):

- TWA-OEL: The time weighted average concentration for an 8 hour work day and a 40 hour work week to which nearly all workers may be repeatedly exposed without adverse health effects.

- STEL (Short Term Exposure Limit): A 15-minute TWA exposure which should not be exceeded at any time during a workday even if the 8-hour TWA is within the OEL-TWA. Exposures above the OEL-TWA up to the STEL should not be longer than 15 minutes and should not occur more than four times per day. There should be at least 60 minutes between successive exposures in this range. An averaging period other than 15 minutes may be recommended when this is warranted by observed biological effects.

- C (Ceiling): An instantaneous concentration which must never be exceeded during any part of the working exposure.

In the South African Occupational Health and Safety (OHS) Act (No. 85 of 1993) there are two types of OELs specified in Annexure 1 of the regulations, namely: Time-Weighted Average Occupational Exposure Limit-Control Limit (TWA OEL-CL) and Time-Weighted Average Occupational Exposure Limit-Recommended Limit (TWA OEL-RL). These limits were adopted from the United Kingdom's Control of Substances Hazardous to Health Regulations (COSHH). An OEL-RL is set at a level which there is no indication of a risk to health and an OEL-CL at a level where a residual risk to health may exist taking into account socio-economic factors (South African Department of Labour, 1995).

2.6 South African standards for OELs and carcinogens

Studies done on the overall level of OELs for South African legislation have concluded not only that OELs currently enforced in South African legislation are outdated and at a too high level when compared to the levels of OELs being enforced in developed countries, but also that they do not adequately protected the workers in the industrial and mining sectors of South Africa (Viljoen, 2012; Viljoen, 2014). The OHS Act and the Mine Health and Safety (MHS) Act both contain regulations that relay the set OEL values for the industrial and mining sectors, independently, but there is no indication in these regulations as to which HCSs are carcinogenic and the carcinogenic risk involved working with these HCS.

2.6.1 OHS and MHS Acts and their regulations

South Africa has two types of industries that require OELs to protect the workers, these industries are the general industry and the mining industry. Two sets of legislation have thus been compiled, one that applies to the general industry, namely the OHS Act and one that applies to the mining industry, namely the MHS Act.

The OHS Act was implemented in 1993 by the Department of Labour and contains regulations. In these regulations (Regulations for Hazardous Chemical Substances (RHCS)) OELs can be found that were set by technical committees of the Department of Labour, which were based on the United Kingdom's OEL values available at the time as previously mentioned. The OELs are listed in two tables, Table 1 and 2. Table 1 contains HCSs with OEL-CL that are more hazardous such as carcinogens whilst Table 2 contains HCSs with OEL-RL and are less hazardous (South Africa Department of Labour, 1995). One

amendment has been made to the RHCS since 1993 but a revision of these OELs is currently in process (SAIOH, 2015).

The MHS Act was implemented in 1996 by the Department of Minerals and Resources. The OELs are described in Regulation 22.9 of the Mine Health and Safety Act (1996). The Mining Occupational Health Committee (MOHAC) is responsible for setting the OELs and based these OELs on the ACGIH and NIOSH values. The OELs listed in the MHSR was updated and revised in 2006 (South African Department of Minerals and Resources, 1996).

2.6.2 Setting OELs for carcinogens

Cancers that are induced by exposure to contaminants in the atmosphere usually have a latency period which varies depending on the substance, intensity and length of exposure and the individual that was exposed. To determine practical limitations for exposures to these substances in the workplace epidemiological and experimental studies (animal experiments) are performed but the latency period of occupational cancers may inhibit classifications of carcinogens. Exposure thresholds for humans that define a no-effect level have been theorised, but these thresholds are hard to identify and confirm from the evidence obtained in epidemiological or animal studies (Ministry of Business, Innovation and Employment, 2013).

For carcinogenic HCSs, OELs are more of a “practical threshold” since this is the level of exposure that does not pose a significant cancer risk. This was based on the concept that humans have evolved mechanisms to handle carcinogens that naturally occur in the diet and that these same mechanisms may play a role in the detoxification of small amounts of chemicals found industrially (Paustenbach *et al.*, 2011). Whether there is truly a level at which exposure to a carcinogenic HCS will not cause cancer development is still debatable matter since some risk may still be present for cancer development at exposure to the practical threshold as was stated by Paustenbach *et al.* (2011).

Many groups including the ACGIH TLV committee believe it may be likely for thresholds for carcinogens to exist at very low doses while other groups believe little or no evidence exists for thresholds of HCS that are genotoxic. The reason for this being that animal experiments and NOELs do not describe the large differences for humans in the general population. The types of low-dose extrapolation models are the one-hit, multistage, Weibull, multistage, logit and probit. Low-dose extrapolation models do not incorporate the biological repair

mechanisms of the body. These models presume that no matter how small the dose/exposure to a HCS a response could occur when the population is large enough and an increased lifetime cancer risk is then selected to represent the minimum level of risk for that HCS (Paustenbach *et al.*, 2011). This minimum level is considered virtually safe doses and regulatory agencies cannot give absolute safe levels of exposure or thresholds which will ensure exposure below that threshold will show no response. Statistical models follow the criteria that if 1 of 100 to 1 of a 1000 workers develop occupational cancer from exposure to a carcinogenic HCS, the threshold is safe or acceptable to protect the worker in the workplace (Cherrie, 2009). Approaches used to set various limits of exposure to carcinogens (with their own risk criteria) differ since the population at risk is different and in some cases workers are aware of the risks associated with their jobs and are compensated for accepting these risks (Paustenbach *et al.*, 2011).

The Unit Risk (U.R.) is a quantitative assessment of carcinogenic risk which is based on human data associated with lifetime exposure to a certain level of carcinogens in the air. The WHO and US EPA uses the following formula to calculate the U.R.:

$$UR = P_0 (R-1) / X$$

- P_0 = Background lifetime risk
- R = Relative risk (Ratio between observed and expected number of cancer cases reported in exposed population)
- X = Lifetime average exposure

The US EPA U.R. applies a correction factor since it is believed that workers are exposed at levels 8 times higher than the general population with the formula to calculate the additional risk being:

$$A.R.\ (w) = (U.R. \times C) / 8$$

- A.R. (w) = Additional risk
- C = Exposure level

The faction representing the lifetime a worker is exposed to carcinogenic HCS for $1/8^{th}$ of their lifetime (Valente and Cavariani, 1998).

2.7 OEL comparison with the geometric mean method and interval method

In order to compare the OELs set within countries and jurisdiction a method was developed by Hansson (1998) which is known as the geometric means method. Since there is a variation in what OELs are protecting exposed workers against in each country and jurisdiction there is also a variation the OEL set in each country and jurisdiction (Schenk *et al.*, 2008a). Hansson (1998) found that the best indicator of the difference between the OELs of different countries or jurisdiction is to calculate the quotient. The geometric mean is then calculated for all these different ratios which indicate the overall level of the complete list of a specific country or jurisdiction (Schenk *et al.*, 2008b). The concept of the geometric mean method can be illustrated by the following example: Three HCSs have OELs listed within List *A* and *B*. In List *A* the OELs are as follows: substance I - 20 mg/m^3, substance II - 15 mg/m^3 and substance III – 10 mg/m^3. In List *B* the same substances are listed but the OELs are as follows: substance I - 200 mg/m^3, substance II - 15 mg/m^3 and substance III – 1 mg/m^3. The arithmetic means of ratios for *B/A* or *A/B* both equal 3.7 which gives the impression that List *A* or List *B* have set higher OELs. In this case the list which will be perceived as having the higher set OELs depends on which list was used as the denominator (Schenk *et al*., 2008a; Ding *et al*., 2011). The geometric mean for A/B ratios is greater than 1 only if ratios for B/A is below 1 since the product of the two geometric means must always be equal to 1 (Schenk *et al*., 2008a). When list A is used as the comparison list the geometric mean is calculated to be 1, whilst when list B is used as the comparison list the geometric mean is also equal to 1. The ratios calculated for these examples were similar which shows that there is no difference between the two lists being compared. A geometric mean equal to 1 indicates that there is no difference in the OELs for a substance on both lists. A geometric mean below 1 indicates that an overall lower level of OELs is present on the list being compared whilst a geometric mean higher than 1 indicates an overall higher level of OELs (Schenk *et al*., 2008a; Viljoen, 2012). The lower the calculated geometric mean, the lower the over-all OELs that are being compared are (Schenk *et al.*, 2008b).

Previous studies have been conducted by Viljoen (2012) and Viljoen (2014) to compare the overall level of South African OELs contained in the RHCS and MHSR with developed countries' OELs. In Viljoen (2012), the focus was on HCSs that were common throughout the countries' lists that were used while Viljoen (2014) focused on the groups of HCS included in the RHCS and MHSR namely: pesticides, metals, dusts and fibres. Viljoen (2012) compared the number of HCSs regulated by countries/jurisdictions as well as the overall level of the OELs set for the different HCS. The study found that there is an

unsystematic setting of OELs among countries/jurisdictions as well as a difference in the overall level of OELs between developed countries and developing countries. Viljoen (2014) found that the OELs contained in the RHCS and MHSR for pesticides, metals and fibres were aligned with the OELs listed for the HCS in these groups in developed countries but that the HCSs in the dust group differed the most from developed countries' OELs. Both studies found that the levels at which South African OELs are set when compared to developed countries' OELs are not adequate to protect workers in the industrial and mining sectors against exposure to HCSs in their work environment. However, the overall level at which carcinogenic HCSs' OELs compare to developing countries have not been established since there is no clear indication within the RHCS and MHSR which substances are carcinogenic to humans.

In order to compare the OEL for a specific HCS listed in two sets of legislation the interval method, which was first used by Tynkkynen (2015), can be applied. The number of HCSs with OELs between 95-105% of the OEL listed in the comparison list is considered to be similar, less than 95% of the OEL is considered lower and an OEL exceeding 105% is considered a higher OEL. The concept of the interval method can be illustrated by the following example: Acrylamide (79-06-1) has a TWA-OEL of 0.3mg/m^3. If the comparison list has a TWA-OEL between 0.285 – 0.315 mg/m^3 the TWA-OEL will be considered to be similar. If the TWA-OEL is less than 0.285 mg/m^3 it will be considered lower and if the TWA-OEL is more than 0.315 mg/m^3 it will be considered higher.

2.8 Conclusion

Carcinogenesis is a multistage process which can occur as a result of genetic predisposition but occupational exposure to chemicals during a workers lifetime may also result in the development of cancer (Environmental Chemistry, Toxicology and Ecotoxicology resources, 2010; McCormack and Schüz, 2012; Klaunig, 2013). In order to prevent this, five organisations have established ways of classifying the risk associated with the use of carcinogenic HCSs and how likely they are to cause cancer to develop. In addition to the classification of carcinogens some organisations such as the ACGIH also have OELs that accompany this classification. Whether a threshold for carcinogens can truly be set is debatable, the ACGIH believes it may be likely for thresholds for carcinogens to exist at very low doses while other groups believe little or no evidence exists for thresholds of HCS that are genotoxic (Paustenbach *et al.*, 2011). South Africa has made no provision for

carcinogens within the OHS Act and MHS Act that govern the industrial and mining industries respectively. This leaves South African workers exposed to the risk of developing adverse health effects such as occupational cancer from exposure.

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Chapter 3

Article

Guidelines to Authors

This article will be submitted to the *Annals of Occupational Hygiene*. The author's instructions are as follows:

- The journal only publishes original work that is not up for consideration elsewhere and that is research and developmental related to the reduction of risk and ill-health resulting from work.

- *Paper structure.* Paper should generally conform to the pattern: Introduction, Methods, Results, Discussion and Conclusions – consult a recent issue for style of headings. A paper must be prefaced by an abstract of the argument and findings, which may be arranged under the headings: Objectives, Methods, Results, and Conclusions. Keywords should be given after the list of authors.

- *Brevity.* The necessary length of a paper depends on the subject, but any submission must be as brief as possible consistent with clarity. The number of words, excluding the abstract, references, tables and Figures, must be stated as a message to the Editor at the time of submission. If this length is more than 5000 words, a statement must be included justifying the extra length, and papers without this information may be returned unread.

- *Units and symbols.* SI units should be used, though their equivalent in other systems may be given as well.

- *Figures.* Good quality low resolution electronic copies of figures, which include photographs, diagrams and charts, should be sent with the first submission. It is helpful to reviewers to incorporate them in the word-processor text or at the end. The revised version, after review, should be accompanied by high resolution electronic copies in a form and of a quality suitable for reproduction. They should be about the size they are to be reproduced in, with font size at least 6 point, using the standard Adobe set of fonts.

- *Tables.* Tables should be numbered consecutively and given a suitable caption, and each table typed on a separate page. Footnotes to tables should be typed below the table and should be referred to by superscript lowercase letters.

- *References.* References should only be included if essential to the development of an argument or hypothesis, or which describe methods for which the original account is too long to be reproduced, only publications which can be obtained by the reader should be referenced. References in the text should be in the form Jones (1995), or Jones and Brown (1995), or Jones *et al.* (1995) if there are more than two authors. For example: Jones and Brown (1995) observed total breakdown control… or Total breakdown of control has sometimes been observed (Jones and Brown, 1995).

- At the end of the paper, references should be listed in alphabetical order by name of first author, using the Vancouver Style of abbreviation and punctuation. Examples are given below. ISBNs should be given for books and other publications where appropriate. Material unobtainable by readers should not be cited. Personal Communications, if essential, should be cited in the text in the form (Professor S.M. Rappaport, University of California). References will not be checked editorially, and their accuracy is the responsibility of authors. Examples of the reference style at the end of each chapter is given below:

Simpson AT, Groves JA, Unwin J, Piney M. (2000) Mineral Oil Meta Working Fluids (MWFs)-Development of practical Criteria for Mist Sampling. Ann Occup Hyg; 44: 165-72.

Vincent JH. (1989) Aerosol Sampling: Science and Practise. Chichester, UK: John Wiley. ISBN 0 471 92175 0.

Swift DL, Cheng Y-S, Su Y-F, Yeh H-C. (1994) Ultrafine Aerosol Deposition in the Human Nasal and Oral Passages. In Dodgson J, McCallum RI, editors.Inhaled Particles VII. Oxford: Elsevier Science. p. 77-81. ISBN 0 08 040841 9 H.

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Recommendation of a classification system and occupational exposure limits for chemical carcinogens

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Abstract

Introduction: The rise in the number of reported occupational cancers in developing countries can be attributed to, amongst others, exposure of workers to hazardous chemical substances (HCSs) in their working environment. In developing countries such as South Africa exposure in the workplace is still a major problem reflected in the number of occupational cancer cases reported annually. This can be attributed to the lack of a carcinogen classification system as well as the occupational exposure limits (OELs) being applied in the industrial and mining sectors not being updated in recent years. OELs are the maximum level at which exposure is allowed without experiencing adverse health effects. Implementing a carcinogen classification system such as the International Agency for Research on Cancer (IARC), the American Conference of Governmental Industrial Hygienists (ACGIH) or the European Union (EU) will help with the identification of HCSs that have a carcinogenic risk associated with them. Incorporation of such a system into South African legislation may reduce the number of occupational cancers developed by the South African workforce.

Aim: To identify a carcinogen classification system that is reasonably practicable for use within South African occupational health legislation and to compare the level at which the OELs of known carcinogenic HCSs listed within the Regulations for Hazardous Chemical Substances (RHCS) and Mine Health and Safety Regulations (MHSR) to OELs for the same HCS in developed countries' legislation.

Method: A carcinogen classification system was identified by making use of set criteria points. Thereafter, the HCS that were considered human carcinogens were identified in the RHCS and the MHSR using the selected carcinogen classification's notations. The OELs listed in the RHCS and MHSR for these HCSs were then compared to the OELs listed for the same HCSs within ten developed countries/jurisdictions with the help of the geometric means method. The interval method was also used in the comparison of the number of MHSR OELs that are similar, lower or higher than that of the RHCS.

Results: The carcinogen classification system with the highest score was the IARC. Therefore, this study used the HCSs classified as human carcinogens by the IARC. The RHCS contained two tables that listed OELs for HCSs namely Table I and Table II. The total number of HCS listed in the RHCS (Table I = 22 HCS and Table II = 55 HCS) was 77. It was found that the country/jurisdiction with the lowest geometric mean when Tables I and II were combined was Finland with a geometric mean of 0.300. It was found that there is no

statistical significant difference (p = 0.138) between the geometric means of the RHCS's Table I and II. The database for the MHSR only contained 76 substances listed as carcinogenic by the IARC. Finland also had the lowest geometric mean of 0.475. When the interval method was used to determine the number of MHSR OELs for carcinogens that are similar, lower or higher than the RHCS OELs it was found that 64.5% of the RHCS OELs are similar to the MHSR and 34.2% of the MHSR OELs were lower than the RHCS OELs.

Conclusion: The carcinogen classification best suited for use within South African legislation is the IARC's carcinogen classification which classified a total of 481 substances of which the RHCS contained 77 substances and the MHSR contained 76 substances classified as carcinogenic to humans (Group 1, Group 2A and Group 2B). It was found that South African OELs are at a higher level than the OELs listed by some developed countries. The geometric mean values calculated for most developed countries were below 1 with the exception of OSHA in the RHCS. In the MHSR it was found that OSHA, Australia and the United Kingdom had a geometric mean >1. When the RHCS's OELs were compared to the MHSR a geometric mean of 0.651 was calculated that confirmed the overall level at which OELs of the MHSR are set were at a lower level.

3.1 Introduction

When work-related deaths are reported the first thing that comes to mind is usually fatal injuries, but in truth occupational diseases should receive more attention as a cause for these deaths (Bianco and Demers, 2013). The link between the induction of cancer by chemicals found in most working environments has been well documented over the last three centuries (Klaunig, 2013). It has been estimated that 23% of the workforce that falls under the European Union (EU) are exposed in their workplace to one or more substances that were listed as occupational carcinogens by the International Agency for Research on Cancer (IARC) (Dryson *et al.*, 2005). Avoidable exposure to carcinogens in the workplace is still a major concern in developing countries since economic considerations and the lack of modern occupational health and safety legislation form barriers for improvement in the working conditions found in these countries (Verma *et al.*, 2002).

South Africa is an economically developing country (The World Bank, 2013). One of the major problems facing developing countries is an increase in cancer cases reported, which can be attributed to a variety of factors such as environmental (heating/cooking fuels), diet (adopting a westernised diet) and behavioural (smoking and being less physically active) (Brawley, 2011; Jemal *et al.*, 2011). A study conducted by McCormack and Schüz (2012) revealed that the most common type of cancers found in South Africa was lung cancer (15.4% in men and 6.9% in women during 2008). This cancer was not just as a result of environmental factors (e.g. heating/cooking fuels) but also as a result of the occupations followed by the workforce in the industrial and mining sectors.

Chemical carcinogens found in industry, agriculture and commercial processes may lead to development of cancer. These chemicals cause cancer by direct action on cellular DNA or through mechanisms that cause chemical species to develop that can enter the cell nucleus and cause mutations in the cellular DNA (Environmental Chemistry, Toxicology and Ecotoxicology Resources, 2010). Chemical carcinogens are classified as either genotoxic or non-genotoxic hazardous chemical substances (HCSs). Genotoxic HCSs cause DNA damage directly to the nuclear DNA of cells whilst non-genotoxic HCSs cause cancer through other mechanisms which do not include direct binding, damage and interaction with the nuclear DNA of cells (Klaunig, 2013). Genotoxic carcinogens usually have a practical threshold for exposure if there is significant evidence to base this threshold on, but many HCSs have insufficient evidence to establish such a practical threshold (Paustenbach *et al.*, 2011). Since cancer develops years after exposure to a carcinogenic HCS the collection of data about a certain carcinogenic HCS may take years and, therefore, a lack of sufficient

evidence for some HCS exist. Non-genotoxic HCSs follow a dose-response relationship which makes it easier to determine the level of exposure that will not lead to the development of cancer, this is known as the No-Observed-Adverse-Effect-Level (NOAEL) (Bolt and Huici-Montagud, 2008). The difference between the types of carcinogens and their method of causing cancer has led to the question of whether there is truly a safe level of exposure to carcinogenic HCSs since a practical threshold only states that there is no significant risk, but some risk may still be present (Paustenbach *et al.*, 2011).

Since these chemical carcinogens are mainly found in workplaces, systems to classify the carcinogenic risk associated with exposure to a HCS were established. Currently there are several agencies or organisations in developed countries which have a system for classifying the carcinogenic potential of HCSs. The three main role players internationally for classifying carcinogens according to Prevor (2013) are the International Agency for Research on Cancer (IARC), the American Conference of Governmental Industrial Hygienists (ACGIH) and the European Union (EU).

To prevent health effect due to exposure to HCSs in the workplace each country has list that state the levels employees can be exposed during a work shift. These are known as occupational exposure limits (OELs). An Occupational Exposure Limit (OEL) can be defined as the maximum level, given in a numerical concentration, to which a worker can be exposed to a HCS without experiencing adverse health effects (Ding *et al*., 2011; Paustenbach *et al.*, 2011; Ding *et al*., 2014). These OELs are incorporated into occupational health legislation for each country and aim to protect the health of the working population. For carcinogenic HCSs, OELs are more of a “practical threshold” since this is the level of exposure that does not pose a significant cancer risk. This was based on the concept that humans have evolved mechanisms to handle carcinogens that naturally occur in their diet and that these same mechanisms may play a role in the detoxification of small amounts of chemicals found industrially (Paustenbach *et al.*, 2011).

In South Africa there are two sets of occupational health and safety legislation, namely the Occupational Health and Safety (OHS) Act (No. 85 of 1993) where the Regulations for Hazardous Chemical Substances (RHCS) state OELs in Tables 1 and 2 and the Mine Health and Safety (MHS) Act (No. 29 of 1996) with the OELs being given in Section 22.9 of the MHS Act’s Regulations (MHSR). Tables 1 and 2 of the OHS Act will be referred to in this study as Table I and Table II as to avoid confusion with the tables contained in the text of this study. Henceforth, the acronym RHCS will refer to the Regulations for Hazardous

Chemical Substances of the OHS Act and the acronym MHSR will refer to Section 22.9 of the MHS Act's Regulations.

It is generally accepted that the HCS listed in Table I of the RHCS are more hazardous to health since Occupational Exposure Limit – Control Limits (OEL-CL) are specified for these HCSs. An OEL-CL is the maximum level to which employees may be exposed to under any working conditions and exposure to these HCSs should be kept as far below the set OEL-CL as possible. Table II lists substances has an Occupational Exposure Limit – Recommended Limits (OEL-RL) which means that if exposure exceeds the stated OEL adverse health effects can develop. These risks can be reduced if control measures e.g. Personal Protective Equipment (PPE) is used to reduce exposure to the level of the OEL-RL since the OEL-RL is regarded as adequate control. The level at which OEL-CL are set are influenced by socio-economic factors since economical and technical feasibility is taken into account when these OELs are set (South African Department of Labour, 1995; Schenk *et al.*, 2008b). The absence of carcinogen classification in South African legislation may have a negative impact on the health of the workforce in South Africa in the form occupational cancers developing and is a shortcoming that needs urgent attention.

The OELs currently being used by other countries can be compared to evaluate the overall levels at which the OELs in a specific country are set. This comparison is done with the help of the geometric means method. This method was first applied by Hansson (1998) and is regarded as the best indicator of the difference between the OELs. The interval method can be used to establish the degree of similar, lower or higher OELs contained in the two sets of occupational legislation applicable in South Africa.

This study aims to identify a carcinogen classification system that is reasonably practicable for use within South African occupational health legislation. A recommendation will be made on which classification system or combination of classification systems can be incorporated into the RHCS and MHSR. This study will also then compare the level at which the OELs of carcinogenic HCSs listed within the RHCS and MHSR compare to the OELs of developed countries.

3.2 Method

3.2.1 Carcinogen classification systems

The carcinogen classification systems considered in this study were decided on after a thorough study of published literature to establish the most regarded and used authorities and organisations responsible for assigning notations to HCSs used within the industrial and mining sector. Only the latest versions of the classification system's notations available were included in the study. The classification systems that were included in this study are the ACGIH, the IARC, the Global Harmonized System of Classification and Labelling of Chemicals (GHS) of the EU, the Report on Carcinogens (RoC) system of the National Toxicology Programme (NTP) and the United States Environmental Protection Agency (US EPA).

To select a classification system that can be applied within South African occupational health legislation a predetermined criteria was established and used to analyse the carcinogen classification systems. These criteria points are listed in Table 1. The criteria points were weighed on importance and, therefore, used a numerical value assigned to a "Yes" (numerical value of 2) or "No" (numerical value of 1) answer. There, however, was one exception where the reversed was applied. This criteria point was "Does documentation available to the public/user incur financial expenses?". Since South Africa is still a developing country, the financial implication of having to buy documentation may deter the use thereof in the process of updating legislation or even the acquisition of these documents by industry in order to understand the carcinogen classifications. The classification with the highest score (maximum 20 marks) was considered as the carcinogen classification system to be recommended for incorporation into South African legislation.

Table 1: Criteria points used to determine a carcinogen classification system for use within South African occupational health legislation.

Criteria point	Yes	No
Are the methods followed during epidemiological studies available to public?	2	1
Are there references listed in the official documentation?	2	1
Is this documentation updated on a frequent basis? (Annually etc.)	2	1
Are the notations assigned to carcinogens simple and easy to understand?	2	1
Number of notations efficient to cover all necessary factors that have to be considered?	2	1
Is the list of chemicals with their notations easy to find and accessible?	2	1
Does documentation available to the public/user incur financial expenses?	1	2
Can documentation be downloaded from the internet?	2	1
Is the system established in developed countries and have they been in use successfully for years?	2	1
Are all chemicals considered or only a certain group? (E.g. Pesticides)	2	1
	Maximum marks = 20	

3.2.2 Lists of OELs

A study conducted by Viljoen (2012) identified different countries and jurisdictions of developed countries most referred to in literature which are considered influential in setting of OELs to be used in occupational health and safety legislation. The most recently published versions of the OEL lists were systemically collected. The lists of OELs obtained were from: Australia, Canada (British Columbia), Finland, Germany, Japan, United Kingdom (UK), United States of America (USA) (ACGIH and Occupational Safety and Health Administration (OSHA)), Sweden and the binding and indicative OELs published by the EU. The OELs for South African HCSs were listed in the RHCS and MHSR respectively.

The Chemical Abstracts Service (CAS) number was used to identify the chemicals. The list of synonyms compiled by Viljoen (2012) was used to eliminate HCSs from the South African legislation that may be listed more than once under different names. Since the HSCR does not list the CAS numbers of HCSs, the CAS numbers listed within the MHSR were used as guideline in conjunction with the list of synonyms identified by Viljoen (2012).

3.2.3 Database

A database was compiled that contained the HCSs listed within the South African regulations which are considered carcinogenic. The database was divided into four lists namely: a list with Table I and II combined (RHCS), a list for Table I of RHCS only, a list with Table II of the RHCS only and a list for the MHSR. After a carcinogen classification system was identified by the predetermined criteria, the carcinogenic notations assigned to the HCSs from that classification system were allocated to the HCSs of the RHCS and MHSR in the database. OELs of the other countries/organisations included in this study were added to the database. The 8 hour time weighted average (TWA) OELs were the only values included. For a HCS with only a short term exposure limit (STEL) value, the values were adjusted using the conversion factor as recommended by the ACGIH (Table 2) (Schenk *et al.*, 2008b).

Table 2: Factors for calculating an 8 hour TWA average from a STEL value (As first suggested by ACGIH in 1963).

TWA (ppm or mg/m^3)	Conversion factor
X ≤ 1	3
1 < X ≤ 10	2
10 < X ≤ 100	1.5
100 < X ≤ 1000	1.25
1000 < X	1

The OELs were noted in mg/m^3 (milligrams per cubic metre) and where applicable a ppm (parts per million) was converted to mg/m^3 using the formula (Schenk *et al.*, 2008a; Ding *et al.*, 2011; Viljoen, 2012):

Concentration (mg/m^3) = (Concentration ppm) (molecular weight) / 24.45 at 25 °C and pressure of 1 atmosphere.

For some substances a molecular weight was not available and, therefore, a conversion from ppm to mg/m^3 could not be done e.g. gasoline. A HCS that could not be converted to an mg/m^3 notation or only had a ceiling value was excluded from further analysis.

3.2.4 Statistical analysis

3.2.4.1 Geometric means method

In order to compare the OELs from South African occupational health legislation to the OELs of developed countries the geometric means method which was first applied to OELs by Hansson (1998) was used. The best indicator of the difference between the OELs for a HCS is to calculate the quotient. The geometric mean is calculated for all the different ratios since this is the best indicator of the overall level of the complete list of a specific country or authority (Schenk *et al.*, 2008b). The concept of the geometric mean method can be illustrated by the following example: Three HCSs have OELs listed within List *A* and *B*. In List *A* the OELs are as follows: substance I - 20 mg/m^3, substance II - 15 mg/m^3 and substance III – 10 mg/m^3. In List *B* the same substances are listed but the OELs are as follows: substance I - 200 mg/m^3, substance II - 15 mg/m^3 and substance III – 1 mg/m^3. The arithmetic means of ratios for *B/A* or *A/B* both equal 3.7 which gives the impression that List *A* or List *B* have set higher OELs. In this case the list which will be perceived as having the higher set OELs depends on which list was used as the denominator (Schenk *et al*., 2008a; Ding *et al*., 2011). A geometric mean equal to 1 indicates that there is no difference in the OELs for a substance on both lists. A geometric mean below 1 indicates that an overall lower level of OELs is present on the list being compared whilst a geometric mean higher than 1 indicates an overall higher level of OELs (Schenk *et al*., 2008a; Viljoen, 2012). The lower the calculated geometric mean, the lower the over-all OELs that are being compared (Schenk *et al.*, 2008b). The RHCS's OELs were compared to developed countries OELs and similarly for the MHSR's OELs and the developed countries.

3.2.4.2 T-test comparison of the geometric means method

Since OELs are listed in Table I and Table II of the RHCS, a geometric mean value was calculated for each table. To determine if there was a significant statistical difference between the geometric mean of the tables a dependent t-test was conducted. A $p \leq 0.05$ was considered as significant.

3.2.4.3 Interval method

In order to compare the number of HCSs that have an OEL in the MHSR that are similar, higher or lower than the OEL listed in the RHCS an interval method was applied (Tynkkynen *et al.*, 2015). A MHSR OEL value within 95-105% of the RHCS OEL was considered a similar OEL (Tynkkynen *et al.*, 2015). The 5% lower value was calculated by multiplying the current OEL for a specific HCS with 0.05 and subtracting it from the current OEL (e.g. Acrylamide (79-06-1): 0.3mg/m^3 - (0.3mg/m^3 * 0.05)). The 5% higher value was calculated in the same way (e.g. Acrylamide (79-06-1): 0.3mg/m^3 + (0.3mg/m^3 * 0.05)).

3.3 Results

3.3.1 Selection of a carcinogen classification system

The selection of a carcinogen classification system for use in South African legislation was determined from the criteria depicted in Table 3. The IARC had the highest score and was, therefore, selected as the system to be recommended for use in South African occupational health legislation. The results that follow will, therefore, be based on the database that only contained the HCSs classified as carcinogenic by the IARC.

Table 3: The scores attained by each carcinogen classification system according to the predetermined criteria.

System/Organisation					
Criteria point	*IARC*	*ACGIH*	*EPA*	*NTP*	*EU*
Are the methods followed during epidemiological studies available to public?	1	2	2	1	1
Are there references listed in the official documentation?	2	2	2	2	2
Is this documentation updated on a frequent basis? (Annually etc.)	2	2	2	2	1
Are the notations assigned to carcinogens simple and easy to understand?	2	2	2	2	2
Number of notations efficient to cover all necessary factors that have to be considered?	2	2	2	1	1
Is the list of chemicals with their notations easy to find and accessible?	2	1	1	2	1
Does documentation available to the public/user incur financial expenses?	2	1	2	2	2
Can documentation be downloaded from the internet?	2	1	1	2	2
Is the system established in developed countries and have they been in use successfully for years?	2	2	2	2	2
Are all chemicals considered or only a certain group? (E.g. Pesticides)	2	2	1	2	2
Score (Maximum = 20)	19	17	17	18	16

3.3.2 Hazardous Chemical Substance Regulations

3.3.2.1 Carcinogen classification of HCSs

A total of 155 HCSs that had synonyms in the RHCS and MHSR were removed from the database. The total number of HCSs listed in the RHCS when Tables I and II of the RHCS were combined and IARC classified carcinogens were considered was 77, with 22 listed in Table I and 55 in Table II. The IARC classification of Group 3 (Not classifiable as to its carcinogenicity to humans) and Group 4 (Probably not carcinogenic to humans) were excluded from the database because they are not applicable to humans.

3.3.2.2 Level of OELs

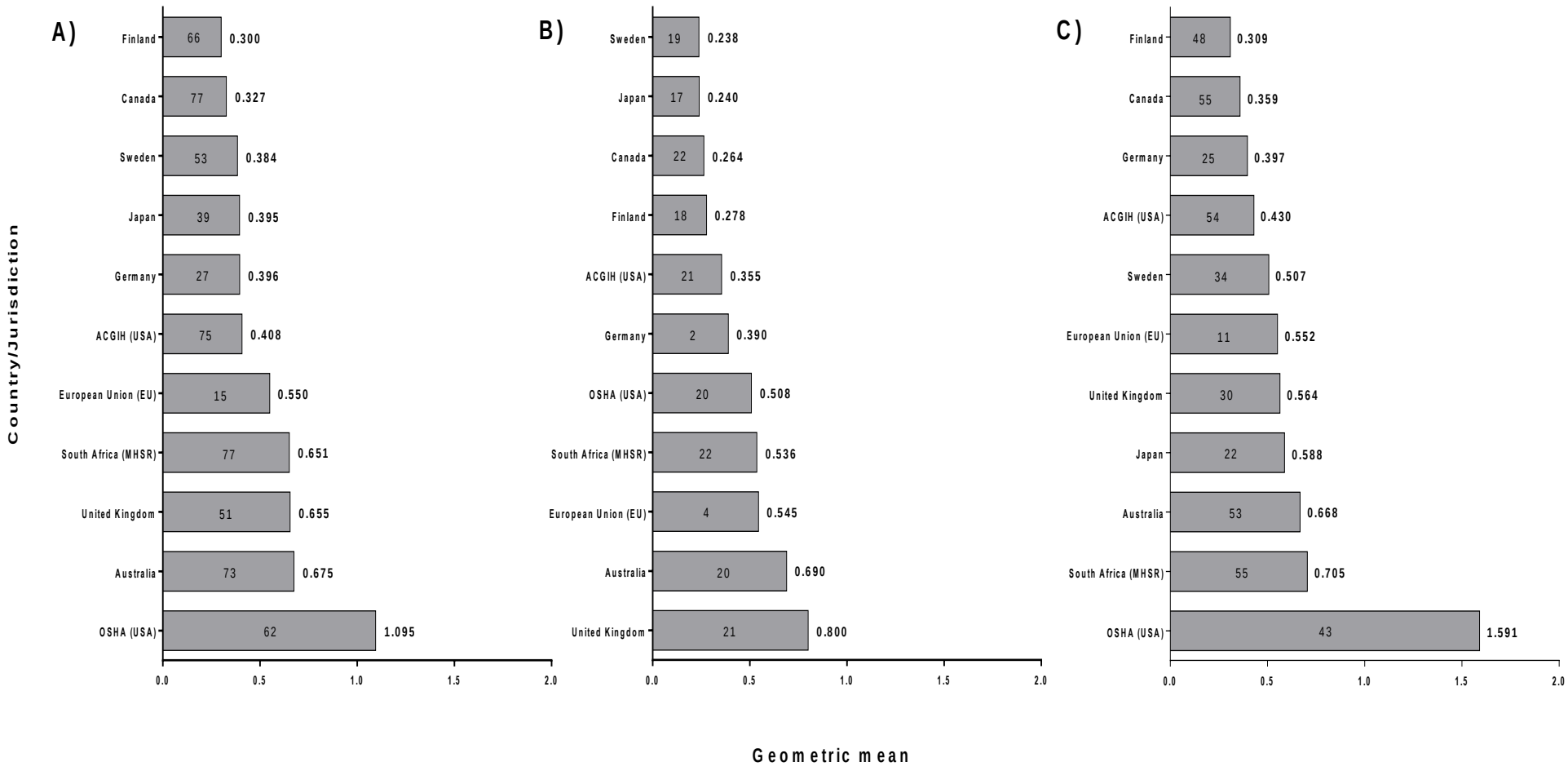


Figure 1: Comparison of geometric mean values for IARC listed substances of the RHCS for **(A)** combined values of Table I and II of the RHCS; **(B)** Table I only and **(C)** Table II only in ascending order. (The number of substances used from each country is indicated inside the bar with the geometric mean value indicated next to the bar).

To compare the overall levels of the OELs for HCS classified as carcinogens by the IARC of developed countries to the overall level of the OELs listed within the RHCS, the geometric means method was used. Since the RHCS lists the OELs for HCSs in two tables namely, Table I and II, a geometric mean was calculated for each table. A geometric mean value was also calculated by combining Table I and II to compare with the individually calculated geometric mean of Table I and II. Figure 1A illustrates the geometric means when IARC classified HCS were included for Table I and II combined. Most of the countries/jurisdictions had a geometric mean below 1 with the exception of OSHA (USA) which had a geometric mean of 1.095. There were five countries/jurisdictions that had a geometric mean below 0.400 namely: Finland (0.300), Canada (0.327), Sweden (0.384), Japan (0.395) and Germany (0.396). Figure 1B is the geometric mean values for Table I only, and all the geometric means were below 1. The United Kingdom had the highest geometric mean of 0.800. The countries/jurisdictions that had a geometric mean below 0.400 were Sweden (0.238), Japan (0.240), Canada (0.264), Finland (0.278), ACGIH (USA) (0.355) and Germany (0.390). Figure 1C illustrates geometric mean values for Table II with most of the geometric means being below 1 except for OSHA (USA) which had a geometric mean of 1.591. The countries/jurisdictions that had a geometric mean value that was below 0.400 included Finland (0.309), Canada (0.359) and Germany (0.397).

3.3.3 Mine Health and Safety Regulations

3.3.3.1 Carcinogen classification of substances

The IARC carcinogen for the MHSR list contained a total of 76 substances. As stated previously HCSs with a Group 3 (Not classifiable as to its carcinogenicity to humans) and Group 4 (Probably not carcinogenic to humans) notations were excluded from the database because they are not applicable to humans.

3.3.3.2 Level of OELs

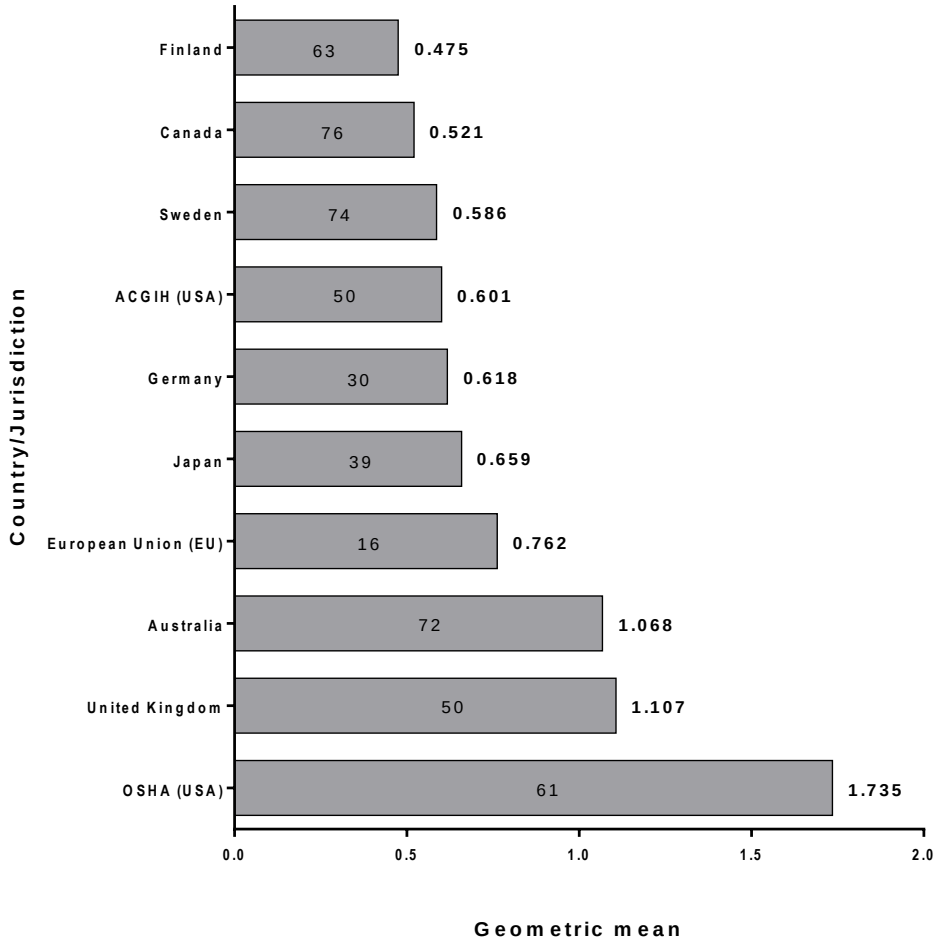


Figure 2. Geometric mean values for IARC listed substances of the MHSR in ascending order. (The number of substances used from each country is indicated inside the bar with the geometric mean value indicated next to the bar).

Figure 2 illustrates the geometric means of the MHSR when IARC classified HCS were included. The geometric means for most of the countries/jurisdictions were below 1 with the exception of Australia (1.068), the United Kingdom (1.107) and OSHA (USA) (1.735). The lowest geometric mean was calculated for Finland with a value of 0.475.

3.3.3.3 Comparison of number of carcinogenic HCSs with an OEL similar, lower or higher in SA legislation

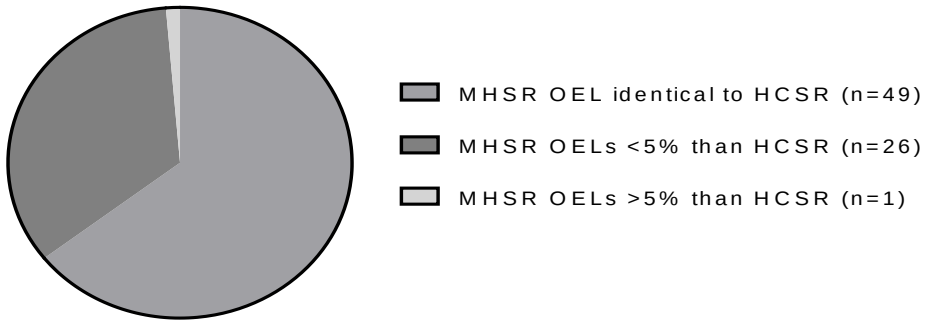


Figure 3. The interval method was used to compare the OELs from the RHCS (Table I and II combined) and the MHSR to establish the fraction of OELs higher, lower and identical to the RHCS's OELs.

Figure 3 illustrates the carcinogenic HCSs identified in the RHCS (Table I and II combined) compared to the OELs listed by the MHSR. The total number of HCSs was 76. It was found that 49 HCSs (64.5%) had OELs that were similar to the OELs of the RHCS, 26 HCSs (34.2%) had OELs lower than those in the RHCS and 1 HCS (1.3%) had an OEL higher than that of the RHCS.

3.4 Discussion

South Africa is a mineral rich country and the price of extracting that wealth sometimes comes at a much higher price for the workers employed in the mining and industrial sector. Environmental and occupational exposure to carcinogens in countries such as South Africa present situations where unnecessary exposures at high levels may occur, leaving the worker at risk of developing occupational cancer (McCormack and Schüz, 2012). Occupational cancer can be avoided when the right control measures for carcinogenic exposure are put in place and can ultimately reduce the global occupational cancer burden (Blair *et al.*, 2011; Brawley, 2011). The first step in controlling carcinogenic exposure is to identify the carcinogenic HCSs being used in the industrial and mining sectors by means of assigning a notation to HCSs that shows how prone they are in causing the development of cancer.

The use of a combination classification system may be impractical since the notations assigned by a classification system used different experimental procedures, epidemiological data and

animal to human extrapolation to determine a notation for a HCS. Since each organisation has their own objectives and final use for the information acquired during risk assessments a large margin of uncertainty exists surrounding risk assessment even when formalised (Valente and Cavariani, 1998; Pausenbach *et al.*, 2011). Therefore, the use of only one carcinogen classification in South African legislation is recommended.

The most noteworthy carcinogen classification systems were evaluated with the IARC's carcinogen classification system receiving the highest score during the completion of the criteria set for evaluation of these systems. The IARC is part of the World Health Organisation (WHO) and the notations assigned to each HCS that are considered carcinogenic are published in the monographs of which 112 volumes were available at the time of this study (IARC, 2015).

The IARC is tasked with the collection of information, toxicology data and scientific data regarding chemical carcinogens, occupational exposures and lifestyle factors. The HCS that are classified as carcinogens undergo critical reviews and evaluations to relate the carcinogenicity of these HCSs to human exposure. International agencies use the IARC findings on carcinogens to supplement their own carcinogen classification systems (IARC, 2015). An example of an agency that uses IARC based data on carcinogenic HCSs to supplement their own data in their carcinogen classification system is the ACGIH. The ACGIH excludes HCS from carcinogenic classification if there is no human or experimental animal data available for a HCS (ACGIH, 2015). The US EPA mainly classify the carcinogenic hazards of pesticides (EPA, 2015), which means they have a specialised list of carcinogens that are not always used in the mining and industrial industries of South Africa. The National Toxicology Programme (NTP) is mainly focused on identifying HCS that pose a carcinogenic risk to the population of the USA (NTP, 2015).

It was found that that only 77 of the HCSs listed in Table I and II of the RHCS were considered carcinogenic according to the IARC. In the MHSR 76 of the HCSs were considered carcinogenic according to the IARC. The difference can be explained by 2-Nitrotoluene (CAS 88-72-2) which did not have an OEL listed in the MHSR but did have a specified OEL in the RHCS. The results for the IARC concerning the RHCS showed that the geometric means for Tables I and II were all below 1 which indicated that an overall lower level of OELs was present on the list that the RHCS were being compared to, with the exception of the geometric mean for OSHA (USA) in Table II which was 1.591. Even when Tables I and II were combined the geometric mean

calculated for OSHA (USA) was still the only value above 1 (1.095). Viljoen (2012) also found that the OELs for the OSHA had a geometric mean >1. The OSHA (USA) OELs used within this study were the OEL values published in 1970 and have not been updated since that time with OSHA acknowledging this fact (OSHA, 2015). These values were the most up to date and as a result may be considerably higher than the OELs listed within the RHCS which was implemented in 1995 with only one amendment made over the last 20 years (South African Department of Labour, 1995). The countries/jurisdictions which had a geometric mean below 0.400 when Tables I and II of the RHCS were combined were Finland (0.300), Canada (0.327), Sweden (0.384), Japan (0.395) and Germany (0.396). The geometric mean for these countries/jurisdictions indicated that the lowest OELs can be found on these lists for HCSs since their geometric means were so far below 1. Viljoen (2012) found that the ACGIH, Japan and Finland had the lowest overall levels of OELs and that these OELs were health based. When the geometric means of Tables I and II were compared to one another using a dependent t-test it was found that there was no statistical significant difference between the geometric means for Tables I and Table II. This indicated that overall level at which Tables I and Table II were set was consistent even though the Table I contained HCSs with OEL-CL since they are considered more hazardous and are regulated more strictly. Even though the OELs for Table I were set more than 20 years ago it should still be set at an overall lower level than Table II when regarding the type of the HCS contained in Table I.

The OELs listed within the MHSR were revised in 2006 by the Mining Occupational Health Committee (MOHAC) which means the OELs of the MHSR should be more in line with the overall level at which developed countries set their OELs, since the MHSR OELs are 10 years old (South Africa, 2006). The results for IARC classified HCS listed in the MHSR indicated that the following countries/jurisdictions had a geometric mean above 1: Australia (1.068), the United Kingdom (1.107) and OSHA (USA) (1.735). The reason for this may be explained by the list of OELs used from those countries/jurisdictions. As previously mentioned the OSHA (USA) OELs used were the 1970 published values, the United Kingdom's OELs used for this study were the OELs published in 2011, but there were only a few OELs in this list that were revised since 2002 (Health and Safety Executive, 2013) and Australia's Workplace Exposure Limits were the 2013 version but again only a few HCS's had updated OELs (Safe Work Australia, 2013). The OSHA (USA), United Kingdom and Australia based their OELS on the OELs of the ACGIH (Viljoen, 2012). The fact that the geometric means for these countries/jurisdictions fell

within such a close range of one another may be as a result of all three having considered ACGIH OELs when setting their current OELs.

Viljoen (2012) found that the overall level of South African OELs was at a substantially higher overall level than developed countries' OELs with a weak prevalence for uniquely regulated OELs. The ACGIH is one of the most influential organisations when it comes to setting OELs for HCS in the workplace as was stated by Schenk *et al.* (2008a). The ACGIH is still listed in some occupational health and safety documents as a major source of OEL documentation (Schenk *et al.*, 2008b). A comparison between the results from the IARC and results based on the ACGIH can be found in the supplementary material of this study. The geometric means for Tables I and II combined of the RHCS, and Table I and Table II respectively were compared in the same manner as with the IARC (Supplemental Table 1 and Supplemental Table 2). It was found that there is no statistical difference ($p = 0.199$) between the IARC and ACGIH listed HCSs OELs in the RHCS. A statistical difference ($p = 0.003$) was however found between the HCSs listed in the MHSR for the IARC and ACGIH databases.

When the OELs from the RHCS were compared to the MHSR to calculate the percentage of similar, higher or lower OEL contained in the list, it was found that 64.5% of the OELs from the MHSR were similar to those in the RHCS. The fact that the MHSR had 34.2% of its HCS at a lower OEL than the RHCS indicates that the organisations used to base the MHSR's OELs on have a generally lower level at which they set their OELs. Only 1.3% (1 HCS) had a higher OEL than the RHCS. A comparison to indicate the similar, higher or lower OELs from the RHCS compared to the ACGIH can be found in the supplementary data (Supplemental Figure 1) of this study. The results from this supplementary data confirmed that the MHSR's OELs showed greater similarity to the ACGIH's OELs when compared to the RHCS since 31.4% of the MHSR's OELs were considered similar to the ACGIH and only 23.3% of the ACGIH's OELs were considered similar to the RHCS. Since the ACGIH's OELs are lower it can therefore be concluded that the MHSR's OELs are also at a lower overall level.

The difference between the OELs set in the two sets of South African occupational health legislation can be explained by the country/jurisdiction used to base the OELs on. The RHCS are based on the United Kingdom values whilst the MHSR are based on the ACGIH and NIOSH (Department of Labour, 1995; Brandys and Brandys, 2008; Viljoen, 2012). The year the RHCS's OELs were compiled the OELs available were the 1993 values and the MHSR was based on

the 2006 OELs values that were available at the time of revision. This also explains why the OELs listed in the MHSR were at a lower level than the OELs of the RHCS. Since the process of establishing OELs requires a large amount of research and specialised personnel to conduct this research, not all countries can perform their own research programme to cover all the HCS that need to be included. Therefore, research performed by other countries which already have an established research programme to establish OELs is used to compile legislation for developing countries like South Africa (ILO, 1991). Since both South African occupational health legislations that contain OELs are outdated, the level of protection they offer the worker is not what it should be. This leaves the worker susceptible to developing adverse health effects from exposure which can lead to an increase in the number of occupational cancer cases found in the workforce, which in this case is the development of occupational cancer.

3.5 Conclusion

This study found that the carcinogen classification best suited for use within South African legislation is the IARC's carcinogen classification since this system is updated every few months. This system is also internationally recognised and freely accessible on the internet. This system classified 481 substances of which the RHCS contained 77 substances and the MHSR contained 76 substances classified as carcinogenic to humans with Group 1, Group 2A and Group 2B notations being assigned. It was found that South African OELs are at higher level than the OELs listed by developed countries since the geometric mean values calculated for most developed countries were below 1 with the exception of OSHA when compared to the RHCS in South African legislation. In the MHSR it was found that OSHA, Australia and the United Kingdom had a geometric mean >1. When the RHCS's OELs were compared to the MHSR a geometric mean of 0.651 was calculated that confirmed the overall level at which OELs of the MHSR are set were at a lower level. The country/jurisdiction with the lowest geometric mean in the RHCS (Tables I and II combined) database and MHSR database was Finland. This indicated that the lowest overall OELs for carcinogenic HCSs in developed countries are listed by Finland with the latest list being published in 2014.

3.6 Supplementary material

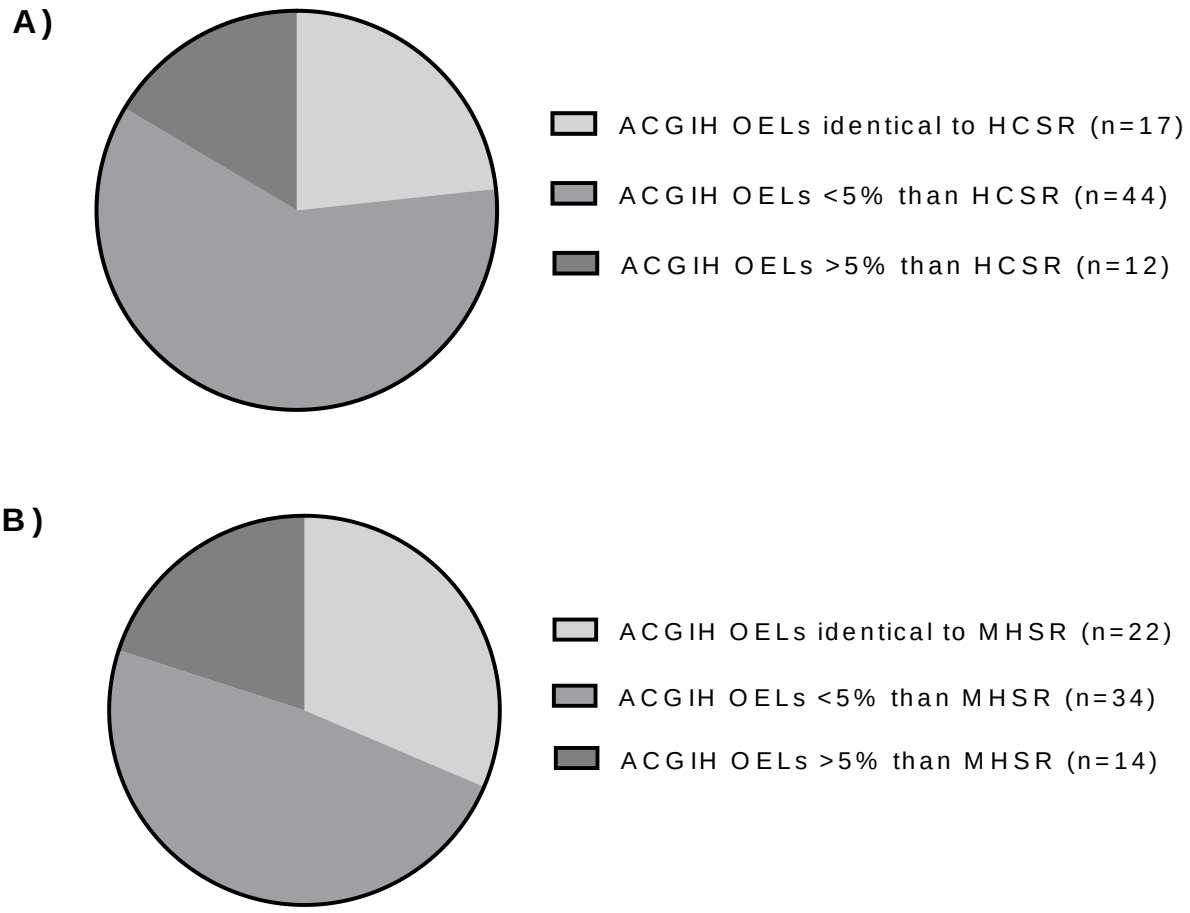
Supplemental Table 1: Geometric means for hazardous chemical substances (HCS) found in Tables I and II of the RHCS that were also classified as carcinogens by the ACGIH. Table I and II's geometric means are shown separately as well as combined. The difference between the geometric means for the IARC and ACGIH classified HCSs was not statistically significant (p = 0.199). The geometric means for Tables I and II combined are listed in ascending order.

	Table 1 and 2 combined	*Number of HCS included*	*Table 1*	*Table 2*
Finland	0.332	96	0.278	0.346
Canada	0.341	110	0.264	0.366
Sweden	0.371	65	0.238	0.449
Japan	0.399	48	0.355	0.529
ACGIH (USA)	0.403	108	0.240	0.415
Germany	0.426	36	0.390	0.428
European Union (EU)	0.451	21	0.545	0.431
South Africa (MHSR)	0.617	110	0.536	0.640
United Kingdom	0.625	67	0.800	0.557
Australia	0.631	105	0.690	0.618
OSHA (USA)	1.047	90	0.508	1.308

Supplemental Table 2: Geometric mean for the HCS listed in the Mine Health and Safety Regulations (MHSR) that are also classified as carcinogenic by the ACGIH. The difference between the geometric means for the IARC and ACGIH classified HCSs was considered highly significant (p = 0.003).The geometric means are listed in ascending order.

	MHSR	*Number of HCS included*
Finland	0.600	92
Canada	0.606	108
Sweden	0.634	64
ACGIH (USA)	0.658	106
European Union (EU)	0.747	22
Japan	0.781	49
Germany	0.815	42
Australia	1.108	103
United Kingdom	1.144	67
OSHA (USA)	1.930	89

Supplemental Figure 1: The interval method was used to compare the OELs from **(A)** the RHCS (Table I and II combined) and **(B)** the MHSR to establish the fraction of OELs higher, lower and identical to the RHCS's OELs.



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Chapter 4

Concluding Chapter

4.1 Conclusions

The aim of this study had a three part approach: Firstly, a recommendation was to be made for a carcinogen classification system that can be used within the South African occupational health legislation. Secondly, the HCSs that are considered to be carcinogenic to humans by the selected carcinogen classification system would be identified in the Regulations for Hazardous Chemical Substances (RHCS) and Mine Health and Safety Regulations (MHSR). Thirdly, the occupational exposure limits (OELs) given in the RHCS and the MHSR for these carcinogenic HCSs would be compared to developed countries OELs to establish the overall level at which South African OELs for these carcinogens compare to OELs set in developed countries.

The system that can be applied to South African occupational health legislation for classification of carcinogenic HCSs in the RHCS and MHSR was the IARC. This was achieved through the use of a system with set criteria points being assigned a numerical value on account of how applicable it would be in South African occupational health legislation e.g. “Is this documentation updated on a frequent basis? (Annually etc.)”. The IARC’s system is updated every few months and is, therefore, the most up to date classification system. The substances included for review within this classification system must meet the criteria of the IARC’s working teams. These teams consist of toxicologists, cancer biologists, epidemiologists of cancer and experts (Environmental Chemistry, Toxicology and Ecotoxicology Resources, 2010). This IARC criteria states that there must be evidence of human exposure and that there is some evidence or suspicion of carcinogenicity (IARC, 2015). Since the data for the IARC’s monographs go through very rigorous assessments and are updated at least once annually this system holds great advantage for use in South Africa. There are no costs linked to the use of the information and the monographs can be downloaded from the internet.

South African occupational health legislation consists of the Occupational Health and Safety (OHS) Act which applies to the industrial sector and the Mine Health and Safety (MHS) Act which applies to the mining sector. Whilst the OELs listed in the regulations of these Acts (OHS Act has the RHCS and the MHS Act has the (MHSR) apply only to the sector the act was intended for, the OELs for some HCSs differ e.g. Acetaldehyde (75-

07-0): RHCS = 45 mg/m^3 and MHSR = 180 mg/m^3. It should also be pointed out that the OELs in the RHCS and MHSR were not based on the same country/jurisdiction. OELs in the OHS Act are based on the United Kingdom's OEL values available at that time (1993) and the MHS Act is based on the ACGIH TLVs and NIOSH PEL values at that time (2006) (South African Department of Labour, 1995; South African Department of Minerals and Resources, 1996, Brandys and Brandys, 2008). This has led to one HCS not having an OEL listed in the MHSR. It was, however, found by a study conducted by Viljoen (2012) that there is a strong agreement between the RHCS and MHSR, which indicates national similarity between the OELs listed in these regulations. It should also be kept in mind that the MHSR were updated in 2006 whilst the RHCS has not been updated in its entirety since 1995 (South Africa Department of Labour, 1995; South African Department of Minerals and Recourses, 1996). Since the HCSs used in each industry are the same, standardizing OELs for carcinogenic HCSs in South Africa should be considered as these HCSs do not have a definite safe biological threshold. Although the workers in each industry (industrial and mining) are not exposed to the same levels of HCS during their workday, choosing the population with the highest exposure and applying intervention strategies to these working environments may be beneficial for a country such as South Africa (Cherrie, 2009). This will reduce the number of workers that develop occupational diseases and most importantly occupational cancer cases in South Africa. Although the theoretical minimum exposure of zero for HCSs with carcinogenic properties are not always possible to achieve since there is always some low-level exposure to environmental or background levels (Concha-Barrientos *et al.*, 2004).

After identifying a carcinogen classification system for incorporation into South African occupational health legislation, the carcinogenic HCS already listed in the RHCS and the MHSR were identified. The OELs listed for these HCSs in the ten developed countries were then compared to the OELs currently listed in the RHCS and MHSR. This reflected the overall level at which carcinogenic HCS's OELs compare to developed countries' OELs. The results of this comparison showed that South African OELs are at a higher level than the OELs listed by developed countries since the geometric mean values calculated for most developed countries were below 1 with the exception of OSHA in comparison to the RHCS in South African legislation. In the MHSR it was found that

OSHA, Australia and the United Kingdom had a geometric mean >1. These were all lists that have not been updated within the last 10 years with Australia's Workplace Exposure Limits being the 2013 version but only a few HCS's had updated OELs (Safe Work Australia, 2013), OSHA (USA) still uses OELs from 1970 (OSHA, 2015) and the United Kingdom's OELs were the OELs published in 2011 (Health and Safety Executive, 2013), but there were only a few OELs in this list that had been revised since 2002.

To ensure all aspects were taken into consideration, HCSs classified according to the ACGIH's were included in a separate database and the same method for calculating the geometric mean was applied. The ACGIH was selected as comparison since this agency is considered the most influential in the setting of OELs and is listed in most OEL documentation of countries/juristictions as a source on which to base their OELs (Schenk *et al.*, 2008a; Schenk *et al.*, 2008b). When a dependent t-test was applied to the calculated geometric means of the MHSR listed OELs, it was found that the geometric means calculated for only the IARC database differed significantly ($p = 0.003$) from the geometric means for the ACGIH database. This can be attributed to the number of HCSs that were included in the ACGIH database. The number of HCSs the ACGIH added to the database was 33. The IARC as carcinogen classifications system does not state OELs for carcinogenic HCSs and only assigns notation to indicate if the HCS is carcinogenic to humans and how likely it is to cause cancer with exposure.

The OELs from the RHCS were compared to the MHSR to calculate the percentage of similar, higher or lower OEL contained in the list. It was found that 64.5% of the OELs from the MHSR were similar to the RHCS. This confirmed the finding that was made by Viljoen (2012) regarding national similarity between the RHCS and MHSR. The fact that the MHSR had 34.2% of its HCS at a lower OEL than the RHCS indicates that the organisations used to base the MHSR's OELs on have a generally lower level at which they set their OELs. Only 1.3% (1 HCS) had a higher OEL than the RHCS. The MHSR have generally lower set OELs compared to the RHCS since 31.4% of the MHSR's OEL were considered similar to the ACGIH and only 23.3% of the ACGIH's OELs were considered similar to the RHCS. The comparison between the RHCS's OELs and the MHSR's had a geometric mean of 0.651 which confirmed the overall level at which OELs

of the MHSR are set were at a lower level since the calculated geometric mean was <1. The MHSR's OELs are, therefore, closer to the level of developed countries when considering that the MHSR has not been updated in the last 10 years. As previously mentioned the MHSR OELs are also based on the ACGIH TLV values which were available in 2006 when the MHSR were revised (Department of Minerals and Resources, 1996; Brandys and Brandys, 2008). The rate of change in the ACGIH OELS since 2006 to an overall lower level is apparent but most of the HCS's OELs have remained greatly unchanged.

The hypothesis for this study: "The OELs set by developed countries and/or organisations for carcinogenic HCSs are at a lower level with geometric mean values <1 than the OELs set at present in both the RHCS and MHSR" is partially accepted. It was found that the current OELs listed in the RHCS and MHSR for carcinogenic HCSs are set at an overall higher level when compared to some developed countries' OELs. With relation to the RHCS the only developed country/jurisdiction which had a geometric mean >1 was OSHA. With relation to the MHSR three countries/jurisdictions had an overall higher level at which their OELs were set, namely: Australia, United Kingdom and OSHA (USA). These countries' OEL lists were not updated in their entirety during the last decade. This creates an environment in the workplace where workers are not adequately protected against exposure to carcinogenic HCSs which can lead to development of occupational cancers.

4.2 Recommendations

The setting of OELs by counties/jurisdictions is an expensive and labour intensive process (ILO, 1991). During the setting of OELs, uncertainty factors (UFs) are usually factored in to ensure that the extrapolation of data obtained from animal studies can be applied as safe human exposure levels (Ministry of Business, Innovation and Employment, 2013). However, there is an exception to this application for HCS that do not have a biological threshold such as genotoxic carcinogens and mutagens. In these cases the general rule is that no safe dose exists and they are treated as posing excess risk, even if it's slight, at any exposure above zero. In these cases the biological threshold is based on dose-response modeling and low dose extrapolation instead of UFs

(Dankovic *et al*., 2015). Since each country/jurisdiction has their own risk policies and risk assessment methodology it is often found that there is a considerable variation in the OELs set for one HCS in each country/jurisdiction (Deveau *et al*., 2015).

For the RHCS there were two tables that contained OELs for the OHS Act namely: Tables I and II. Table I contained 22 carcinogenic HCS and Table II contained 55 carcinogenic HCS which brought the total of carcinogenic HCS listed in the RHCS to 77. In the MHSR of the MHS Act 76 carcinogenic HCSs were listed. The total HCS for the RHCS and MHSR differed by 1 HCS since 2-Nitrotoluene (CAS 88-72-2) did not have an OEL listed in the MHSR but did have a specified OEL in the RHCS.

Recommendation 1: It would be beneficial for the committees responsible for deciding which OELs to use in the RHCS and MHSR to co-ordinate their efforts with regards to carcinogenic HCS's OELs. The HCSs included in the RHCS and the MHSR are similar with the exception of one HCS that the MHSR did not include in its OEL list. The MHSR also has lower set OELs when compared to the RHCS since the MHSR was revised in 2006.

Recommendation 2: South Africa should consider using the lowest available OELs for carcinogenic HCS available from the ten developed countries (Australia, Canada (British Columbia), Finland, Germany, Japan, United Kingdom (UK), United States of America (USA) (ACGIH and OSHA), Sweden and the binding and indicative OELs published by the EU)) considered influential in setting OELs for occupational settings. Tables 1 and 2 (follows on page 65 and 66) state the lowest available OEL for each carcinogenic HCS list in the RHCS (Table I of the RHCS only and Table II of the RHCS only) and Table 3 (follows on page 68) contains the lowest OELs for the carcinogenic HCSs listed in the MHSR.

Recommendation 3: South Africa's occupational health legislation should assign the carcinogenic notations from the IARC to the HCSs currently listed in the RHCS and MHSR. The HCSs that are considered carcinogenic to humans should be assigned these notations since it will indicate the risk posed by handling these HCSs and how likely occupational cancer will develop after exposure.

Recommendation 4: The RHCS should assign Chemical Abstracts Service (CAS) numbers to Table 1 and Table 2 listed HCSs to assist in the identification of synonyms listed as well as ease the identification of the listed HCSs.

Table 1. Recommended OELs for HCSs listed in Table I only of the RHCS.

Substance	CAS #	IARC Classification	RHCS SA (TWA) (mg/m^3)	Recommended OEL (mg/m^3)	Country/Organization OEL is listed in
Acrylamide	79-06-1	2A (1994)	0.3	0.03	ACGIH (USA); Australia; OSHA (USA); Sweden; Canada; Finland
Acrylonitrile	107-13-1	2B (1999)	4	(4.3)*	Australia; Japan
Arsenic & compounds, except arsine (as As)	7440-38-2	1 (2012)	0.1	0.003	Japan
Benzene	71-43-2	1 (2012)	16	1.5	Sweden
Bis (chloromethyl) ether (BCME)	542-88-1	1 (2012)	0.005	0.005	*All
Buta-1,3-diene	106-99-0	1 (2012)	22	1	Sweden
Cadmium & cadmium compounds, except cadmium oxide fume and cadmium sulphide pigments (as Cd)	7440-43-9	1 (2012)	0.05	0.005	OSHA (USA)
Chromium (VI) compounds (as Cr)	7440-47-3	1 (2012)	0.05	0.005	OSHA (USA); Sweden; Finland
1,2-Dibromoethane (ethylene dibromide)	106-93-4	2A (1999)	4	(0.78)*	Finland
Dichloromethane	75-09-2	2A (in prep)	350	120	Sweden
2,2'-Dichloro-4,4'methylene dianiline (MbOCA)	101-14-4	1 (2012)	0.005	0.005	United Kingdom; Japan
Ethylene oxide	75-21-8	1 (2012)	10	(0.18)*	Canada
Formaldehyde	50-00-0	1 (2012)	2.5	(0.12)*	Japan
Lead, elemental, and inorganic compounds (as Pb)	7439-92-1	2A (2006)	0.15	0.05	ACGIH (USA); OSHA (USA); Canada
Nickel (Metal)	7440-02-0	2B (1990)	0.5	0.01	Finland; Japan
Nickel, inorganic compounds (as Ni)		1 (2012)			
soluble compounds	7440-02-0	1 (2012)	0.1	0.01	Japan
insoluble compounds	7440-02-0	1 (2012)	0.5	0.01	Finland
Silica, crystalline	14808-60-7	1 (2012)	0.1	0.025	ACGIH (USA); Canada
Styrene	100-42-5	2B (2002)	420	43	Sweden
Trichloroethylene	79-01-6	1 (2014)	535	50	Sweden; Finland
Vinyl chloride	75-01-4	1 (2012)	17.89	2.5	Sweden
Wood dust (hard wood)		1 (2012)	5	1	ACGIH (USA); Australia; Canada

LEGEND:

( )* - parts per million value that was converted to milligrams per cubic meter. The value was rounded to a whole number in the SA legislation by the committees responsible for setting OEL values in the OHS Act and MHS Act. This has led to the false impression that SA has a lower OEL for selected HCSs.

***All** - All countries that had a listed OEL for that HCS had the same value listed, including the RHCS and MHSR.

****** - Value listed in developed countries is higher since revision of the HCS.

Table 2. Recommended OELs for HCSs listed in Table II only of the RHCS.

Substance	CAS #	IARC Classification	RHCS SA (TWA) (mg/m^3)	Recommended OEL (mg/m^3)	Country/Organization OEL is listed in
Acetaldehyde	75-07-0	2B(1999)	180	36	United Kingdom
Aniline	62-53-3	2B(1999)	10	(1.9)*	OSHA; Finland
o-Anisidine	90-04-0	2B(1999)	0.5***	0.5	ACGIH (USA); Canada; Japan
Asphalt, petroleum fumes	8052-42-4	2B(2013)	5	0.5	ACGIH (USA); Canada
Aziridine (Ethyleneimine)	151-56-4	2B(1999)	10	(0.09)*	ACGIH (USA)
Benzyl chloride	100-44-7	2A(1999)	5	2.6	United Kingdom; Finland
Beryllium	7440-41-7	1(2012)	0.002	0.00005	ACGIH (USA); Canada
Bis-(2-ethylhexyl) phthalate (Di-(2-ethylhexyl) phthalate (dioctyl phthalate)	117-81-7	2B(2013)	5	3	Sweden
Bromoethylene (Vinyl bromide)	593-60-2	2A(2008)	20	(2.19)*	ACGIH (USA); Canada
Carbon black	1333-86-4	2B(2010)	3.5	3	ACGIH (USA); Australia; Canada
Carbon tetrachloride	56-23-5	2B(1999)	12.6	(0.63)*	Australia (WHS)
Catechol (o-Dihydroxybenzene) (Pyrocatechol)	120-80-9	2B(1999)	20***	20	Sweden. Revised 2011.
Chlordane (ISO)	57-74-9	2B(2001)	0.5	0.5	*All
1-Chloro-2,3-epoxypropane (Epichlorohydrin)	106-89-8	2A(1999)	8	(0.38)*	Canada
Chloroform (Trichloromethane)	67-66-3	2B(1990)	9.8	2.5	Germany
Coal tar pitch volatiles (as cyclohexane solubles)	65996-93-2	1(2012)	0.14	0.2**	ACGIH (USA); Australia; Canada. Revised 2013
Cobalt metal - dust and fumes	7440-48-4	2B(1991)	0.1	0.02	Sweden; Canada; Finland
Cristobalite, respirable dust (Sillica,cristaline)	14808-60-7	1(2012)	0.1	0.025	ACGIH (USA); Canada
Cumene (Isopropyl benzene)	98-82-8	2B(2013)	120	50	Germany
DDT	50-29-3	2B(1991)	1	1	*All
DDVP (Dichlorvos)	62-73-7	2B(1991)	1	0.1	ACGIH (USA); Canada
4,4'-Diaminodiphenylmethane (DADPM) (4,4 metylene dialinine)	101-77-9	2B(1987)	0.8	0.08	Australia; Finland
1,4-Dichlorobenzene (p)	106-46-7	2B(1999)	150	6	Germany
1,2-Dichloroethane (Ethylene dicloride)	107-06-2	2B(1999)	40	4	Sweden; Finland
1,3-Dichloropropene, cis and trans isomes	542-75-6	2B(1999)	5	4.5	Australia
Diethanolamine (2,2'-Iminodiethanol)	111-42-2	2B(2013)	15	1	ACGIH
Dimethyl sulphate	77-78-1	2A(1999)	0.5	0.16	Finland
2,4-Dinitrotoluene	121-14-2	2B(1996)	1.5	0.2	Finland
1,4-Dioxane, tech. grade	123-91-1	2B(1999)	90	35	Sweden

Divanadium pentoxide (inhalable dust and fume) (vanaduim pentoxide)	1314-62-1	2B(2006)	0.5	0.02	Finland
1,2-Epoxy-4-epoxyethyl-cyclohexane (Vinyl cyclohexene dioxide)	106-87-6	2B(1994)	60	2.9	Finland
Ethanol (Ethyl alcohol)	64-17-5	1(2012)	1900	960	Germany
Ethyl acrylate	140-88-5	2B(1999)	20	20	Australia; Sweden
Ethylbenzene	100-41-4	2B(2000)	435	(86.84)*	ACGIH (USA)
Heptachlor and heptachlor epoxide	76-44-8; 1024-57-3	2B(2001)	0.5	0.05	ACGIH (USA); Canada; Germany; Finland
Hexachloroethane (vapour)	67-72-1	2B(1999)	50	(9.68)*	ACGIH (USA); Canada
Hexachloroethane (inhalable)	67-72-1	2B(1999)	10	(9.68)*	ACGIH (USA); Canada
Hexachloroethane (respirable)	67-72-1	2B(1999)	5	(9.68)*	ACGIH (USA); Canada
Hexone (Methyl isobutyl ketone)	108-10-1	2B(2013)	205	80	Finland
Hydrazine	302-01-2	2B(1999)	0.1	(0.013)*	Australia; Canada; Finland
alpha Methyl styrene (2-Phenylpropene)	98-83-9	2B(2013)	600	(48.34)*	ACGIH (USA); Canada
Naphtalene	91-20-3	2B(2002)	50	0.05	Germany
Nitrobenzene	98-95-3	2B(1996)	5	1	United Kingdom; Germany; Finland; EU
Nitromethane	75-52-5	2B(2000)	250	(49.93)*	ACGIH (USA); Canada
2-Nitropropane	79-46-9	2B(1999)	36	7	Sweden
2-Nitrotoluene	88-72-2	2A(2013)	None	6	Sweden
Pentachlorophenol	87-86-5	2B(1999)	0.2	0.5	ACGIH (USA); Australia; OSHA (USA); Sweden; Canada; Finland; Japan
Perchloroethylene (Tetrachloroethylene)	127-18-4	2A(2014)	335	70	Sweden; Finland
Phenyl-2,3-epoxypropyl ether (phenyl glycidyl ether)	122-60-1	2B(1999)	6	(0.61)*	ACGIH (USA); Canada
Phenylethylene (Styrene) (Vinyl benzene)	100-42-5	2B(2002)	420	43	Sweden
Silicon carbide (inhalable)	409-21-2	2A(in prep)	10	10	*All
Sulphuric acid	7664-93-9	1(2012)	1	0.2	ACGIH (USA); Canada
Titanium dioxide (inhalable)	13463-67-7	2B(2010)	10	0.3	Japan
Trichloroacetic acid	76-03-9	2B(2014)	5	(3.34)*	ACGIH (USA)
1,2,3-Trichloropropane	96-18-4	2A(1995)	300	18	Finland
Tridymite (silica respirable cristaline)	14808-60-7	1(2012)	0.4	0.025	ACGIH (USA); Canada
Vinyl acetate	108-05-4	2B(1995)	30	(17.6)*	United Kingdom; EU

LEGEND:

( )* - parts per million value that was converted to milligrams per cubic meter. The value was rounded to a whole number in the SA legislation by the committees responsible for setting OEL values in the OHS Act and MHS Act. This has led to the false impression that SA has a lower OEL for selected HCSs.

***All** - All countries that had a listed OEL for that HCS had the same value listed, including the RHCS and MHSR.

*** -** Value listed in developed countries is higher since revision of the HCS.

*** -** Value in the RHCS and MHSR is already at the lowest available level in the developed countries included in this study.

Table 3. Recommended OELs for HCSs listed in the MHSR.

Substance	CAS #	IARC Classification	MHSR SA (TWA) (mg/m^3)	Recommended OEL (mg/m^3)	Country/Organization OEL is listed in
Acetaldehyde	75-07-0	2B(1999)	45	36	Australia
Acrylamide	79-06-1	2A(1994)	0.3	0.03	ACGIH (USA); Australia; OSHA (USA); Sweden; Canada; Finland
Acrylonitrile	107-13-1	2B(1999)	4	(4.3)*	Australia; Japan
Anisidine (o)	90-04-0	2B(1999)	0.5***	0.5	*All
Arsenic and compounds (inorganic)	7440-38-2	1(2012)	0.01	0.003	Japan
Asphalt - petroleum fumes	8052-42-4	2B(2013)	5	0.5	ACGIH (USA); Canada
Aziridine (Ethyleneimine)	151-56-4	2B(1999)	1	0.09	ACGIH (USA)
Benzene	71-43-2	1(2012)	3	1.5	Sweden
Benzyl Chloride	100-44-7	2A(1999)	5	2.6	United Kingdom; Finland
Beryllium and compounds	7440-41-7	1(2012)	0.002	0.00005	ACGIH (USA); Canada
Bis(chloromethyl) ether [BCME]	542-88-1	1(2012)	0.005***	0.005	*All
Bis-(2-ethylhexyl) phthalate (Di-(2-ethylhexyl) phthalate (dioctyl phthalate)	117-81-7	2B(2013)	5	3	Sweden
Bromoethylene (Vinyl bromide)	593-60-2	2A(2008)	20	(2.19)*	ACGIH (USA); Canada
Buta-1,3-diene	106-99-0	1(2012)	4	1	Sweden
Cadmium and cadmium compounds	7440-43-9	1(2012)	0.01	0.01	ACGIH (USA); Australia; Canada
Carbon Black	1333-86-4	2B(2010)	3.5	3	ACGIH (USA); Australia; Canada
Carbon Tetrachloride	56-23-5	2B(1999)	12.6	(0.63)*	Australia
Catechol (o-Dihydroxybenzene) (Pyrocatechol)	120-80-9	2B(1999)	20***	20	Sweden. Revised 2011.
Chlordane (ISO)	57-74-9	2B(2001)	0.5***	0.5	*All
1-Chloro-2,3-epoxypropane (Epichlorohydrin)	106-89-8	2A(1999)	2	(0.38)*	Canada
Chloroform (Trichloromethane)	67-66-3	2B(1999)	9.8	(9.77)*	Canada
Chromium VI compounds	7440-47-4	1(2012)	0.05	0.005	OSHA (USA); Sweden; Finland
Coal Tar pitch volatiles - as cyclohexane solubles (respirable)	65996-93-2	1(2012)	0.14	0.2**	ACGIH (USA); Australia; Canada. Revised 2013
Cobalt metal - dust and fumes	7440-48-4	2B(1991)	0.05	0.02	ACGIH (USA); Sweden; Canada; Finland
Cristobalite, respirable dust (Sillica,crislatine)	14808-60-7	1(2012)	0.1	0.025	ACGIH (USA); Canada
Cumene (Isopropyl benzene)	98-82-8	2B(2013)	120	50	Germany
DDT (Dichlorodiphenyltrichloroethane)	50-29-3	2B(1991)	1***	1	*All
DDVP (Dichlorvos (ISO))	62-73-7	2B(1991)	1	0.1	ACGIH (USA); Canada
4,4'-Diaminodiphenylmethane (DADPM) (4,4 metylene dialinine)	101-77-9	2B(1987)	0.08	0.08	Australia; Finland
1,2-Dibromoethane (Ethylene dibromide)	106-93-4	2A(1999)	4	(0.78)*	Finland
1,4-Dichlorobenzene (p)	106-46-7	2B(1999)	150	6	Germany

1,2-Dichloroethane (Ethylene dicloride)	107-06-2	2B(1999)	20	4	Sweden; Finland
Dichloromethane (Methylene chloride)	75-09-2	2A(in prep)	175	120	Sweden
1,3-Dichloropropene cis and trans isomers	542-75-6	2B(1999)	5	(4.5)*	Australia
Diethanolamine (2,2'-Iminodiethanol)	111-42-2	2B(2013)	15	1	ACGIH (USA)
Dimethyl sulphate	77-78-1	2A(1999)	0.5	(0.26)*	United Kingdom
1,4-Dioxane, tech. Grade	123-91-1	2B(1999)	90	35	Sweden
Divanadium pentoxide (inhalable dust and fume) (vanaduim pentoxide)	1314-62-1	2B(2006)	0.5	0.02	Finland
Divanadium pentoxide (respirable dust) (vanaduim pentoxide)	1314-62-1	2B(2006)	0.05	0.02	Finland
1,2-Epoxy-4-epoxyethyl cyclohexane (4-Vinyl cyclohexene dioxide)	106-87-6	2B(1994)	60	0.57	ACGIH (USA); Canada
Ethanol (Ethyl alcohol)	64-17-5	1(2012)	1900	960	Germany
Ethyl acrylate	140-88-5	2B(1999)	20	20	Australia; Sweden
Ethyl benzene	100-41-4	2B(2000)	435	(86.84)*	ACGIH (USA)
Formaldehyde	50-00-0	1(2012)	1.2	0.12	Japan
Heptachlor and heptachlor epoxide	76-44-8; 1024-57-3	2B(2001)	0.5	0.05	ACGIH (USA); Canada; Germany; Finland
Hexachloroethane (vapour)	67-72-1	2B(1999)	10	(9.68)*	ACGIH (USA)
Hexachloroethane (inhalable)	67-72-1	2B(1999)	10	(9.68)*	ACGIH (USA)
Hexachloroethane (respirable)	67-72-1	2B(1999)	5	(9.68)*	ACGIH (USA)
Hydrazine	302-01-2	2B(1999)	0.02	(0.013)*	ACGIH (USA); Australia; Canada; Finland
Lead, elemental and inorganic compounds (as Pb)	7439-92-1	2A(2006)	0.1	0.05	ACGIH (USA); OSHA (USA); Canada
alpha Methyl styrene (2-Phenylpropene)	98-83-9	2B(2013)	240	(48.34)*	ACGIH (USA); Canada
Naphthalene	91-20-3	2B(2002)	50	5	Finland
Nickel (Metal)	7440-02-0	2B (1990)	0.5	0.01	Finland; Japan
Nickel, inorganic compounds as Ni soluble compounds	7440-02-0	1 (2012)	0.1	0.05	OSHA (USA); Canada; Finland
Nickel, inorganic compounds as Ni insoluble compounds	7440-02-0	1 (2012)	0.5	0.01	Finland
Nitrobenzene	98-95-3	2B(1996)	5	1	United Kingdom; Germany; Finland; EU
Nitromethane	75-52-5	2B(2000)	50	(49.93)*	ACGIH (USA); Canada
2-Nitropropane	79-46-9	2B(1999)	18	7	Sweden
2-Nitrotolluene	88-72-2	2A(2013)	12	6	Sweden
Pentachlorophenol	87-86-5	2B(1999)	0.5***	0.5	*All
Perchloroethylene (Tetrachloroethylene)	127-18-4	2A(2014)	170	70	Sweden; Finland
Phenyl-2,3-epoxypropyl ether (phynyl glicydyl ether)	122-60-1	2B(1999)	6	(0.61)*	ACGIH (USA); Canada
Phenylethylene (Styrene) (Vinyl benzene)	100-42-5	2B(2002)	210	43	Sweden
Silicon carbide (inhalable)	409-21-2	2A(in prep)	10***	10	*All

Sulphuric acid	7664-93-9	1(2012)	1	0.05	United Kingdom (HSE); Finland (HTP); European Union (EU)
Titanium dioxide (inhalable)	13463-67-7	2B(2010)	10	0.3	Japan
Trichloroacetic acid	76-03-9	2B(2014)	5	(3.34)*	ACGIH (USA)
Trichloroethylene	79-01-6	1(2014)	268	(53.74)*	ACGIH (USA); Canada
1,2,3-Trichloropropane	96-18-4	2A(1995)	60	18	Finland
Vinyl acetate	108-05-4	2B(1995)	30	(17.6)*	United Kingdom; EU
Vinyl chloride	75-01-4	1(2012)	(17.89)*	2.5	Sweden; Finland
Wood dust, hard wood		1(2012)	1***	1	Australia; Canada

LEGEND:

( )* - parts per million value that was converted to milligrams per cubic meter. The value was rounded to a whole number in the SA legislation by the committees responsible for setting OEL values in the OHS Act and MHS Act. This has led to the false impression that SA has a lower OEL for selected HCSs.

***All** - All countries that had a listed OEL for that HCS had the same value listed, including the RHCS and MHSR.

*** -** Value listed in developed countries is higher since revision of the HCS.

*** -** Value in the RHCS and MHSR is already at the lowest available level in the developed countries included in this study.

4.3 Limitations of the study

During this study certain limitations were identified, namely:

- There is a lack of data surrounding the prevalence of cancers developed as a result of occupational exposure due to the lack of cancer data systems in developing countries such as South Africa.
- The tables found in the RHCS do not contain Chemical Abstracts Service (CAS) numbers. This makes it difficult to identify each unique HCS as different countries often use different names. The CAS numbers listed in the MHSR were used as a guideline to identify the CAS numbers for each HCS.
- Acquiring the OEL lists for each country/organisation is not an easy task since the list is often not in English but in the language of the country the list was intended for.

4.4 Future studies

During the course of this study a certain element was identified that could be helpful in completing the knowledge gap surrounding the setting of OELs for carcinogenic substances and should be considered in future studies:

- Some chemicals e.g. Diesel fuel, as total hydrocarbons (CAS 68334-30-5; 68476-30-2; 68476-31-3; 68476-34-6; 77650-28-3) are not listed within South African occupational health legislation and are considered carcinogenic to humans by developed countries (see Table 4). A study to identify why these HCS are not included within South African legislation may help in bringing the overall level of OEL enforcement within the RHCS and MHSR in line with developed countries legislation.
- Occupational cancers are usually grouped among specific working groups. Identifying the groups of workers in the industrial and mining sectors of South Africa suffering from occupational cancers should be identified. Current and

reliable numbers for the percentage of the population in the work force affected by occupational cancers should be studied.

Table 4. Carcinogenic HCSs (43 in total) not listed in South African legislation (RHCS or the MHSR).

CAS	Substance	IARC classification	ACGIH classification
15972-60-8	Alachlor		A3 (2006)
61-82-5	Amitrole	3(2001)	A3 (1983)
112-07-2	2-Butoxyethyl acetate		A3 (2000)
107-30-2	Chloromethyl methyl ether	1(2012)	A2 (1979)
218-01-9	Chrysene	2B(2010)	A3 (1990)
79-43-6	Dichloroacetic acid	2B(2014)	A3 (2002)
91-94-1	3,3'-Dichlorobenzidine	2B(1987)	A3 (1990)
764-41-0	1,4-Dichloro-2-butene		A2 (1990)
68334-30-5; 68476-30-2; 68476-31-3; 68476-34-6; 77650-28-3	Diesel Fuel, as total hydrocarbons	2B(1989)	A3 (2007)
72-20-8	Engine exhaust, diesel	1(2013)	
79-44-7	Dimethyl carbamoyl chloride	2A(1999)	A2 (2006)
57-14-7	1,1-Dimethylhydrazine	2B(1999)	A3 (1993)
1303-00-0	Gallium arsenide	1(2012)	A3 (2004)
118-74-1	Hexachlorobenzene	2B(2001)	A3 (1994)
87-68-3	Hexachlorobutadiene	3(1999)	A3 (1979)
680-31-9	Hexamethyl phophoramide	2B(1999)	A3 (1990)
542-56-3	Isobutyl nitrile		A3 (2000)
8008-20-6; 64742-81-0	Kerosene/Jet fuels as total hydrocarbon vapor	2B(2013)	A3 (2003)
7758-97-6	Lead chromate as Pb		A2 (1990)
7758-97-7	Lead chromate as Cr		A2 (1990)
1634-04-4	Methyl tert-butyl ether	3(1999)	A3 (1999)
60-34-4	Methyl Hydrazine		A3 (1991)
	Mineral oil, excluding metal (Poorly and mildly refined)	1(2012)	A2 (2009)
92-93-3	4-Nitrodiphenyl	3(1987)	A2 (1992)
62-75-9	N-Nitrosodimethylamine	2A(1987)	A3 (1992)
99-55-8	5-Nitro-o-toluidine	3(1990)	A3 (2006)
95-54-5	o-Phenylenediamine		A3 (1988)
1120-71-4	Propane sultone	2A(in prep)	A3 (1976)
57-57-8	β-Propiolactone	2B(1999)	A3 (1992)

75-56-9	Propylene oxide	2B(1994)	A3 (2000)
75-55-8	Propyleneimine	2B(1999)	A3 (2008)
7789-06-02	Strontium chromate, as Cr		A2 (1989)
	Synthetic vitreous fibers		A3 (1999)
	Synthetic vitreous fibers (Refractory ceramic fibers)		A2 (1999)
79-34-5	1,1,2,2-Tetrachloroethane	2B(2014)	A3 (1995)
116-14-3	Tetrafluoroethylene	2A(in prep)	A3 (1997)
509-14-8	Tetranitromethane	2B(1996)	A3 (1992)
119-93-7	o-Tolidine	2B(1987)	A3 (1992)
95-53-4	o-Toluidine	1(2012)	A3 (1984)
106-49-0	p-Toluidine		A3 (1984)
75-02-5	Vinyl flouride	2A(2008)	A2 (1996)
88-12-0	N-Vinyl-2-pyrrolidone	3(1999)	A3 (2000)
11103-86-9; 13530-65-9; 37300-23-5	Zinc chromates, as Cr		A1 (1992)

LEGEND:

(in prep) – Monograph about agent is in the process of being prepared.

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Chapter 5

Annexure

ENGLISH LANGUAGE EDITING CERTIFICATE

This is to certify that the English Language of the dissertation by

Ms. S. Blake

was edited by Prof L.A Greyvenstein

L. A Greyvenstein (Prof)
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