Comparative analysis of South African BEIs with those of developed countries

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PREFACE

This mini-dissertation is presented in the format of an article in accordance with the General Academic Rules 2015 (section 4.4.2.9) of the North-West University. The *Annals of Work Exposures and Health* was chosen as the potential journal for publication of the article (i.e. Chapter 3) and therefore, the mini-dissertation is written according to the guidelines of *The Annals of Work Exposures and Health*. In order to achieve consistency, the reference style preferred by the potential journal is used throughout the mini-dissertation. This mini-dissertation is presented in English following the British spelling and grammar style. The mini-dissertation was proofread and language edited before submission.

"It is amazing what you can learn by teaching" – CJ van der Merwe

AUTHOR'S CONTRIBUTIONS

A team of researchers were involved in this study and in the writing of this mini-dissertation. Individual contributions are listed below:

Miss Kamogelo R Sekhula (Author):

- Planning and writing of the research proposal.
- Literature research, collection and organisation of data.
- Statistical analysis and interpretation of results.
- Writing of the mini-dissertation and article.

Mr Cornelius J Van der Merwe (Supervisor):

- Assisted with the study concept, planning and write up of mini-dissertation.
- Review of the mini-dissertation.
- Assisted with the graphical representation of results and the technical aspects of the mini-dissertation.

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- Assisted with the study concept, planning and write-up of mini-dissertation.
- Assisted with the graphical representation of results and the technical aspects of the mini-dissertation.
- Reviewed the mini-dissertation.

By signing this document, I declare that I have approved the article and that my role in the study as indicated above is representative of my actual contribution and that I hereby give my consent that it may be published as part of Kamogelo R Sekhula's MSc in Occupational Hygiene mini-dissertation.

_____ _____

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ABSTRACT

The objective of biological monitoring (BM) is to evaluate workplace exposure to hazardous chemical substances (HCSs) by assessing the total systemic exposure of workers. Biological monitoring should be viewed as a complementary assessment tool to the more traditional measurement of airborne concentrations of HCSs in the work environment. It is also used to verify the effectiveness of existing control measures in the workplace used to manage HCS exposure.

The intention of BM is to detect HCSs and/or their associated metabolites in the body before the occurrence of adverse health effects. For BM, a variety of techniques are used to measure bio-indicators usually found in urine, blood or exhaled air. The availability of biological guidance values (BGVs) make BM possible and useful to industry as they serve as concentration limit values for a particular HCS, its metabolites found in biological media or bio-indicators due the chemical's effect.

It is essential that BGVs are reviewed and kept scientifically relevant to achieve the utmost effectiveness in protecting workers from the development of adverse effects resulting from excessive exposure to HCSs. In South Africa, the Department of Employment and Labour is responsible for establishing these BGVs and because it is a regulatory body, BGVs are legally binding to all workplaces to which they may apply. It was noted that since the incorporation of BGVs into legislation in 1995, no attempts were made to revise them. In 2018, revised BGVs were drafted and released for public comment. This study, therefore, explored the suitability of the currently legislated South African biological exposure indices (BEIs) — term used in South Africa to refer to BGVs — by comparatively analysing them relative to those of developed countries. It further explored the newly proposed BEI's and offers general commentary on these.

It should be noted that for this mini-dissertation, "Biological Guidance Value (BGV)" is used as the term under which the various types of index values fall. This is done because individual developed countries/organisations designate different terms for these guidance values.

The aim of this study was achieved by comparing BEIs legislated in the Hazardous Chemical Substances Regulations (HCSR) of the Occupational Health and Safety (OHS) Act of 85 of 1993 with those of organisations representing selected developed countries. These include the American Conference of Governmental Industrial Hygienists (ACGIH), Deutsche Forschungsgemeinschaft (German Research Foundation, DFG), Occupational Safety and Health Administration (OSHA), Health and Safety Authority (HSA), Scientific Committee on Occupational Exposure Limits (SCOEL) and the Japan Society of Occupational Health (JSOH). Countries of origin being: United States, Germany, United States, Ireland, Europe and Japan; respectively. Only HCSs appearing in both the HCSR and the lists of the organisation in question, as well as having similar metabolites, were considered. The overall level of the set concentrations of the BGV was completed using a geometric means (GM) and interval method.

The results obtained from the comparison of the overall coverage of substances between the HCSR and the selected developed countries/organisations indicated noteworthy discrepancies. It appeared that HCSs for which the HCSR designates BEIs are also included in the BGV lists of most developed countries/organisations considered in this study. Only two organisations, SCOEL and JSOH, were found to have a <75% overlap in HCSs coverage with the HCSR. Although there seems to be a lot of similarity in the HCSs coverage, the developed countries/organisations have a greater number of HCSs with established BGVs when compared to those included in the HCSR. The most noticeable difference observed in the results was between the DFG and the HCSR. The DFG designates 85 BGV which are not included in the HCSR, having the highest number of unique HCSs, followed by the ACGIH and HSA; having a total of 21 and 22 unique HCSs compared to the HCSR, correspondingly.

The GM and interval methods were used to compare the overall levels at which the South African BEIs are set relative to those established by developed countries/organisations. Both these methods indicated that the levels at which developed countries/organisations have set their BGVs are more stringent than the BEI levels found in South African legislation. The most stringent organisation was found to be the SCOEL, having a GM value of 0.37; followed by the DFG and ACGIH with GM values of 0.45 and 0.46 respectively.

It may be concluded, based on the results of this study, that significant differences exist between the BEIs found in the HCSR and BGVs established by developed countries/organisations. These disparities are notable in both the levels at which the BEIs are set as well as the overall HCSs coverage.

It may be said that the BEIs established by South African legislation does not reflect the most up to date data. The current review of BEIs is therefore warranted and should be concluded as a matter of urgency.

Key words: Hazardous chemicals substances (HCSs), biological monitoring (BM), biological guidance values (BGVs), hazardous chemical substances regulations (HCSR), geometric means (GM), interval method.

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% - Percentage

µg/l – micrograms per litre

µmol/L – micromole per litre

2,5-HD – 2,5-*Hexanedione*

ACGIH – American Conference of Governmental Industrial Hygienists, United States of America

AIDS – Acquired Immunodeficiency Syndrome

ANC – African National Congress

ANSI – American National Standards Institute

BAR – Biological Reference Values for Workplace Substances

BAT – Biologischer Arbeitsstoff-Toleranz-Wert, Germany

BEIs – Biological Exposure Limits

BGVs – Biological Guidance Values

BLW – Biologischer Leit-Wert

BM – Biological Monitoring

BMV – Benchmark Guidance Value

CAS – Chemical Abstracts Service

CL – Ceiling Exposure Limit

Cr – Creatinine

CSs – Carcinogenic Substances

DFG – Deutsche Forschungsgemeinschaft, Germany

DMF – *N,N-Dimethylformamide*

EC – European Commission

EKA – Expositionsäquivalente für krebserzeugende Arbeitssoffe, Germany

g - gram

g/g – grams per gram

GM – Geometric Means

HCSR – Hazardous Chemical Substances Regulations

HCSs – Hazardous Chemical Substances

HSE – Health and Safety Executive

HSA – Health and Safety Authority

HIV – Human Immunodeficiency Virus

IDLH – Immediately Dangerous to Life or Health

IARC – International Agency for Research on Cancer

ISBN – International Standard Book Number

JSOH – Japan Society of Occupational Health

MA – Mandelic Acid

MACs – Maximum Allowable Concentrations

mg/g – milligram per gram

mg/L – milligram per litre

mmol/L – millimole per litre

mppcf – million particles per cubic foot

MW – Molecular Weight

NMF – *N-methylformamide*

NMF-OH – *N*-Hydroxymethyl-*N*-methylformamide

OELs – Occupational Exposure Limits

OD – Occupational Diseases

OH – Occupational Health

OHHRI – Occupational Hygiene and Health Research Initiative

OHSA – Occupational Health and Safety Act

PGA – *Phenylglyoxylic* Acid

PPE – Personal Protective Equipment

ppm – parts per million

S-PMA – *S-phenylmercapturic* acid

SA – South Africa

SCOEL – Scientific Committee on Occupational Exposure Limits

STEL – Short-Term Exposure Limits

TLVs – Threshold Limits Values

TWA – Time-Weighted Average

UK – United Kingdom

WHO – World Health Organisation

CHAPTER 1: INTRODUCTION

This chapter introduces the concept of Biological Exposure Indices (BEIs) and the application thereof in the workplace. Further, the significance of undertaking a comparative study between South African BEIs and those of developed countries/organisations is highlighted as well as what this study aims to achieve.

1.1 Introduction

Exposure to hazardous chemical substances found in the environment and workplace may lead to adverse health effects. Those that occur in the workplace are of particular concern since such exposure is often encountered in significant amounts (Ding *et al.,* 2011). This topic of interest falls within the scope of occupational hygiene, which aims to protect the worker against the negative health effects that may result from workplace exposure to hazardous chemical substances. Regulatory measures are necessary in these instances in order to achieve this goal, hence the importance of occupational exposure limits (OELs) (Schenk *et al.,* 2008).

OELs are essential in the assessment of employee exposure to various hazards. By definition, they are recognised as limit concentrations of detrimental airborne substances over an eight-hour period. The intent is that they are representative of safe inhalation levels to which most employees may be exposed to over their working lifetime without any resultant disease (Gordon *et al.,* 2014; Nikfar and Malekirad, 2014; Araya *et al.,* 2015). It is important to note that exposure to hazardous chemical substances (HCSs) is not only limited to inhalation but may occur through skin absorption and ingestion (Cocker *et al.,* 2014). In this regard, biological monitoring is very useful as it considers the total uptake, irrespective of the route of exposure. (Cocker, 2014; Sams *et al.,* 2015).

Biological monitoring as a component of medical surveillance is crucial to many occupational health and safety programmes. It should be emphasised that biological monitoring in the work environment should not be regarded as a replacement for the more conventional measurement of airborne concentrations of chemical substances, but rather understood to be complementary to the latter (Morgan, 1997). Chemical analysis of biological media such as blood and urine are required to detect the presence of HCSs or associated characteristic metabolites (HSA, 2011). Biological monitoring is also pivotal in occupational settings where control of exposure is heavily reliant on personal protective equipment. Systematic monitoring aids in assuring that personal protective equipment (PPE) remains adequate in protecting workers (Scheepers *et al.,* 2011).

The application of biological monitoring as a means of measuring and further controlling worker exposure to HCSs, is made possible by the availability of biological guidance values (BGVs) (Huizer *et al.,* 2014).

Although limited in availability, BGVs serve as reference values for biological parameters which are usually detectable in bodily fluids such as blood and urine. The intent is to determine the exposed individual's internal chemical dose. The biological parameter may be the original compound, its metabolites or any characteristic biochemical change resulting from absorption. The set guidance values are representative of the indicator material most likely to be observed in samples collected from a healthy worker solely exposed to the toxicant at the airborne OEL concentration for that specific parent compound. In essence, BGVs are concentration limit values of the HCS in question or its metabolites resulting from exposure; found in the befitting biological medium (HSA, 2011; Morgan, 1997).

The concept of systematically establishing OELs, and consequently BGVs, for workplace application was initially formalised by the American Conference of Governmental Industrial Hygienists (ACGIH) (Paustenbach *et al.,* 2011). This organisation, together with the Deutsche Forschungsgemeinschaft (German Research Foundation, DFG), became the two most influential organisations world-wide involved in the setting of biological monitoring reference values. It is unanimous amongst these organisations that guidance values which they establish represent the fundamental relationship of OELs and the resulting body burden, i.e. BGVs (DFG, 2012; ACGIH, 2015). The approach in application and standardising these reference values, however, differs significantly (Deveau *et al.,* 2015). It is understood that BGVs established by the ACGIH serve as guideline values which, if are to be breached, should be done so over a short period (Jakubowski and Trzcinka-Ochocka, 2004).

The ACGIH is a private institution, having no regulatory authority. It is therefore comprehensible that the OELs, referred to as Threshold Limit Values (TLVs), together with the associated BEIs established by this institute are presented merely as recommendations for good practice (Morgan, 1997). BEIs for a total of 49 substances have been set by the ACGIH (ACGIH, 2015). Conversely; the DFG biological limit values, referred to as Biologischer Arbeitsstoff-Toleranz-Wert (BAT), are comprehensively purposed to demarcate the maximum permissible levels of exposure (ACGIH, 2015).

As ceiling values for healthy workers, BAT values serve to protect against occupational related illness. The DFG has identified over 1000 substances having either OELs or BEIs which are included within the regulations; far exceeding the number of substances for which BEIs are set by the ACGIH (Morgan and Schaller, 1999; DFG, 2015).

Biological guidance values have also been established in the United Kingdom (UK), the majority of which are adaptations from those published by the ACGIH. However, numerous additions have been made to include substances suggested by the country's Health and Safety Executive (HSE) (Jakubowski and Trzcinka-Ochocka, 2004). The collective of BGVs may be divided into two categories, namely: health guidance values and benchmark guidance values.

Similar to the ACGIH, the BGVs categorised as health guidance values are set at levels which indicate that no adverse health effect is likely to occur. Based on the available scientific evidence, if these values are not greatly exceeded, no short or long-term effects are expected to arise. In contrast, the benchmark guidance values of the HSE are set at practicable levels. These are levels accommodating the 90^{th} percentile of biological monitoring results perceived from workplaces considered to practice good occupational hygiene (HSE, 1997).

The existence of various organisations responsible for setting BGVs worldwide, each differing in approach regarding the establishment and scope of application for the indices, results in noticeable discrepancies (Deveau *et al.,* 2015). These discrepancies observed from some of the most prominent organisations such as the ACGIH, DFG and HSE outlines some of the realities encountered in most countries. Disparities are found in the indices recommended by various jurisdictions, the appropriate biological material of interest within the same index as well as the volumes to be extracted when sampling (Howard, 2005).

Setting OELs as well as BGVs is a rather cumbersome and costly process. As a result, very few countries have taken it upon themselves to go about setting these standards and South Africa is no exception. The OELs reflected in the Hazardous Chemical Substances Regulations of 1995 (HCSR) have been appropriated from those developed in the UK as part of their legislation (Myers, 2002; HCSR, 1995). Based on the empirical relationship between OELs and biological exposure indices (BEIs; term used in South Africa for BGVs), it is arguable that both originated from a common source. (Huizer *et al.,* 2014; Maponya, 2016).

As a developing country, South Africa is amid profound economical, occupational and health transitions (Mayosi *et al.,* 2009). In 1994, the African National Congress (ANC) passed a Bill of Rights which accentuated that everyone has the right to an environment that is not harmful to their health and well-being. The Occupational Health and Safety (OHS) Act of 85 of 1993 and the supplementing regulations were developed with the aim of promoting such rights passed in the Bill of Rights (Coovadia *et al.,* 2009; Muraga *et al.,* 2016). This study focuses mainly on the Hazardous Chemical Substances regulations which, since it was incorporated into the legislation in 1995, remained unrevised for the better part of 2 decades until recently in 2018 that this specific regulation was renewed and published for public commentary.

The European Commission (EC) continuously drafts and proposes developments concerning OELs as well as BEIs for approval by the Health and Safety Executive Board. Examples of chemicals which have been revised include N,N-Dimethylformamide, Carbon disulphide and Phenol amongst many others (HSEB, 2008). It is crucial that systemic revision of the South African standards is considered, taking into account the most recently available scientific data, validated sampling methods as well as newly developed means of controlling (if such exists) the chemical hazard in question (WorksafeBC, 2010). To accentuate the integral aim of occupational hygiene, it is imperative that effective protection of workers' health is paralleled by scientifically sound and contemporary OELs and BEIs. Consequently, the validity and applicability of the South African legal requirements is brought into question.

As previously mentioned, the scope of application for the guidance values established by many developed countries is that the OELs and similarly BGVs are set according to data accommodating for a healthy worker. South Africa, like many low to middle income countries, is burdened by grave diseases not related to the occupational setting (Mayosi *et al.,* 2009). In addition to the prevailing non-communicable diseases such as diabetes and chronic respiratory infections, numerous infectious diseases still thrive (Alwan *et al.,* 2010). Socio-economic factors such as minimum wage, lack of facilities, urbanisation and the associated lifestyle changes including diet, tobacco smoking and alcohol consumption seem to be the major risk factors (Dalal *et al.,* 2011). An over-burdened health care system in addition to the contributing socio-economic factors, imply that an increased number of vulnerable workers exist in SA.

This study is relevant as it aims to compare the South African BEI's with those of developed countries/organisation with the intent of gauging the stringency thereof and further; provide a motive for the adaptation of BGVs from these developed countries/organisations should those of the HCSR be found to be lacking. The considered developed countries/organisations are acknowledged to maintain leading health and safety systems as they invest vastly in research to this regard. Thus, developed countries/organisations are forerunners in setting the standards to which South Africa, a developing country, should esteem.

1.2 Aim and Objectives

1.2.1 General aim

The general aim of this study is to comparatively analyse BEIs as reflected in the South African HCSR with those established by leading developed countries/organisations to identify noteworthy differences.

1.2.2 Specific objectives

Specifically, South African BEIs will be compared to those published by various leading developed countries/organisations in the field of occupational health based on the following variables:

(i) The frequency of coverage of each individual BEI; and

(ii) the overall level of the set concentrations of respective BEIs.

1.3 Hypothesis

Studies focusing on the comparison of South African OELs and their corresponding short-term exposure limits (STELs) with those of various developed countries have shown several inconsistencies. These studies are conclusive in that the overall levels of OELs and STELs values included in South African legislation are higher than those set by developed countries. Furthermore, a very low percentage of the total HCSs found in South African legislation were included within the legislation spectrum of the developed countries considered (Viljoen, 2012; Viljoen, 2014; Maponya, 2016). Based on the underlining relationship which exists between OELs and BEIs, the following hypotheses may be postulated:

1. Hypothesis one

"The overall level at which South African BEIs is set, is less stringent than those of developed countries and organisations. A difference of more than 50% will be considered as less stringent."

2. Hypothesis two

"There is less than 75% overlap between South African BEIs and those of developed countries i.e. it appears that developed countries establish BEIs for a greater variety of substances than South African legislation."

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CHAPTER 2: LITERATURE REVIEW

This chapter considers the vast amount of literature available regarding the development of occupational hygiene and how it has evolved throughout the centuries to become a sophisticated field of practice. The establishment of occupational exposure limits (OELs) is reviewed and further explored with regards to how they correlate with complementary biological guidance values (BGVs). A glance is also taken on the demographics of the South African occupational health sector with the aim of giving context to the subsequent discussion and recommendations chapters.

2.1 Occupational exposure limits (OELs)

2.1.1 Occupational hygiene history and exposure limit development

"As with most professions, identifying the origins of the practice of industrial hygiene is difficult, if not impossible" – Vernon E Rose reflected in his chronicles on the origins of industrial hygiene. Sources differ in the recollection of when work related illness and injury became an interest in the field of philosophy and science. The fundamentals of industrial hygiene are centred on the anticipation, recognition, evaluation, control and prevention of hazards from work. It can therefore be conceivable that, even dating as far back as the end of Stone Age when work meant grinding ivory and stone to form tools, the ideology of Industrial Hygiene in its simplest form existed. Contemplate a worker who might have experienced back pain as a result of maintaining awkward postures during grinding who then had the idea to redesign his workplace to better suit his body limits and eliminate discomfort. This worker might have even gone on to pass this concept of redesigning one's work station to fellow workers for them to avoid feeling the discomfort he felt. This, in its simplicity, is an example of recognising ergonomic hazards and solving them, even going further to assist fellow colleagues in anticipating the risk, before any musculoskeletal disorders arise (Rose, 2003).

Since the 15th century, it has been accepted that airborne chemicals and dust particles can inflict grave illness to exposed individuals. Controversies, however, existed regarding the duration and concentration at which ill-effects would be expected to arise (Paustenbach *et al.,* 2011). This was especially apparent in mining, being one of the oldest hazardous occupations which were designated specifically to slaves and criminals as a form of punishment in regions such as Ancient Egypt (Schilling, 1989).

It was only when mining moved away from being a means of punishment to a skilled profession in Europe that the incentive to prevent disease associated with such work became important. In the 19th Century, physicians such as Agricola and Paracelsus recognised diseases that arose in the smelting and mining industries. Significant figures such as Hippocrates and Ramazzini noted the direct relationship between workplace exposure to hazards and the development, of what we now understand to be workplace induced illnesses and diseases. These two pioneers are thought to present significant developments in the field of industrial hygiene (Carter, 2004; Stanton, 2015). Nevertheless, an argument was brought forward questioning whether merely identifying hazards and the results thereof without further exploring possible solutions to eliminate such exposure is sufficient to title individuals as occupational hygienists (Rose, 2003).

Towards the end of the 19th Century and the beginning of the 20th Century, occupational health and safety started moving towards a more formal and professional discipline. It was at this point that it was accepted by the United States government that a stance should be taken in countering the health afflictions arising from poor work conditions in factories following the industrial revolution. One of the first gases to have been assigned a safe exposure concentration was carbon monoxide; in view that it is amongst the most prominent toxic gases to be encountered in the work place (Eddington, 2002; Paustenbach *et al.,* 2011).

Brown (1965) further reasoned that the discipline of industrial hygiene can be said to have originated in South Africa, as it was here that the various parts which contribute to the success of industrial hygiene came together to establish a safe working level for dust exposure. In the South African gold mines, drilling operations exposed miners to large quantities of dust containing high levels of crystalline silica. In order to develop an exposure limit for this dust, an instrument known as a konimeter was used to monitor the airborne concentrations of the silica dust and periodic chest x-ray assessments were done on workers to evaluate the health effects resulting from these exposures. In 1916, the correlations made from the silica dust studies in South African mines allowed for an OEL of 8.5 million particles per cubic foot of air for dust containing 80 – 90% quarts to be established. The process followed above created a consistent approach that could be reproduced by industrial hygienists worldwide (Brown, 1965; Paustenbach *et al.,* 2011).

Figure 2-1 Describes the various developmental stages in the chronology of OEL developments until 1970, when OELs were incorporated into legislation (Stanton and Ross*,* 2003; Paustenbach *et al.,* 2011).

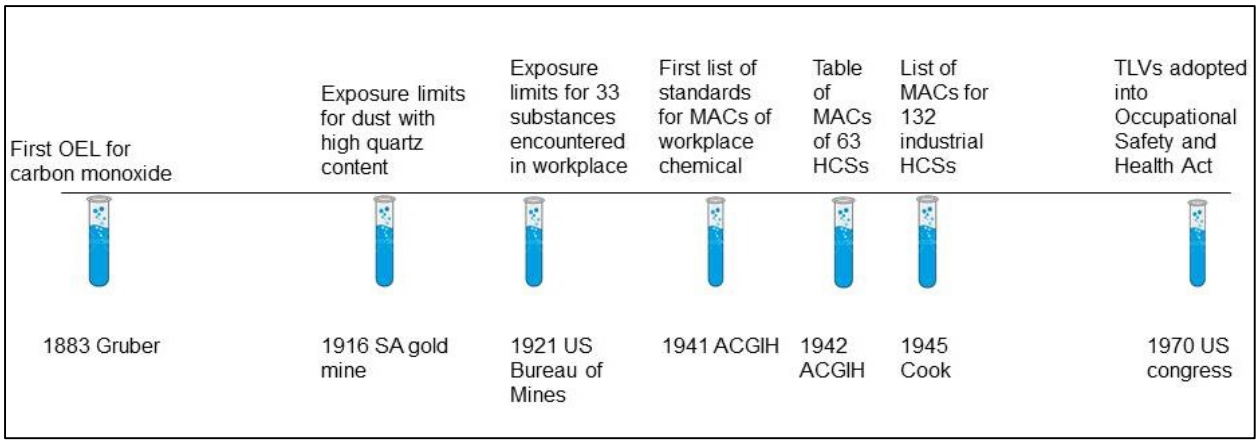

Figure 2-1: Chronology of milestones in OELs until 1970 (adapted from Paustenbach, 2012).

2.1.2 American Conference of Governmental Industrial Hygienists (ACGIH) introducing OELs

Referring to the chronology of exposure limit development (Figure 2-1), it is evident that the ACGIH did not disseminate the very first OEL list. It was, however, the ACGIH that introduced a systematic approach in OEL setting, headed by a committee that investigated, recommended and reviewed exposure limits every year. (Skowron and Czerczak, 2015). The organisation's history can be traced back to 1938. In 1946 they released their first list of chemical substance limit values (Ziem and Castleman, 1989; ACGIH, 2018a). This list primarily relied on data initially documented by Warren Cook, a renowned icon in the developmental stages of occupational hygiene; and to a lesser extent limits developed by the American Standards Association, currently known as the American National Standards Institute (ANSI). In consecutive years, the ACGIH annually released lists of limits and formally referred to them as Maximum Allowable Concentrations (MACs) (Borak and Brosseau, 2015). It is intriguing to recognise the initial stance taken by the ACGIH committee on the safety of these MACs. The ACGIH stated during its release that "the list is not to be construed as recommended safe concentrations" (Ziem and Castleman, 1989).

Cook, from whose paper 118 of the substances were adopted, emphasised that the intention was merely to "provide a handy yardstick to be used as guidance for the routine control of these health hazards – not that compliance with the figures listed would guarantee protection against ill health". Cook also stressed that maintaining these limits should not be considered a replacement for medical monitoring (Cook,1945).

This release of MAC values was followed by massive international criticism, expressing that the MACs were released without further definition nor technical guidance, which could possibly convey the idea that these were indeed safe levels to which workplaces should adhere (Stouten *et al.,* 2008).

Initially, the ACGIH were not in favour of defining what the MAC values meant precisely or even to state the time frame that these limits were not to be exceeded, with the disclaimer that individuals respond differently to varying exposure to hazards. With this resolute challenge, the ACGIH acknowledged it is indeed a challenge attempting to protect workers from ill-health while being practical to the manufacturers (Ziem and Castleman, 1989)

ACGIH then later introduced the term Threshold Limits Values (TLVs) and in 1953 added a preface and supporting documentation in an effort to alleviate the confusion (Schenk, 2011). In these documents, the TLVs were defined as maximum averaged airborne concentrations to which employees may be exposed to for 8-hours daily without experiencing any resulting ill health. This definition underlined that the ACGIH were offering a guarantee that these were comprehensible as health-hazard threshold (Ziem and Castleman, 1989). The impact imposed by the released TLVs was tremendous as various agencies adopted these values as national OELs, a practice which would lead to the concept of OELs being increasingly employed in the management of chemical exposure in multiple working environments (Piney, 1998).

2.1.3 Current rationale of exposure limits

The basic reasoning behind the concept of OELs is that exposure to a HCS at acceptably low amounts should not result in health impairment. The dose and the expected response will differ according to the characteristics of individual chemicals. Scientific evidence suggests that for some chemicals, health impairment will only appear when a certain level of exposure is exceeded. This implies that it is theoretically possible to achieve safe levels of exposure. However, the reality is for other chemicals, scientific knowledge to establish a safe level is insufficient and thus an acceptable OEL cannot be established (Schenk, 2011). Considering technological advancements, it is inevitable that industries continue to rely on chemical substances to facilitate production and service delivery. In addition to an increase in demand by industries, an increase in the complexity of chemicals used is also clear (Hämäläinen *et al.,* 2009). It is especially these relatively newer HCSs with increased complexity that sufficient scientific data lacks to establish safe levels. This provides motive to invest time and effort in research in order to keep up with the ever-evolving industrial developments.

OELs provide measurable guideline variables which assist industries in managing airborne substances exposure in the workplace, which may be detrimental to the workers when exposure takes place over prolonged time periods (Gordon *et al.,* 2014).

Various factors affect the level at which a specific OEL is set, such as results derived from a risk assessment based on the latest scientific information. Information derived from human experimental and epidemiological studies serve as a basis in this regard (Haber and Maier, 2002).

2.1.4 Types of OELs

So as not to conceptualise that a single OEL is accommodating for all types of exposure, various conditional OELs have been established depending on either the types of exposures to be expected in typical working environments or time limit reference. There are four different categories of OELs, namely: time-weighted average (TWA), short-term exposure limit (STEL), ceiling exposure limit (CL) as well as the immediately dangerous to life or health (IDLH) category.

2.1.4.1 Time-weighted average

This is the most commonly applied type of OEL for chronic health effects encountered across industries. It marks a time-weighted average for an 8-hour work day which ultimately amounts to a 40-hour work week (this does not include the asbestos OEL which is time weighted over a 4-hour period). The rationale being that workers may be continuously exposed to these set levels, on a daily basis, with no resulting undesirable health effects encountered by workers throughout their entire work life (Warren, 2016).

2.1.4.2 Short-term exposure limit

Short-term exposure limits represent maximum weighted average limit values to which workers may be exposed for durations not exceeding 15 minutes during the work shift; even if the overall 8-hour exposure is below the OEL-TWA. Some countries/organisations go further and regulate that exposure to these STEL concentrations should be limited to at most four times a day with at least 1-hour intervals in between exposures. In such instances, a hazardous chemical substance would have two exposure limit values; the OEL-TWA as well as the STEL value. STEL value are to be applied only in normal working conditions and not in emergency situations such as chemical spills (SCOEL, 2010; CCOHS, 2018).

2.1.4.3 Ceiling exposure limits

Ceiling exposure limits are set at concentration values that should not at any point during the work shift be exceeded. While STEL values and OEL-TWA permit restricted excursions above the set levels (provided that for STEL levels it is not for a period longer than 15 minutes and for OEL-TWA the time period falls within 8 to 10 hours); CLs are never to be exceed at any point during the work day (Howard, 2005; CCOHS, 2018).

2.1.4.4 Immediately dangerous to life or health limits

The fourth category of OELs is those that are applicable in emergency chemical exposures. Exposure to airborne contaminants at these levels is known to most likely result in permanent adverse health effects, immediate incapacitation (which may prevent escape from such emergency situations) or even death. The intent of setting these limits is to ensure that workers are able to escape the toxic environment without the danger of having severe respiratory tract or ocular irritation as well as permanent health impairments (NOAA, 2018).

Nonetheless, the most commonly used limit regarding control of exposure remains the OEL-TWA. A note of caution is that the aforementioned limits only consider the atmospheric concentration of HCSs. In some instances, other routes of exposure significantly contribute to the total exposure of the individual which limits the application of OELs (Schenk and Johanson, 2010).

2.2 Biological monitoring as complementary assessment tool

Considering the shortfall of OELs with regards to alternative exposure routes, biological monitoring (BM) is an advantageous tool in the assessment of the total human systemic exposure to HCSs. As a component of medical surveillance, it is crucial to occupational health and safety programmes (Cocker *et al.,* 2014). It should be emphasised that BM in the work environment should not be regarded as a replacement for the more conventional measurement of airborne concentrations of chemical substances, but rather understood to be complementary to the latter (Morgan, 1997). Chemical analysis of biological media such as blood and urine is required to detect the presence of the HCSs or associated characteristic metabolites (HSA, 2011).

Biological monitoring is also pivotal in occupational settings where control of exposure is heavily reliant on personal protective equipment. Systematic monitoring aids in ensuring that personal protective equipment (PPE) remains adequate in protecting workers (Scheepers *et al*., 2011).

BM is not only limited to occupational settings, but also play a role in studies concerning exposure to HCSs in the environment on a public health scale to assist in population monitoring studies (Cocker, 2014). Professionals in diverse fields make use of BM as a means of assessing exposure. These include, but are not limited to, occupational hygienists and physicians, researchers, regulators and epidemiologists.

Although differing in the objective of application, which ranges from assessing compliance with regulations to researching agents causing diseases, all these aforementioned professions maintain the invariable objective to prevent ill-health (Foa and Alessio, 2012). The progression of possible events leading to the development of ill-health is schematically outlined in Figure 2-2.

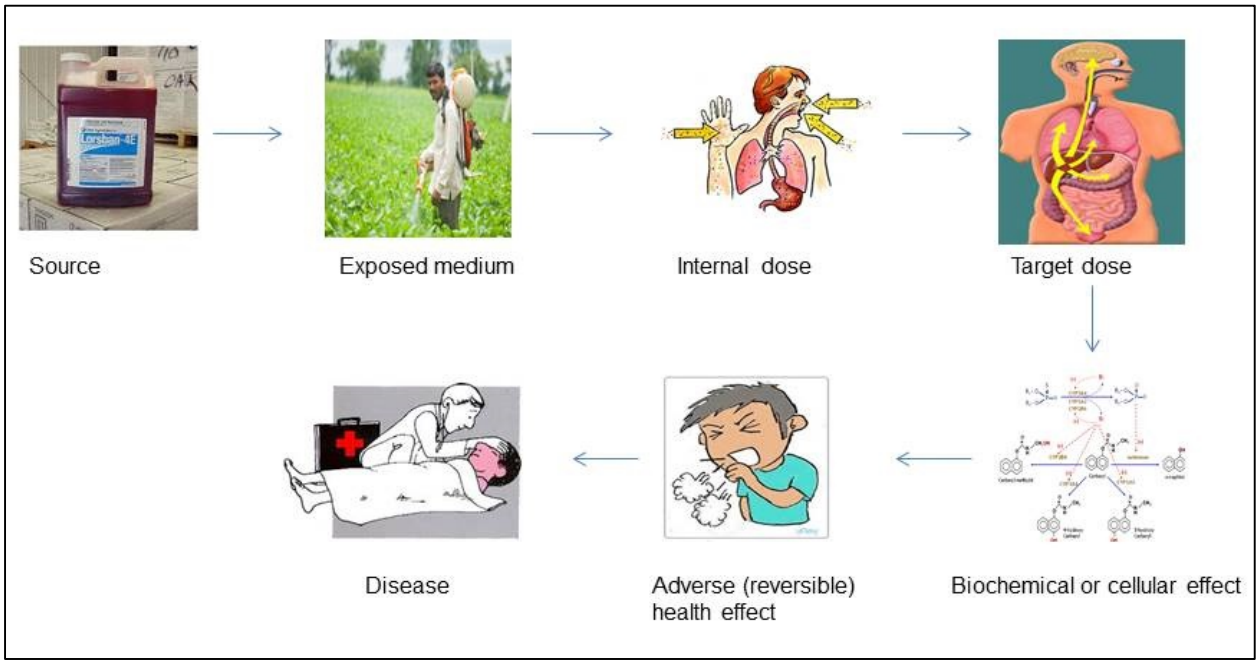

Figure 2-2: Progression of exposure to development of disease (Adapted from Foa and Alession, 2012).

Following absorption, an internal dose of a HCS and/or characteristic metabolites is retained within the body and is detectable in systemic fluids having undergone distribution and metabolism. The HCS will interact with receptors located in and around critical organs. These are organs that, after exposure, demonstrate the first or most crucial adverse effect. As a result, either the induced biochemical change or the internal dose may be measured through BM (Coombs and Schillack, 2009).

2.2.1 Biological Guidance Values (BGVs)

The application of BM as a means of measuring and further assessing worker exposure to HCSs is made possible by the availability of biological guidance values (BGVs) which aid in the interpretation of results (Huizer *et al.,* 2014). Although limited in availability, BGVs serve as reference values for biological indicators as observed in matrices such as urine and blood. The biological indicator may be the original compound, its metabolites or any characteristic biochemical change resulting from absorption (Morgan, 1997).

The intent is to determine the exposed individual's internal chemical dose. Guidance values are representative of the indicator material most likely to be observed in samples collected from a healthy worker solely exposed to the airborne concentration of the OEL for that specific parent compound. In essence, the core fundamental concept of BGVs is that they are concentration limit values of the HCS in question, its metabolites or bio-indicators of the chemical's effect found in the befitting biological medium (HSA, 2011; Morgan, 1997).

Similar to OEL standardisation, the ACGIH and the German Research Foundation (DFG) recognised the benefits of BM in the mid-1900s. The modern ideal of BGVs utilised by many organisations stems from the foundational work of Elkins which started in 1954. He gathered clinical data which was necessary to interpret results that relate metabolism of certain chemicals to external exposure, thus allowing comparison between external chemical exposure and internal dose. He then published a sequel of recommended BGVs for a number of solvents (Elkins, 1954; Morgan, 1997).

The DFG founded the committee responsible for BGVs in 1979 and similar to the ACGIH, consists of a group of independent scientists from various related study fields. The group formulated the concept of protecting workers from adverse effects arising from exposure to HCSs based on biological indicators. Emanating from this, biological tolerance values were established. The ACGIH together with the DFG remain the two most influential organisations in the designation of BGVs (Deveau *et al.*, 2015).

In 1982, the ACGIH's board of directors decided to appoint a committee of volunteer scientists involved in various fields (toxicology, chemistry, occupational medicine etc.) to recommend biological exposure indices which may be quantified based on available scientific literature. The group set out to develop a fitting description and interpretation of the proposed reference values. By 1984, index values were published for ethyl benzene, carbon monoxide, styrene, trichloroethylene, toluene and xylene (Morgan, 2011).

2.2.2 Health-based BGVs

Various organisations/countries concern themselves with applying threshold limit values with a similar goal. These health-based values aim to prevent the worker from acquiring any occupational related diseases even after a lifetime of exposure. For the purpose of this mini-dissertation, "BGV" is used as the term under which the various types of limit values fall.

2.2.2.1 Biological Exposure Indices (BEIs)

BEI values are representative of the body's overall biological burden. A BEI represents the concentration value of a certain metabolite that would be found in biological samples obtained from a healthy worker that was exposed to the HCS in question at the TLV level through inhalation (ACGIH, 2015). For some chemicals, however, different criteria are used to establish the respective BEIs. This is done for those HCSs whose TLVs are set with the sole purpose of preventing non-systemic conditions (respiratory conditions or localised irritation).

BM becomes a necessary tool in such instances as it takes into account the possibility of absorbing these HCSs through alternative routes such as the skin, which may result in systemic adverse effects. For these HCSs, BEIs are intended for the prevention of systemic effects. Thus, the BEIs do not correspond with the expected internal dose arising from inhalation exposure at concentrations equivalent to the TLV. Examples of such chemicals are lead, methemoglobin inducing chemicals and acetyl cholinesterase inhibitors. Their BEIs completely disregard the TLV and accounts for the risk of systemic health impairment (ACGIH, 2018b).

Since most BEIs are associated with TLVs, the scope of application remains consistent with the fundamentals proposed by the TLV committee. In essence, they are regarded as conditions to which most workers may be exposed without developing occupational related diseases (Rosenberg and Rempel, 1990).

A precise demarcation between hazardous and non-hazardous exposure is not clearly defined. Moreover, due to biological variation, it may be possible for some individuals to exhibit an internal dose exceeding the recommended BEIs without increasing any risk to health. Nonetheless, if it is observed that a worker or group of workers within the same vicinity persistently present results exceeding the BEI, investigation and implementation of adequate control measure should follow (Rosenberg and Rempel, 1990).

The development process involved in establishing a recommended value scrutinises the scientific data available on the pharmacokinetics regarding the relationship between intensity of exposure and resultant biological effects. It is required that the data is collected from human exposures in controlled settings and should also be based on peer reviewed scientific literature (Morgan, 1997).

2.2.2.2 Biologischer Arbeitsstoff-Toleranz-Wert (BAT), Biological tolerance values

BAT values are recognised as maximum permissible levels of the HCS, associated metabolites or any resulting modification from the normal biological parameter as a result of HCS exposure (DFG, 2015). These values serve the same function as CLs (Morgan and Schaller, 1999; EHS, 2012).

Toxicological and medical criteria used in order to prevent the emergence of adverse health effects form the ground work in establishing the appropriate safety margins that make up the BAT values. The effects of exposure are determined by considering the functional changes, i.e. deviation from the biological norm (Göen *et al*., 2011).

The available scientific literature, however, allows for the assumption that not all functional changes imply disease. Some changes are deemed tolerable, provided that after long term exposure, they:

i. do not disrupt the normal functioning of affected systemic sites;

ii. allow for compensation mechanisms to take place following exposure;

iii. may be reversed after the working shift;

iv. do not render the worker more susceptible to other external factors; and

v. do not in any way affect reproduction (Fiserova-Bergerova and Ogata, 1990; Henschler, 1990).

An essential component of BATs is that they are purely reliant on scientific data derived from human subjects. To clearly distinguish between the aforementioned BGVs, BATs are directly linked to the expected health effects, whereas BEIs are based on an indirect relationship which exists between health effects and their corresponding TLVs (Morgan and Schaller, 1999).

2.2.3 Pragmatic (Non-health) based values

These values refer to substances for which heath-based threshold limits cannot be sufficiently determined. Some organisations consider that no value can, with the currently available scientific knowledge, be regarded as harmless. This particularly applies to carcinogenic and genotoxic substances. For such substance, BM is unquestionably essential (Göen *et al.,* 2012).

2.2.3.1 Expositionsäquivalente für krebserzeugende Arbeitssoffe (EKA) exposure equivalents for carcinogenic substances (CSs)

The DFG reviews CSs solely to quantify the chemical levels in exposed individuals, for occupational medicine purposes. A correlation between the exposure levels to CSs and the increased risk of cancer development is deduced in epidemiological studies. The proportionality between the workplace air concentration of a CS and the biological indicators is investigated (DFG, 2015).

As an outcome, the body burden resulting exclusively from inhalation of the said substances may be determined. The organisation does not in any way intend for the these EKA levels to be understood as BAT values (DFG, 2015).

2.2.3.2 Biologischer Leit-Wert (BLW)

Similar to BAT values, BLWs is a systemic measure of the HCS, its metabolites or the resulting deviation from a biological norm caused by exposure to that HCS. If this set parameter is adhered to, most toxic effects will be avoided, leaving only the risk of carcinogenicity. To illustrate this, the substance acrylamide is assigned a BLW of 550 pmol/g (picomol per gram) globin of the metabolite N-(2-carbonamideethyl) valine. Neurotoxic ailments may be prevented if the body burden is kept within this limit. However, the risk of cancer still exists. BLW are only allocated to carcinogens and probable carcinogens, as well as substances for which insufficient data is available to base a definite BAT value (Göen *et al.,* 2012; DFG 2015).

2.2.3.3 Benchmark guidance value (BMV)

BMV are set at the 90th percentile of available data. The data is gathered from BM results collected from workplaces considered to have a high standard of occupational health working practices. The BMV thus represents levels which are achievable for most industries by making use of good occupational hygiene practices. A value exceeding a given BMV does not imply that adverse health effects will occur; it only serves to alert the responsible parties to the inadequacy of exposure control (HSE, 1997).

Table 2-1: Commonly encountered BGVs together with the countries in which they are used.

Threshold category	Recognised threshold value	Country of recognition
Health based values	BEI	United States of America; South Africa
	BAT	Germany
	BMGV	United Kingdom
	Occupational Exposure Limits Based on Biological Monitoring (OEL-B)	Japan
Pragmatic based values	EKA	Germany
	BLW	
	BAR	
	BGV	European Union

2.3 Biological matrices used

Each BGV recorded for any given HCS is highly dependent on the appropriate biological matrix. The biological matrix chosen when applying BM is essential and is chosen depending on the characteristics of the HCS in question. Properties such as volatility or lack thereof, hydrophobicity or hydrophilicity, its persistency in the body and stability are considered. Other considerations include the applicable biomarker, the availability of monitoring resources and the feasibility of monitoring techniques. For ethical reasons, it is also important to review the nature of the procedure required to collect the data from the exposed population (Dinis-Oliveira *et al.,* 2010). A wide range of both non-invasive and invasive matrices are available for BM (Table 2-2).

Undoubtedly, non-invasive procedures are primarily desired since these do not require specialised skills and equipment, are less time-consuming and generally workers feel more comfortable with such methods. In the occupational hygiene field, common matrices include exhaled air, urine and blood (Dinis-Oliveira *et al*., 2010).

2.3.1 Exhaled air

Monitoring end-exhaled air makes for a non-invasive procedure that enables the detection of oxidative stress and pulmonary inflammation caused by volatile HCSs. Research shows that over 250 volatile HCSs can be detected from end-exhaled air using gas chromatography. It is, however, not recommended to monitor through this matrix for HCSs inhaled in the form of aerosols, gases and vapours. This is also the case for HCSs that break down when coming into contact with bodily fluids. Highly water-soluble HCSs such as ketones are good examples of chemicals for which this matrix would not be useful (Fiserova-Bergerova *et al.*,1989, Corradi and Mutti, 2005).

2.3.2 Urine

Some trace metals, hydrophilic compounds and organic analytes, in conjunction with their metabolites, are preferably monitored through urinalysis with urine as the biological matrix (AIHA, 2004). The biomarker concentration in urine is a reflection of the mean plasma level of the substance since the last urination (Lowry *et al.,*1989).

Solvents, which are known to be excreted rapidly, are detected in samples collected directly after the work shift. In workplace settings, routine collection of urine is more feasible, however, a confounder such as urine dilution needs to be adjusted for when determining the biomarker concentration. Diagnostic laboratories usually report urine creatinine as the correction of the dilution or concentration of the urine specimen (Teass *et al.,* 1998; Hadland and Levy, 2016).

2.3.3 Blood

Contrary to the aforementioned commonly used matrices, blood BM requires invasive procedures performed by trained individuals. However, it is still an important matrix for the examination of exposure to inorganic chemicals such as some metals and also for organic chemicals that are metabolised slowly.

As blood is the transport medium for HCSs and their associated metabolites throughout the body, it is expected that most of the biomarkers are found within this medium following exposure. Because of the dynamic equilibrium state of the human body, the concentration of a biomarker will differ between regions of the circulatory system, making the point of extraction very specific for individual HCSs (Teass *et al.,* 1998).

Table 2-2: Variety of biological media.

Non-invasive media	Invasive media
• Urine • Nasal swab • Breath • Saliva • Breast milk • Sputum • Hair • Semen • Faeces • Nail clippings	• Blood and blood vessels • Tissue (Adipose, liver, lung) • Bone and bone marrow • Amniotic fluid • Broncho-alveolar lavage • Follicular fluid

2.4 Specimen Collection

Equally as important as the biological matrices, the collection of the HCS and/or characteristic metabolites is highly dependent on the time at which the specimens are taken. The concentration of the biomarker found within the biological matrix is subject to change; owing to the chemical nature of the parent HCS absorbed. Variables arising from environmental and physiological parameters affect the level of the biomarker found in the biological matrix. As a result, it is only acceptable that biological monitoring samples are collected at a point where the levels of the biomarker are at 90% of the steady state concentration within the befitting matrix. BGVs can only be accurately applied when the selected biomarker is in a steady state within the biological matrices (Fiserova-Bergerova and Vlach, 1997; ACGIH, 2015).

Where metabolites exhibit rapid elimination, samples should be collected relative to either the beginning or end of work shift. The results of biomonitoring collected for such chemicals will only indicate exposure that occurred within the past several hours. It is therefore critical that specimens are collected as close as possible to the exposure time, but also taking into account the “waiting period” required for the biomarker to reach steady state. On the other hand, some HCSs have longer half-lives which could ranging from several weeks to even years. The resultant biomarkers can be used in assessing exposure even long after it has occurred.

The exposure duration in conjunction with the length of employment become the vital factors in such instances; as opposed to individual work shifts (NRC, 2006). It is, therefore, imperative that sampling time be distinguished when a BGV is assigned and furthermore, that this assigned sampling time is observed during biological monitoring of employees in the work place.

2.5 Advantages and limitations of BM as opposed to environmental monitoring

Because BM and environmental monitoring (EM) are regarded as complementary aspects of occupational health (OH), it is logical to compare the two in any discussion regarding either one. EM may be understood as the methodical sampling of air, soil and water with the aim of evaluating the environment. EM plays an important role by assisting industries to comply with regulations as well as providing them with a tool that assists with managing the prevention of excess exposure to HCSs in the workplace (Artiola *et al*., 2004; Klaassen, 2013).

Contrary to environmental monitoring, BM provides a more focused and target based approach in assessing the risk posed to exposed individuals, especially for chemicals that exert toxicity after entering the human body.

The most essential facet of BM is that it brings us closer to understanding the systemic effects of chemicals. Furthermore, BM allows for risk assessment over prolonged periods of time and overall exposure, accounting for different sources of exposure. The amount of HCS absorbed by the individual depends on both extrinsic (ventilation, climate, physical effort necessary for work activity) and intrinsic factors (age, sex, genetics, etc.) (Manno *et al.,* 2010).

There are some disadvantages to BM and the associated BGVs. In the case of acute exposure, results obtained through BM will be selective for substances that are metabolised rapidly. Another considerable disadvantage is that BGVs are limited in availability due to the lack of sufficient scientific data to establish the relationship between exposure and possible health effects for many chemicals. It is also not clear from BGVs if the level expressed reflects cumulative or acute exposure (Foa and Alessio, 2012).

2.6 South Africa: A case of developing countries

Having explored the various facets of BM, it is rational to state that it plays a crucial role in occupational health and safety; contributing to the protection of workers against occupational related disease and injury (Tshoose, 2011). The proper enforcement of occupational health and safety (OHS) principles primarily relies on awareness in the workplace to aid in the reduction and prevention of occupational diseases (ODs).

Awareness regarding OHS remains insufficient in many work environments, leaving ODs as a major concern on both national and international scale (Hämäläinen *et al*., 2009; Schenk and Johanson, 2010). Globally, an estimated 2 022 000 fatalities are reported every year due to work related ailments (Takala *et al.,* 2014).

It was approximated in 2015 that nearly one million workers died because of work place exposure to HCSs. When compared to estimated figures in 2011, these fatalities increased by close to 9% (Hämäläinen *et al.,* 2017). Fatalities due to ODs resulting from HCSs exposure may be classified into three groups according to their causative agents. The first group of ODs are mainly attributable to physical, chemical and biological agents; followed by those specific to target organs such as the skin and respiratory tract and lastly; those which are classified as occupational cancers (Driscoll *et al*., 2005; ILO, 2014).

South Africa, like many developing countries, is faced with social, political and economic challenges. A characteristic of the changing socio-economic climate is the change observed in the health demographics of the country, which has seen an increase in non-communicable diseases in a population already heavily burdened by infectious diseases; maternal and perinatal disorders. (Mayosi *et al*., 2009).

The World Health Organization Country Office of South Africa reported that approximately two out of five deaths in the country are caused by non-communicable diseases. A contributing factor being the elevated prevalence of risk factors including excessive alcohol consumption, tobacco use, unhealthy nutritional habits, inactivity and obesity (WHO SA, 2014). The immense pressure that is placed on chronic and acute health care systems neglects research on OD (Figure 2-3) (Wandai and Day, 2015).

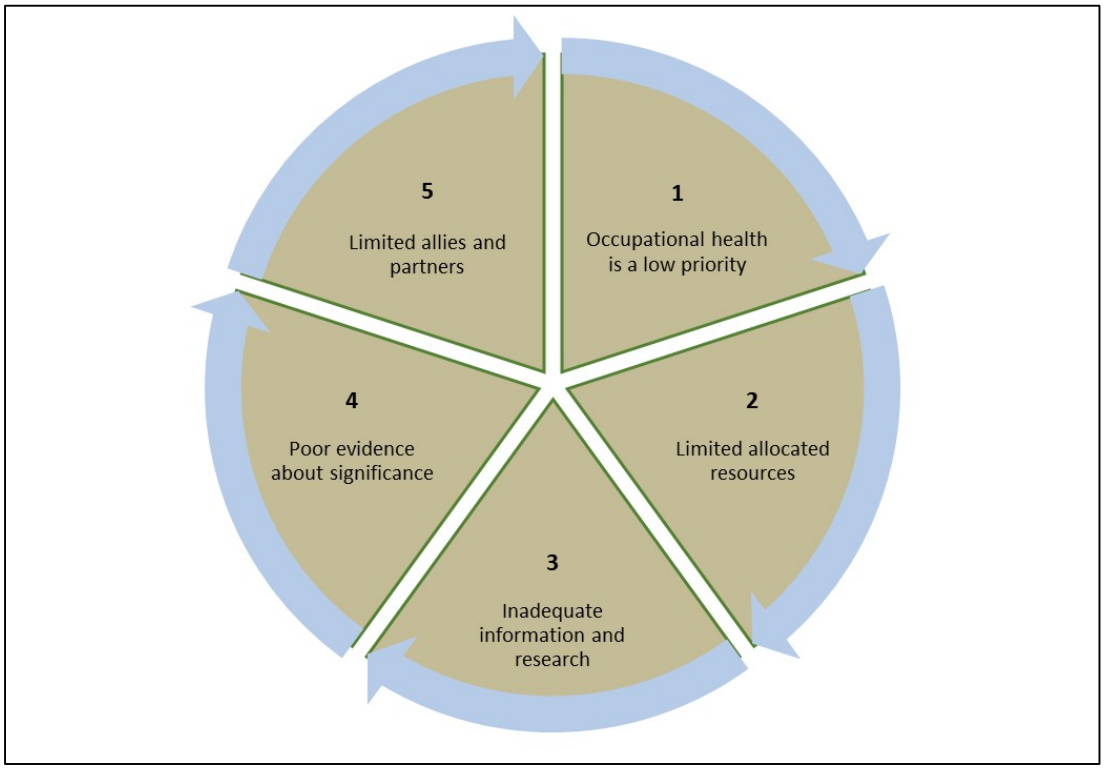

Figure 2-3: Developing countries' occupational hygiene neglect cycle (Nuwayhid, 2004).

While it is accurate that OD primarily stem from work-related risk factors, the contrary is true for a developing country such as South Africa. Silicosis and asbestosis represent conspicuous instances where OD moved outside the confines of the workplace to become environmental and public health concerns. With time these diseases were eventually contemplated as social related diseases rather than that of occupational settings. Risk factors mentioned above as contributory to non-communicable disease serve as risk factors in this regard as well (Nuwayhid, 2004).

A look into the South African mining industry shows that the HIV/AIDS epidemic plays a significant role in the concerns for public as well as occupational health. Workers infected with HIV are at a much higher risk of developing respiratory diseases such as tuberculosis, which in turn increases susceptibility to OD such as silicosis and asbestosis (Hermanus, 2007; Naidoo, 2013).

It should be emphasised that having a positive outlook on growing and investing in the field of OH is vital to the development of low-income countries. Good OH practices are especially needed in low income countries because they have the potential to improve productivity as a result of having a healthier workforce (Lim *et al*., 2012).

Regulations, such as those governing HCSs exposure, needs to be kept current and relevant by taking into consideration the most recently available scientific data, validated sampling methods as well as newly developed means of controlling (if such exists) the chemical hazard in question (WorksafeBC, 2010). To accentuate the integral aim of occupational hygiene, it is imperative that effective protection of workers' health is paralleled by scientifically sound and contemporary OELs and BEIs.

The South African Department of Employment and Labour, charged with the responsibility of establishing and maintaining the country's OELs as well as BEIs, is currently in the process of revising the HCSR. A draft proposal, now titled Regulations of Hazardous Chemical Agents, has been released for public commentary prior to the publication for regulatory enforcement (SAIOH, 2018).

The proposed changes, on specifically the BEIs, are observed to be extracted from the ACGIH's 2018 handbook of TLVs and BEIs. The proposed changes in the South African legislation will include the following:

- The addition of Chemical Abstracts Service (CAS) numbers. This will assist in better identification of the HCSs covered and eradicate misidentification due to synonymous naming of chemicals.

- Addition of 21 BEIs which are not included in the currently regulated list of BEIs in the HCSR. This widens the spectrum of coverage for South Africa.

- A revised and more comprehensive definition for the term BEI. In the current HCSR, the term is defined as a reference guideline value intended for the evaluation of potential health hazards. In the newly proposed regulations, BEIs are defined as reference values used in the assessment of results obtained from BM. They are guidelines intended to evaluate the likelihood of adverse health effects. Further, they represent the level of determinants that are most likely to be observed in specimens collected from healthy employees who have been exposed to chemicals with inhalation exposure at the OEL.

- Removal of notation “A” from the HCSR. Biological exposure indices given this notation are disclaimed to be unprotective to certain populations as they indicate increased susceptibility to the effects arising due to the specific HCSs’ exposure. However, a new notion has also been added to the proposed regulation which is used in identifying those HCSs which could not be assigned BEIs as there is currently insufficient scientific data. This disclaimer goes further to emphasise that, although there is currently no BEI available, BM should still be considered based on the toxic nature of those HCSs.

The chapters hereafter will compare the currently regulated BEIs from the HCSR with those of selected developed countries to assess the stringency and HCS coverage. General commentary will also be provided on the proposed draft regulations of hazardous chemical agents in comparison to the currently regulated BEIs.

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CHAPTER 3: ARTICLE

3.1 Instructions for authors: Annals of work exposures and health

The *Annals of Work Exposures and Health* publishes innovative research and developmental material that assists in the reduction of ill-health risk which results from work, and welcome submissions in that regard. In preparation for submission, these aspects are to be considered:

Language

The submitted manuscripts must be written in English and in a clear and concise manner. Either British or American writing style and spelling may be used consistently throughout the manuscript. The author should avoid words or phrases which might be unclear in other parts of the world or make efforts to clearly explain.

Brevity

Any manuscript submitted must be as brief as possible consistent with clarity. The number of words, excluding the abstract, references, tables and figures, must not exceed a total of 5000. The exact total number of words must be stated as a message to the Editor during submission. Provided the length exceeds 5000 words, a justifying statement is required to clarify the extra length, and papers without this information may be returned unread.

Title, abstract and keywords

A title should be constructed to shortly describe the main issue or question examined by the paper and should not in any way imply the research outcomes as truthful. Recognisable, searchable terms and keywords must be included to provide a more convenient internet search. Essentially, the author should write the abstract in a style that will intrigue readers and encourage reading the full paper.

Authorship

Named authors should only be included if they have made considerable contributions to the intellectual development or design of the work, or the acquisition, analysis or interpretation of data for the work AND have approved the accuracy of the final version of the manuscript to be published. Other contributions may be recognised by acknowledgement at the end of submission.

Structure of the paper

Primarily, papers should be structured according to the following pattern: Introduction, Methods, Results, Discussion, and Conclusions, unless these are unsuitable. A paper must be prefaced by an abstract of the argument and findings, which may also be arranged under the same headings.

Design and analysis

The quality of the data and analysis must always be good enough to justify the deductions drawn. Particular attention should be given to design of sampling surveys — which should be planned using modern statistical principles — and to the treatment of results below the limit of detection.

Units and symbols

SI units must be used, though their equivalent in other systems may be given additionally.

Figures

Good quality low resolution copies of Figures, including diagrams, charts and photographs should be sent together with the initial submission. These Figures, diagrams or charts can either be incorporated into the text or at the end of the manuscript. After review, the paper should be accompanied by high-resolution electronic copies in a form and of a quality suitable for reproduction.

Tables

Tables should be numbered consecutively with suitable captions. As with Figures, it is advised that they are included into the text of the first submission. However, following revision, each table should be presented on a separate page. Footnotes to tables should be provided below the table and should be referred to by superscript lowercase letters.

References

Only references which advance an argument or hypothesis, or which describe methods for which the original account is too long to be reproduced should be included. 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, and they should be incorporated naturally into the text as follows:

Jones and Brown (1995) and Hospath et al (2006) observed total breakdown of control..., or Total breakdown of control has sometimes been observed (Jones and Brown, 1995; Hospath et al., 2006).

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. 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 (e.g., Professor O.H. Poobah, Institute for Dusty Sciences). Internet material can be referred to if it is likely to be permanently available; the date on which it was last accessed should be given.

The following examples are given:

Simpson AT, Groves JA, Unwin J, Piney M. (2000) Mineral oil metal working fluids (MWFs)—Development of practical criteria for mist sampling. Ann Occup Hyg; 44: 165–72.

Vincent JH. (1989) Aerosol sampling: science and practice. 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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Morse SS. (1995) Factors in the emergence of infectious diseases. Emerg Infect Dis [serial online] 1995 Jan–Mar;1(1). Available from: URL: http://www.cdc.gov/ncidod/ EID/eid.htm (accessed 25 Oct 2010).

Comparative analysis of South African BEI's with those of developed countries

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3.2 Abstract

Introduction

Biological monitoring aspires to evaluate workplace exposure to hazardous chemical substances (HCSs) by assessing the total systemic exposure of workers. Biological monitoring is also essential in verifying the effectiveness of implemented control measures. The intention of biological monitoring is to detect HCSs in the body before the occurrence of adverse health effects. To successfully achieve this, it is critical that biological guidance values (BGV) are kept scientifically relevant. This study, therefore, explored the stringency of the South African biological exposure indices (BEIs) by comparatively analysing them relative to those of selected developed countries. It should be noted that for this mini-dissertation, “Biological Guidance Value (BGV)” is used as the term under which the various types of limit values fall. This is done because the various developed countries/organisation considered, designate different terms for these limit values.

Methods

This study was conducted by comparing BEIs legislated in the Hazardous Chemical Substances Regulations (HCSR) of the Occupational Health and Safety (OHS) Act of 85 of 1993 with those of various organisations representing selected developed countries. These include the American Conference of Governmental Industrial Hygienists (ACGIH), Deutsche Forschungsgemeinschaft (German Research Foundation, DFG), Occupational Safety and Health Administration, Health and Safety Authority (HSA), Scientific Committee on Occupational Exposure Limits (SCOEL) and the Japan Society of Occupational Health (JSOH). Countries of origin being: United States, Germany, United States, Ireland, Europe and Japan; respectively. Only chemicals appearing in both the HCSR and the guidelines of the organisation/developed country in question, as well as having similar metabolites, were considered when calculating. The overall level of the set concentrations of the BGV was analysed using a geometric means (GM) and interval method. The remaining chemicals which could not be included in the calculations were reviewed through available scientific data and discussed individually.

Results and discussion

It was found that HCSs for which the HCSR designates BEIs, are also included in the BGV lists of most developed countries/organisations considered in this study. In only two instances an overlap of less than 75% exists, that of SCOEL and JSOH. Despite the overlap in HCSs coverage, developed countries/organisations have a greater number of established BGVs when compared to those included in the HCSR.

The most noticeable difference observed in the results was between the DFG and the HCSR. The DFG designates 85 BGV which are not included in the HCSR, having the highest number of unique HCSs, followed by the ACGIH and HSA; having a total of 21 and 22 unique HCSs compared to the HCSR, respectively.

The GMs and interval methods indicated that the levels at which developed countries/organisations have set their BGVs are more stringent than the BEI levels in South African legislation. The most stringent organisation was found to be the SCOEL, having a GM value of 0.37; followed by the DFG and ACGIH with GM values of 0.45 and 0.46 respectively. Amongst the selected developed countries/organisations, the HSA was found to exhibit the most leniency, with a GM value of 0.53. However, this organisation remains more stringent than the HCSR.

Conclusion

There are notable differences in the variety of HCS coverage as well as the level at which BGVs are set between South Africa and developed countries/organisations. BEIs previously established by the South African legislation were not based on scientifically up to date data and interpretation to work place exposure of HCSs. Regular review of these BEIs is necessary to reflective contemporary scientific data.

3.3 Introduction

Dating as far back as the fifteenth century, many chemical substances were recognised to pose a spectrum of health risks to humans and were classified as hazardous. Even in the contemporary world, industries continue to use these HCSs. Precautionary measures are, therefore, necessary to manage exposure to these substances (Paustenbach *et al.,* 2011). Occupational exposure limits (OELs) were introduced for this purpose. In essence, OELs represent safe levels of airborne concentrations to which employees may be exposed throughout their working lifetime without the prospect of developing adverse health effects (Gordon *et al.,* 2014). Although OELs are useful in the management of worker exposure, they are limited in that only inhalation exposure is considered, leaving other routes of exposure unaccounted for (Cocker, 2014). Biological monitoring, in contrast, considers total systemic body burden irrespective the route of exposure (Sams *et al.,* 2015).

Biological monitoring (BM) involves measuring bio-indicators usually found in urine, blood and exhaled air through a variety of analytical techniques. Following HCS exposure, a fraction of the HCS is absorbed and distributed throughout the body tissues via the bloodstream. It is then metabolised and/or excreted. The absorbed dose can be measured using BM (Barr *et al.,* 2005; Foa and Alessio, 2012). BM is made possible in occupational settings due to the availability of biological guidance values (BGVs). BGVs are concentration limit values of a particular HCS, its metabolites or bio-indicators of the chemical's effect found in biological media (Foa and Alessio, 2012).

The idea of formalising a systematic approach in establishing BGVs was initiated by the American Conference of Governmental Industrial Hygienists (ACGIH). The ACGIH together with the Deutsche Forschungsgemeinschaft (German Research Foundation, DFG) remain at the forefront of establishing both OELs and BGVs (Deveau *et al.,* 2015). Various other organisations establish BGVs, all of which differ in the approach of standardising and applying the set BGVs. Biological guidance values can be divided into two categories: health-based and non-health based values. The availability of scientific data is a large determining factor in the categorisation of BGVS (Morgan, 2011). Health-based BGVs are so categorised because the currently available scientific data allows for the determination of values that, when adhered to, no adverse health effects are expected to arise throughout a life-time of exposure. The fundamental concept of all health-based values is that they represent the body burden as obtained from a healthy worker as a result of inhalation exposure equivalent to the OEL set for that particular HCS. Examples of health based BGVs include Biological Exposure Indices (BEIs) established by the ACGIH and Biologischer Arbeitsstoff-Toleranz-Wert (Biological tolerance values, BAT) from the DFG (Göen *et al.,* 2011; ACGIH, 2015; DFG, 2015).

For carcinogens and genotoxic substances, the available scientific evidence is, however, inadequate to set a level of exposure which can be said to inflict no harm on the exposed population. Other approaches are therefore used in evaluating data collected from BM. These are known as the non-health based BGVs category. The DFG, for example, has classified groups of BGVs as Expositionsäquivalente für krebserzeugende Arbeitsstoffe (Exposure equivalents for carcinogenic substances, EKA) and Biologische Leit-Werte (biological guiding values, BLW). EKA values are formulated from epidemiological studies which focus on reviewing the inhalation exposure levels to the carcinogenic substances and the increased risk of cancer development. However, to fully comprehend the exposure and risk relationship, these epidemiological studies need to have both information on incidents of cancer occurrence as well as measurements of exposure levels at which these cancer incidents occurred.

In reality, only workplace ambient air exposure levels are available and so in some instances animal experiments and pharmacokinetic calculations are used to extrapolate the cancer risk that would occur in humans. The relationship between the workplace air concentration of carcinogenic substances and resulting body burden is documented. It is important to underline that the EKA values are in no way meant to be applied in the same manner as either BEIs or BAT values (Göen *et al.,* 2012; Muller and Angerer, 2012; DFG, 2015).

Biologische Leit-Werte on the other hand are set parameters which, when adhered to, prevents most toxic effects with the exception of the risk of cancer development. For instance, the DFG designate a 50-µg arsenic/l BLW in urine for arsenic and all inorganic arsenic compounds. When this parameter is adhered to, it is understood that the development of all neurotoxicity effects associated with exposure to arsenic and its inorganic compounds may be avoided. However, the risk of cancer development in humans as observed in epidemiological studies may still persist (Göen *et al.,* 2012; Muller and Angerer, 2012; DFG, 2015).

An assigned BLW represents the quantity of a HCS's metabolites or any deviation from the normal components of human biological material; caused by exposure to the HCS in question. Any exposure to a HCS that results in an excursion above the BLW in biological material should alert industries of the necessity to implement protective measures (Göen *et al.,* 2012; Muller and Angerer, 2012; DFG, 2015).

One other subset category falling under the class of non-health based values is the benchmark guidance value (BMV). These are achievable levels for most industries when good occupational hygiene practices are reinforced. Exceeding BMVs does not imply that occupational related diseases (ODs) will or will not occur, but only outlines the necessity of implementing more stringent exposure control measures (HSA, 2011).

Like many developing countries, South Africa is undergoing tremendous political, social and economic changes. In 1994, the African National Congress (ANC) government set out a new Bill of Rights which included sections dedicated to the right to an environment that is not harmful to health and well-being. The Occupational Health and Safety (OHS) Act, 85 of 1993 was formulated to assist in promoting these rights. Studies were, however, conducted on the health care system, including the occupational health sector, several years after the Bill of Rights was passed. Based on these studies, conclusions were reached that even though some changes have been made in various factors affecting the socio-economic, health and work practices demographics in the country; a lack of solid progress persists. In essence, fundamental health care policies instituted by the ANC government have not been effectively implemented (Jeebhay and Jacobs, 1999; Mayosi *et al.,* 2009; Coovadia *et al.,* 2009; Muraga *et al.,* 2016).

To encourage an environment that is not harmful to the health and well-being of workers of South Africa, measures developed with the purpose of promoting these rights, such as the OHS Act 85 of 1993 together with the complementary regulations, need to be kept current and relevant in line with technological progress (EH&W, 2008). This study focuses mainly on the HCSR which, since it was incorporated into the legislation in 1995, remained unrevised for the better part of two decades. Only in 2018 new regulations were published for public comment.

The integral aim is to compare the South African BEIs with those of developed countries/organisation with the intent of gauging the stringency thereof and further; provide motive for the adaptation of BGVs from these developed countries/organisations should those of the HCSR be found to be lacking. The considered developed countries/organisations are acknowledged to maintain leading health and safety systems as they invest vastly in research to this regard. It is therefore the expectation that developed countries/organisations are forerunners in setting the standards to which South Africa — a developing country — should esteem.

3.4 Research methodology

This section details the method applied to compare South African BEIs to those of selected developed countries/organisations; from starting the selection, to identifying the similarities and discrepancies in the databases.

3.4.1 Database of BEIs

The South African list of BEIs was extracted from the HCSR, table three of annexure one. The HCSR were promulgated under the auspices of the OHS Act 85 of 1993. The South African list of BEIs served as the reference list. The study was, furthermore, based on a collection of BGVs which were most recently published by various organisations representing selected developed countries. The lists of interest were sourced using website sources, libraries as well as through communication with the relevant authorities. The organisations were selected based on their apparent dominance in literature. A total of six organisations were considered, namely: ACGIH, DFG, Occupational Safety and Health Administration (OSHA), Health and Safety Authority (HSA), Scientific Committee on Occupational Exposure Limits (SCOEL) and the Japan Society of Occupational Health (JSOH). Countries of origin being: United States, Germany, United States, Ireland, Europe and Japan; respectively. Research indicates that the development of BGVs is rather a cumbersome exercise and a great deal of developed countries reference those which have been developed by well recognised organisations such the ACGIH and the DFG. The selected six organisations were found to have individuality in establishing BGVs.

3.4.2 Coverage and selection of substances

A master list was compiled using an Excel spreadsheet containing the list of BGVs of each organisation/country. The list included information regarding the concentration limit values of the chemical and/or metabolite, the unit of measurement as well as the biological matrix concerned. The list was then filtered to exclude some substances and metabolites which did not appear in both South African legislation as well as the comparative organisation in question. However, to maintain a relatively significant data sample size, some chemicals and metabolites from the selected developed countries/organisations were included in the database even though they did not precisely parallel that which is found the HCSR. The basis for inclusion or disregard could be justified according to literature and these distinctive HCSs are discussed individually in discussion section.

Since BGVs are a measure of the total body burden as reflected in the befitting biological medium, the biological media from which the HCS and/or metabolite is determined was a vital consideration. The master list was furthermore divided into subsets, according to the biological media in question, referred to by the South African BEI list. Blood, urine or end-exhaled air are considered as biological media in South African BEIs.

Another factor that had to be considered in order to enable a legitimate comparison was the unit of measurement. The most dominant unit of measurement for each BGV was chosen after which the values of those BGVs that used another unit of measurement were converted. The necessary conversions were calculated according to Table 3-1 in order to standardise the unit of measurement across the categories.

Table 3-1: Conversion factors

From	To	Conversion
mg/l	mg/g Creatinine	/ 1.36 g Creatinine[a]
mg/g Creatinine	mg/l	× 1.36 g Creatinine[a]
mg/l	µg/l	× 1000
g/g	mg/g	× 1000
µmol/l	mmol/l	/ 1000
mmol/l	mg/l	× MW
µg/l	µg/100ml	/ 10

MW = Molecular weight

[a] It is approximated that 1 litre of urine contains 1.36 g of creatinine (HSA, 2011).

3.4.4 Data analysis

For the purpose of comparison between two lists of BGVs, only substances appearing in both the South African list and in that of the comparative organisation could be compared. Another requirement was that the HCS and/or metabolite in question had to be the same. Those substances that appeared to the selected developed country/organisation but did not precisely parallel those found in the HCSR were individually reviewed from literature and included in the discussion section. Furthermore, HCSs unique to either the HCSR or the developed country/organisation in question were separated and graphically illustrated.

The geometric mean (GM) was calculated for the three different subset categories. The resulting three GM unit-less values were averaged to obtain an average overall GM for South Africa vs. developed country/organisation in question. See below for further detail.

3.4.4.1 Geometric means method

The comparison on the general levels of BGVs found on two lists being compared was conducted using the geometric means method, first applied by Hansson (1997). This method was further deemed valuable when comparing overall levels of OELs by Schenk *et al.* (2008). It was essential for this study to make use of the GM as the statistical variable as opposed to the arithmetic mean or median.

When applying the latter, the list considered as having higher values will depend on the denominator. Consider the following, list A and B both appoint BEIs for three HCSs. List A assigns substances I 20 ppm, substance II 15 ppm and substance III 10 ppm, whereas list B designates 200 ppm, 15 ppm and 1 ppm respectively. The results to be obtained using the arithmetic mean of the ratios B/A yields 3.7, implying that list B has higher values. Alternately, A/B also yields 3.7; giving the impression that list A has higher values. In both instances the GM is 1, indicating that the average levels do not differ (see Table 3-2) (Ding *et al*., 2011; Schenk *et al*., 2008).

A GM result of less than 1 suggested that the list being compared has an overall BEI level lower than the reference list, and the converse was true. In this manner, the GM alleviated the challenge presented by the arithmetic method.

Table 3-2: Geometric means calculations.

	List		Ratio	
	A	B	B/A	A/B
Substance I	20	200	10	0.1
Substance II	15	15	1	1
Substance III	10	1	0.1	10
Arithmetic mean			3.7	3.7
Geometric mean			1	1

3.4.4.2 Interval method

The interval method was used to determine the disparities and similarities between levels of BEIs using the 95 – 105th interval. Quite often, when conversions are applied, it is encountered that resultant values on two lists may appear close in proximity rather than identical. Employing the interval method, a unit difference of 5% between values implied that they were indeed identical. Values outside this range were considered as significantly higher or lower (Tynkkynen *et al*., 2015).

3.4.4.3 Ethical aspects

After the study proposal was considered by the Health Research Ethics Committee (HREC) of the North-West University, the study was deemed not to required ethical approval. See letter attached as annexure.

3.5 Results

3.5.1 BGVs coverage

The number of substances covered by the respective countries was compared relative to that which is found in the list of the HCSR. The results thereof are shown in Figure 3-1. The criteria used to classify the substances covered involved separating chemicals according to those which are unique to the HCSR, those which overlap between the HCSR and the country/organisation in question; and lastly, chemicals which are unique to the developed country/organisation. The highest overlap is observed between the HCSR and ACGIH, HSA as well as the OSHA. These countries/organisations show a total of 30 chemical substances overlap, this is the total number of substances having a designated BEI in the South African Legislation. The SCOEL of the European Union had the lowest overlap with only 11 substances in common with the HCSR.

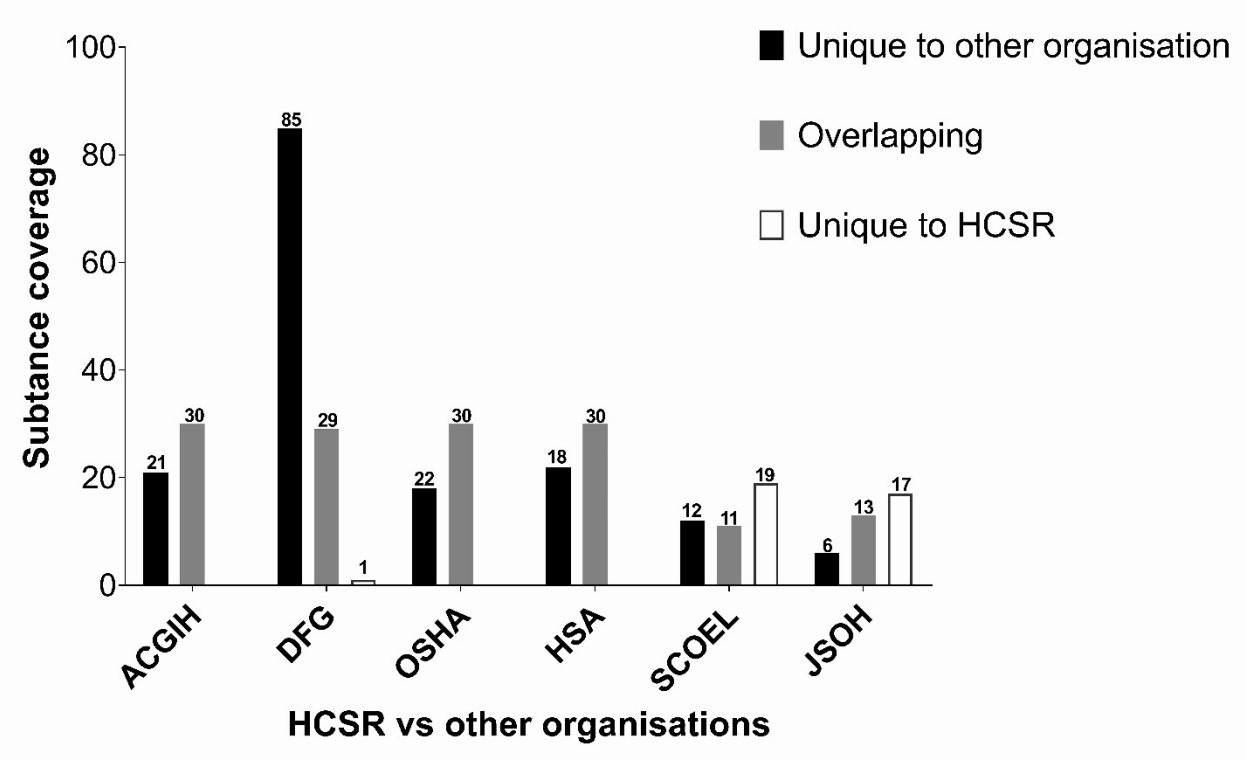

Figure 3-1: Chemical substance coverage disparities and similarity between the South African HCSR and six developed countries. The precise number of chemicals which overlap and are unique to either the HCSR or other country/organisation are stated on individual bars of the graph representing each respective country/organisation.

3.5.2 BGVs levels

3.5.2.1 Geometric means method

The comparison of the overall BGVs was done using the geometric means (GM). The BGVs from a developed country/organisation were divided by the corresponding values found in the HCSR to derive at a list consisting of ratios. The GM was then calculated from those ratios. However, because of the different biological matrices, GMs were first calculated for BGVs having similar matrices as subset categories. Thereafter the overall GM was arrived at for the overall list of BGVs.

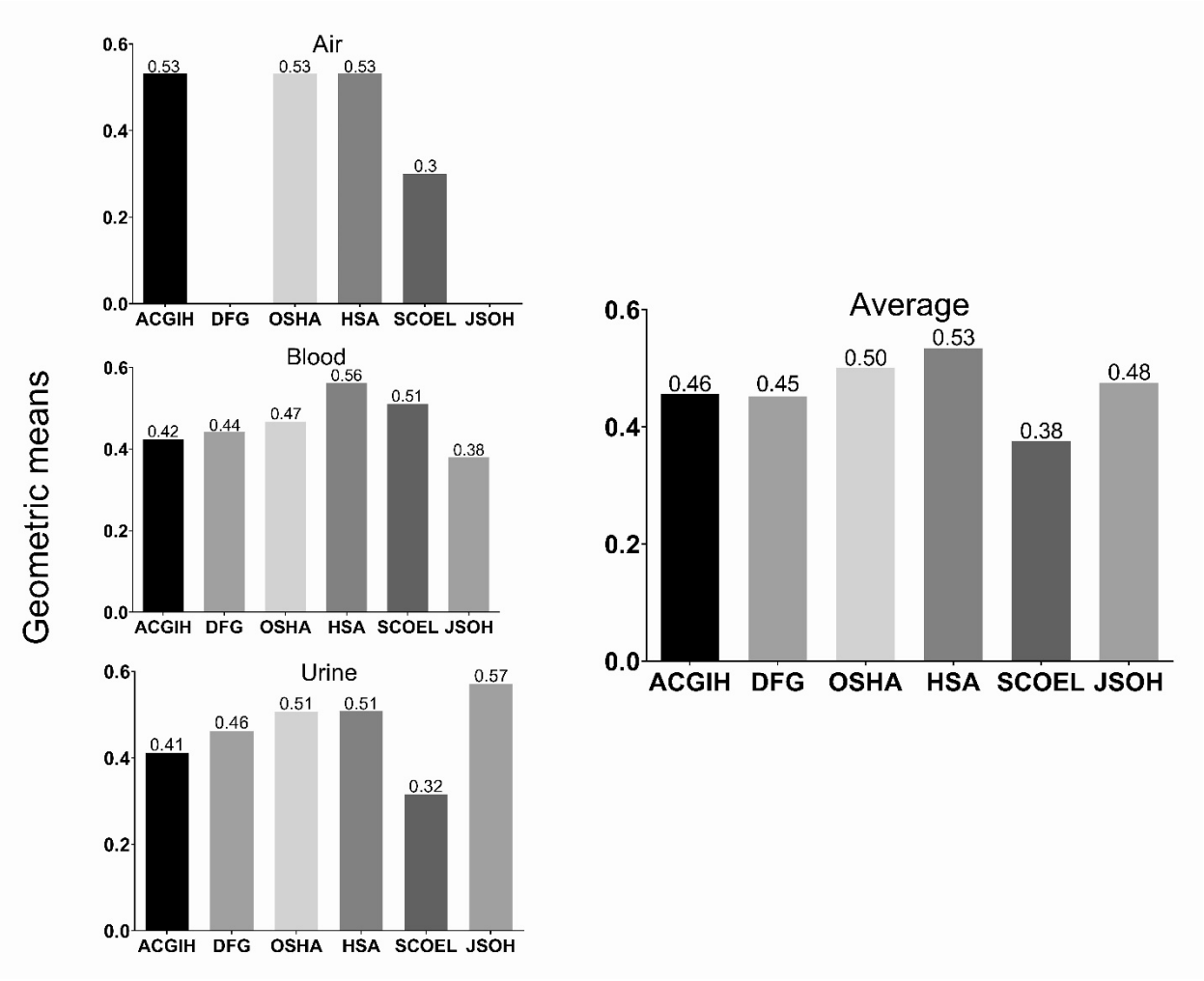

Figure 3-2: Geometric mean values calculated using ratios of BGVs overlapping between the HCSR and various developed countries/organisation depending on biological matrix. The precise GM value of each respective bar are shown.

3.5.2.2 Interval method

Discrepancies between BGVs were evaluated using the interval method. When a BGV from a developed country/organisation falls within 95 – 105% of the BGV found in the HCSR, it is considered identical to that which is found in the HCSR. However, when a unit difference of more than 5% between values is observed, it is considered either significantly higher or lower.

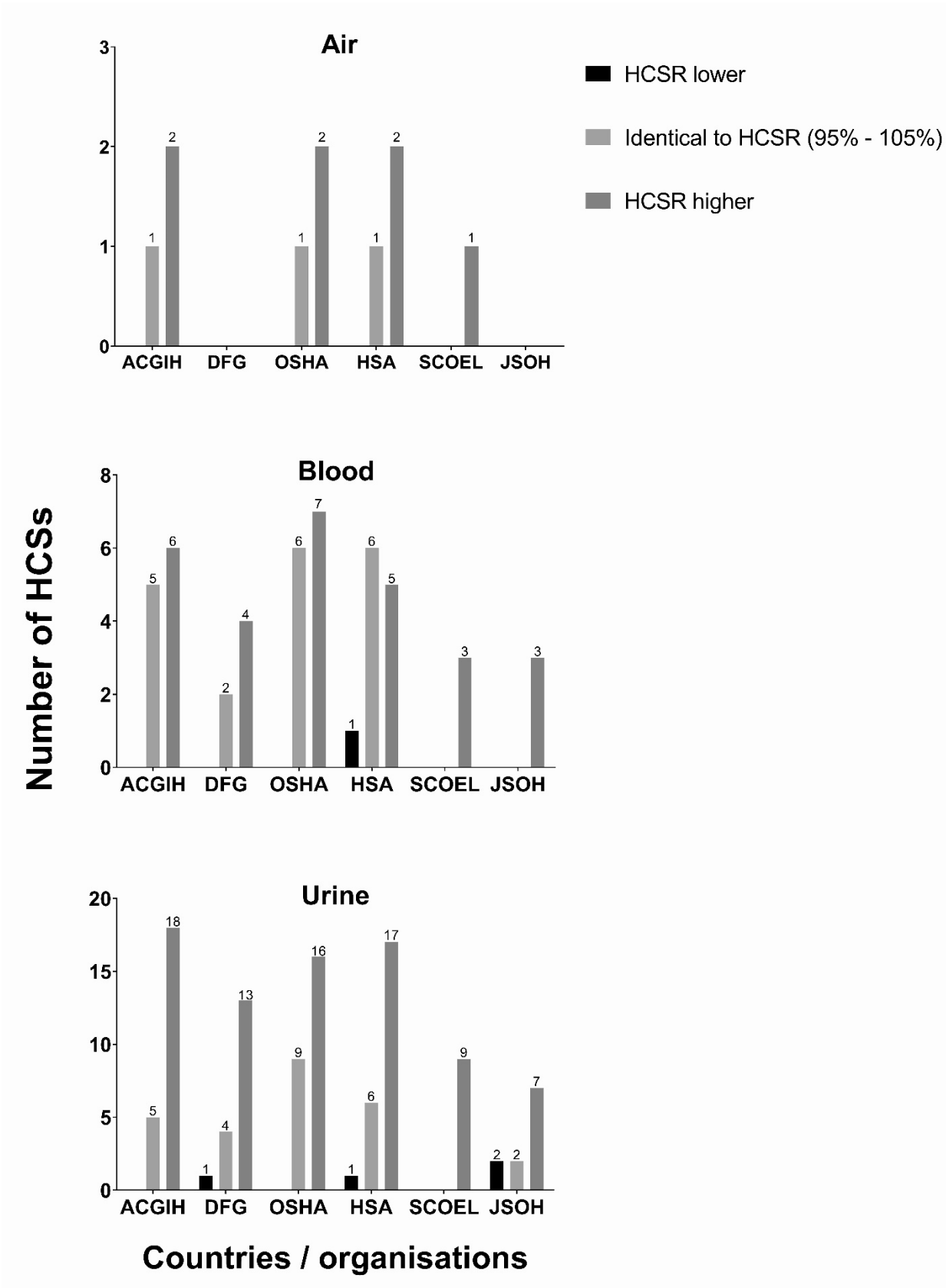

Figure 3-3: Comparison of the HCSR BGVs and six developed countries / organisations with respect to air, blood and urine as respective biological matrix.

3.6 Discussion

3.6.1 Identical chemicals and their metabolites

In this study, BGVs found in the HCSR were compared with those listed by six leading developed countries/organisations with the aim of establishing similarities and differences. The number of BGVs as well as the overall level at which BGVs are set were closely examined; having the BEIs provided by the HCSR as the basis of comparison.

3.6.1.1 Comparison of substance coverage

As depicted in Figure 3-1, the study indicates that there are variations regarding the BGVs established by the different organisations/countries. Considering the overall coverage of HCSs, the BEIs provided by the HCSR was observed to have a 100% overlap with HCSs covered in three developed countries/organisations. The HCSR vs DFG indicated a 97% overlap; with the remaining two countries/organisations exhibiting a < 50% overlap with HCSR. In essence, the HCSR indicated an overall parallel in HCSs coverage of just over half of the developed countries/organisations considered in this study. The lowest overlap is seen when comparing the HCSR to the Scientific Committee on Occupational Exposure Limits (SCOEL) with only 37% similarity in HCSs coverage. This finding is consistent with the entirety of HCSs for which the SCOEL designates BGVs. The SCOEL has 23 BGVs, a very low total which is staggering to expectation; considering it is a committee meant to cater for the European Union collectively. An uncomplicated explanation may be offered as to the differences in social, industrial and constitutional climates which exists within the European countries which has prevented the early establishment of harmonised occupational standards. As a result, many European countries have predominantly made use of BGVs set out by the DFG together with those set by the ACGIH. The SCOEL only set out to propose BGVs and a general strategy for standardisation thereof during the early 21st century. The SCOEL may therefore be considered a relatively new role-player in this regard (Bolt and Thier, 2006).

Even with a considerable number of countries/organisations having 100% overlap with HCSs regulated by the HCSR, discrepancies out-number the similarities substantially. The total HCS coverage by countries/organisations considered in this study range from 23 to 120, outlining the general discrepancies in BGV designation. The setting of OELs and consequently BGVs by developed countries/organisations is attributable not only to the country/organisation's health and safety needs, as determined by risk assessments on the scope of works and industrial variations, but also the socioeconomic status and technological advancements (Ding *et al.,* 2011).

Resources necessary for some chemical evaluation and biological monitoring may not be easily available from organisation to organisation, subject to the developmental stages of that particular country/organisation (Ding *et al.,* 2011). The most noticeable difference observed in Figure 3-1 lies within the comparison between the DFG and the HCSR. The DFG designates 85 BGV which are not included in the HCSR, having the highest number of unique HCSs and, needless to say, the highest total collection of BGVs compared to any other country/organisation considered in this study.

Germany ranks fourth in the world's largest economies and is known to be highly industrialised. The robust occupational health and safety system which has been in existence for over a century, in partnership with federal government, constantly seeks an all-inclusive approach for employees throughout all enterprises of varying sizes and public sectors (WHO, 2012). The aforementioned may explain why Germany has an overall coverage of HCSs larger in variety than the collective of developed countries/organisations considered for this study; and more so when compared to the HCSR.

Subsequent to the DFG is the HSA followed by the ACGIH; having 22 and 21 BGVs which are not included in the HCSR, respectively. The ACGIH has for decades been the predominant organisation for setting OELs and BGVs in the United States. The ACGIH published its first list of BGVs in 1984, which covered only 6 HCSs. This list has grown over the years as the organisation annually reviews and makes additions when deemed necessary. Various contributing factors are considered when a HCSs is added to the list, such as the use and prevalence of the HCS in industry; the most recent scientific data as well as the number of employees in the specific industry that are at risk of exposure to that certain HCS (Adkins *et al.,* 2009; Morgan, 2011; ACGIH, 2015).

It is therefore inevitable that as industries grow and with an increase in scientific knowledge, the list of BGVs should increase with each annual review. The ACGIH remains one of the largest and most internationally recognised organisations in the setting and revision of OELs as well as BGVs. Although the AGCIH has no legal authority, it is frequently used as a basis by other countries/organisations for establishing occupational limit values and BGVs (Adkins *et al.,* 2009). One such organisation is the HSA, a significant number of the BGVs covered by the HSA have been adopted from the ACGIH and as such, a lot of similarity exists in the overall HCSs coverage between these two organisations (HSA, 2011).

The remaining countries/organisations are OSHA, having a total of 18 unique HCSs to the HCSR; SCOEL with 12 and JSOH with only six unique HCSs. The JSOH representing Japan was found to have the least amount of HCSs covered in the list of BGVs. With only 19 BGVs, even the HCSR's coverage of HCSs exceeds those found in the JSOH.

Monitoring workplace exposure in Japan is enforced by regulations based on the Working Environment Law. A considerable number of HCSs are used in industry that are not covered in the said regulations, whose exposure is left to the discretion of the employer (Takahashi and Higashi, 2006). To ensure that the employers are taking appropriate risk-based prevention strategies, a provision was made in the Industrial Safety and Health law which impels employers to make all reasonable efforts to protect their worker's health from excessive exposure to HCSs. This law enforces that each year several unregulated HCSs are selected according to their toxicity and officially designated as the main subjects for risk assessments industry wide. All employers that produce or make use of 500 kg or more of any of the specific HCS are to disclose all relevant information regarding their processes to the Labour Standard Inspection Office. The Labour Standard Inspection Office then evaluates all the information and targets those workplaces perceived to have increased risk of exposure to the HCSs. Further evaluations such as personal exposure assessments are carried out at these workplaces and commentary is subsequently made by the public as well as specified committees as to whether regulatory action is required for any of the selected HCSs (Takahashi and Higashi, 2006; Sakurai, 2012). In this way, a pragmatic approach is taken on the control of exposure to HCSs that are relevant to the industrial environment in Japan.

The range in HCSs coverage by each individual country/organisation indicates that general discrepancies exist between countries, whether developed or developing. The onus lies with each individual country to designate BGVs based on that country's risk assessments and its industrial climate. Setting appropriate BGVs levels as well selecting the spectrum of HCSs covered is a complex process that takes into consideration biological monitoring and associated components.

It varies between countries/organisations, but the following fundamental considerations remain constant. Selecting BGVs and subsequently setting the levels thereof, is reliant on the availability of highly sensitive and valid analytical methods. A countries'/organisations' progressiveness in fields such as analytical chemistry and occupational hygiene are important driving forces (DFG, 2002). Other contributors are varying prioritisation of socio-economic factors and the feasibility of achieving such set standards considering the country's/organisation's economic status thus leading to highly variable BGVs levels and HCS coverage. An additional contributing factor into varying BGVs levels, may be the differing time frames at which these are revised by each country/organisation; to take into account technological improvements (Ding et al., 2011).

3.6.1.2 Levels of BGVs

The GM method was used in this study to compare overall levels of BGVs. Taking into consideration the different biological matrices, calculations were first done according to the subset categories. Throughout the countries/organisations most HCSs are designated a urine based BGV. Although urine is regarded a waste product, it contains a vast amount of information that gives valuable insight to chemical exposure.

It ranks amongst the top preferred screening tests in analytical methods and it is non-invasive, unlike screening through plasma and blood count methods (Delanghe and Speeckaert, 2014). Having separated the different matrices (Figure 3-2) and established the GM value thereof, overall GM values were obtained. In Figure 3-2 the overall GM values are graphically represented. The GM calculated for the six developed countries/organisations arrived at values which were less than 1, implying that all BGVs of these developed countries/organisations are set at levels which are more stringent to those found in the HCSs.

The results of this study make it is clear that the South African BEIs, in comparison to those of developed countries/organisations, are lagging in terms of the levels at which the BGVs are set as well as the spectrum of coverage. The literature review allows for the assumption to be made that the lower BEIs of developed countries/organisations are established based on contemporary scientific evidence. It may then be concluded that the South African BEIs, which were established in 1995, are outdated and cannot be perceived to offer workers protection against adverse effects. The lack of consistent revision on the regulations governing OELs and subsequently BEIs, may allude to a lack of governmental interest, which in turn ripples into substandard data collection systems as well as health and safety regulation enforcements (Nuwayhid, 2004).

This confirms the hypothesis that propels this study and those similar: South Africa, like many other developing countries, is considered to maintain poor Occupational Health and Safety systems which may be explained as a characteristic of poor governmental interest.

The HSA, an organisation responsible for instituting OELs as well as BGVs for Ireland, was observed as having the highest GM value of 0.53. Although the HSA remains more stringent than the HCSR, the overall level of BGVs published by this organisation ranks closest to those of the HCSR than any of the other developed countries/organisations considered. One explanation for this lesser stringency than other countries/organisations could be that the HSA includes the so-called benchmark guidance values (appropriated from the Health and Safety Executive, United Kingdom); which are pragmatic values set at the 90th percentile of data collected from industry (HSE, 1997).

The data is gathered from BM results collected from workplaces considered to have a high standard of occupational health working practices. The BMV thus represents levels which are achievable for most industries by making use of good occupational hygiene practices (HSE, 1997). The inclusion of this implies that the HSA reserves some leniency by considering BGVs which are more practicable than those which primarily take into account health factors. The SCOEL had the lowest GM value of 0.38. Although this society representing the EU has at present only standardised BGVs for a few HCSs, the levels at which they are set is by far uncompromising. This organisation indicates the most stringency in comparison to the HCSR than any of the other developed countries/organisations in this study.

The two countries/organisations known to be at the forefront of BGV establishment, the ACGIH and the DFG, ranked in close proximity with GM values ranging between 0.46 and 0.45 when compared with South Africa's BEIs. The close proximity between the ACGIH and DFG is an anticipated finding, considering that the two organisations revise both the HCS coverage as well as the levels at which the BGVs are set on an annual basis to take into consideration the most recently available scientific evidence. Thus, it is quite sensible that the two countries/organisations utilise similar scientific sources and analytical methods.

Similar observations to those made when the GM was applied — that the BGVs established by developed countries/organisations are set at levels much more stringent than those of the HCSR — were still clear when the 95 – 105th interval method was applied to analyse the similarities and discrepancies. All three the biological matrix subsets, as indicated in Figure 3-3, are conclusive in that a considerable portion of the BGVs as shown in the HCSR are set at levels which are significantly less stringent when compared to the developed countries/organisations.

Altogether, the discussed discrepancies identified by this study are in agreement with similar studies which focused on the comparison of South African OELs, short-term and ceiling exposure limits with those of similarly developed countries/organisations (Viljoen, 2012; Maponya, 2016).

3.6.2 Discussion on individual chemicals

In the process of analysing the data collected from various countries/organisations, chemicals and/or metabolites were assessed individually and consequently, some HCSs were either disregarded or included in the database. Disregarded HCSs were excluded from the database collection as they did not parallel either the metabolite or parent HCS as outlined in the HCSR. In order to maintain a relatively significant data sample size, some chemicals and metabolites were included in the database even though they did not precisely parallel that which is found the HCSR.

The basis for inclusion or disregard could be justified according to literature and these distinctive HCSs are discussed individually in this section.

3.6.2.1 Aniline

Aniline is known as an intermediate organic base used in the production of dyes, pesticides and pharmaceuticals. Exposure may occur through any of the three routes of exposure and resultant effects include blood disorders where oxygen transportation is impaired (ATSDR, 2002). This HCS was not considered when the overall statistical analysis was applied for Germany (DFG) relative to South Africa. The HCSR mandated by South Africa monitors for the metabolite p-aminophenol found in urine and the induction of methaemoglobin in blood.

Contrary to this, the DFG monitors the chemical unchanged in urine as well as that which is released from an aniline-haemoglobin conjugate following exposure. Approximately 15 – 60% of the total absorbed aniline enters an oxidative process which results in the production of p-aminophenol, which is then excreted in urine. Less than 6% of the dose remains unchanged and is excreted as the primary substance in urine. While it is true that the main metabolic bi-product of exposure to aniline is p-aminophenol, its presence in urine may also be a result of exposure to a few other chemicals including nitrobenzene and pesticides such as Fenuron (Van Bocxlaern *et al.,* 1997). In addition, low levels of p-aminophenol may be detected in urine as a result of paracetamol intake. It is then debatable that the presence of p-aminophenol in urine may not yield the most accurate results as a parameter for evaluating exclusive exposure to aniline, especially in instances of mixed chemical exposure.

Using blood as an assessment matrix, the DFG remain consistent in their preference for evaluating the original chemical. Aniline is extracted from the haemoglobin conjugate and the amount thereof becomes the framework against which the extent of exposure is gauged. Following exposure, aniline is converted to phenylhydroxylamine which is then oxidised to nitrobenzene in erythrocytes. This oxidative reaction alters the iron found in haemoglobin to the trivalent state, in essence inducing methaemoglobin. Concurrently, nitrobenzene can be converted back to phenylhydroxylamine within the erythrocyte due to the presence of diphorases. Therefore, this cycle intrinsically goes back and forth several times (Lewalter, 2012a). The lack of exposure specificity is again emphasised by this reaction; wherein exposure to chemicals such as nitrobenzene may illicit similar results. Merely quantifying the measure of methaemoglobin induced in red blood cells does not indicate exclusive aniline exposure.

Occupational exposure to a wide variety of other chemicals have the capability of inducing methaemoglobin in erythrocytes; such as aromatic amines in which nitrobenzene is included. For such reasons, many other countries/organisations, such as the DFG, regard methaemoglobin evaluation as a collective approach biological indicator for the group of chemicals categorised as methaemoglobin inducers instead of designating it to a single chemical. It is then justified for developed countries/organisations to prefer the extraction of the parent chemical from biological media for the sake of specificity.

Recommendations

In order to point out exclusive exposure to aniline, a revised bio-indicator should be considered to be incorporated into the HCSR that takes into account the abovementioned scientific data by recommending a BEI that will indicate exclusive Aniline exposure in the same manner as developed countries/organisations.

3.6.2.2 Benzene

Benzene is a highly volatile HCS, used as a solvent in chemical and pharmaceutical environments, which main route of exposure is through inhalation. The principal metabolites, which are predominantly found in urine, are conjugates of phenol. As a result, phenol has been extensively used as the primary biomarker for benzene exposure in occupational settings. Due to this, the HCSR has allocated phenol as the parameter for biological monitoring at a BEI of 50 mg/g Creatinine (Cr). ACGIH on the other hand, favour the evaluation of S-phenylmercapturic acid (S-PMA) and tt-Muconic acid in urine. A study by van Sittert *et al*. (1993); which investigated applying urinary S-PMA for exposure to low levels of Benzene, indicated compelling correlations between phenol and S-PMA urine concentrations. It was found that a urinary concentration of phenol at 50 mg/g Cr is equivalent to an average concentration of 383 mg/g cr. For the purpose of comparison in this study, the HCSR BEI for benzene exposure was then substituted from phenol 50 mg/g Cr to S-PMA 383 mg/g Cr.

The use of phenol as a biomarker for benzene is restricted to inhalation exposure above 5 ppm, i.e. occupational exposure limits (OELs) for an 8-hour time-weighted average concentration at or above 5 ppm. Below this concentration, phenol lacks specificity and sensitivity (Ong *et al.,* 1995; Boogaard and van Sittert, 1995). Many countries, such as the United States and Sweden, have prescribed OELs for airborne benzene equal to or less than 1 ppm. As such, more specific and sensitive biomarkers have been proposed. These include S-PMA and, trans- muconic acid.

Recommendations

It is crucial that a holistic approach is taken when revising the HCSR. Amendment of the set benzene OEL at 5 ppm should be considered when looking at the carcinogenic and clastogenic (mutagen which induces breakage and other disruptions of chromosomes, resulting in chromosome deletion or rearrangement) nature of the HCS. Critical toxicity studies are a challenge when considering carcinogenic substances. The DFG, have roughly estimated the carcinogenic risk using a range of technical exposure limit methods. According to these studies, the risk of cancer development increases by 5 to 15-fold with an exposure range of 1 to 10 ppm (Muller and Angerer, 2012). This is attributable to 44 and 152 cases per 1000 exposed individuals, respectively. With the revision of the OEL, new and more sensitive biomarkers for urine analysis should be established.

3.6.2.3 Cadmium

Cadmium is a by-product found in the refining and smelting of zinc and lead. It can also be found in significant quantities in sewage sludge used as fertiliser (ATSDR, 2008). Cadmium was included in the database collection when comparisons between the HCSR and the DFG were done. Cadmium qualifies for individual discussion because the DFG does not designate a traditional biological tolerance (Biologische Arbeitsstof-Referenzwerte- BAT) value, rather the HCS is assigned a biological reference value for workplace substances.

Biological reference values for workplace substances (BAR) are set according to investigations conducted on a reference population of persons within their working age and who are not occupationally exposed to the HCS in question (DFG, 2015). The principal of BAR values seeks to differentiate between work-place and environmental-related exposures. The protocol is that, if during biological monitoring procedures it is found that a HCS and/or its associated metabolites exceed the set BAR value, investigations are initiated to quantify the extent of occupational exposure.

The implication is that the stringency of the DFG is such that, any exposure that exceeds the normal background value which concurrently exists and is found in non-occupationally exposed individuals is considered significant. The chemicals assigned a BAR value are those which presently cannot be assigned a health-based threshold value due to lack of sufficient scientific data; however, exposure assessments are critical due to the toxic effects of that HCS (Göen *et al.,* 2012).

Since Cadmium is classified as a known human carcinogen, such stringency is warranted. Further experimental and epidemiological studies are required to quantify the extent of carcinogenic risk as well as clearly establish all main target sites. Nonetheless, studies done by the United States National Toxicology Program together with the International Agency for Research on Cancer (IARC) indicated that there is indeed an increased risk of cancer development as a result of exposure to cadmium. The target organs being the lungs, liver, kidneys and prostate. These two institutions have thus – based on the results of those studies – concluded that the findings are sufficient to classify cadmium as a known human carcinogen (Lehnert *et al.,* 2016; Waalkes, 2000).

3.6.2.4 N,N-Dimethylformamide (DMF)

This HCS is mainly found in industries that produce surface coatings, fibres and films. It is used as solvent which mainly enters the body through inhalation (EPA, 2000). When making the comparison of DMF and its associated metabolites between the HCSR and DFG; it was found that, like most developed countries/organisations, the HCSR evaluate N-methylformamide (NMF) in urine while the DFG take into consideration the sum of N-Hydroxymethyl-N-methylformamide (NMF-OH) and NMF. It was only in 2006 that the DFG amended the BAT value from monitoring for NMF independently to including NMF-OH and increasing the value from 15 mg/l to 35 mg/l (Miyauchi *et al.,* 2014).

Closely observing the physiological metabolism and kinetics of the said chemical, it is noted that subsequent to absorption, primary metabolism occurs in the liver and the metabolites are rapidly excreted in urine. The main metabolic pathway involves the enzymatic oxidation of methyl moieties, resulting in the production of NMF-OH. Further decomposition of NMF-OH yields N-hydroxymethylformamide and NMF separately. Lastly, further demethylation produces Formamide. These metabolites are excreted in urine, the most significant bi-product being NMF-OH and NMF; with Formamide found only in trace amounts (Long *et al.,* 2001).

In this study, the NMF designated by the HCSR and the NMF plus NMF-OH evaluated by the DFG were considered synonymous; according to the justification offered by the DFG when the parameter was amended to include the sum of the two predominate biomarkers. It is asserted by the DFG that to correctly quantify DMF exposure, the complete sum of NMF and NMF-OH needs to be accounted for. In analytical chemistry, the extraction of the metabolites in excreted urine is done through gas chromatography analysis, applying specific methods such as thermionic sensitive detection and mass spectrometry (Schaller and Drexler, 2012; Will *et al.,* 2016).

As abovementioned, both NMF and NMF-OH are found in urine, however, temperatures above 250°C applied during the extraction process cleave the hydroxymethyl group associated with the NMF-OH and results in the formation of NMF. Thus, the resultant NMF acquired after laboratory analysis is representative of the naturally excreted NMF in urine as well as that which is produced during gas chromatography process from NMF-OH (Schaller and Drexler, 2012; Will *et al.,* 2016).

Recommendations

With the revision of the HCSR, context should be included that will outline such HCSs and metabolites that are chemically altered as a result of analysis and the level at which the BEI level is set should take such alterations into consideration.

3.6.2.5 Ethylbenzene

Ethylbenzene is a naturally occurring aromatic hydrocarbon found in petroleum. In industry, ethylbenzene is used in the production of styrene as well as synthetic rubbers (ATSDR, 2010). In the case of ethylbenzene, it was found that the HCSR make use of mandelic acid excreted in urine as the single indicator of exposure. In contrast, all other developed countries/organisations considered in this study, evaluate the sum of mandelic acid (MA) with phenylglyoxylic acid (PGA).

Biotransformation studies indicate that as much as 90% of the total absorbed dose of ethylbenzene is excreted as MA and PGA; with the remaining 10% consisting of minor metabolites such as 4-ethylphenol (Gagnaire *et al.,* 2007; ATSDR, 2010). Figure 3-4 illustrates a simplified biotransformation of ethylbenzene.

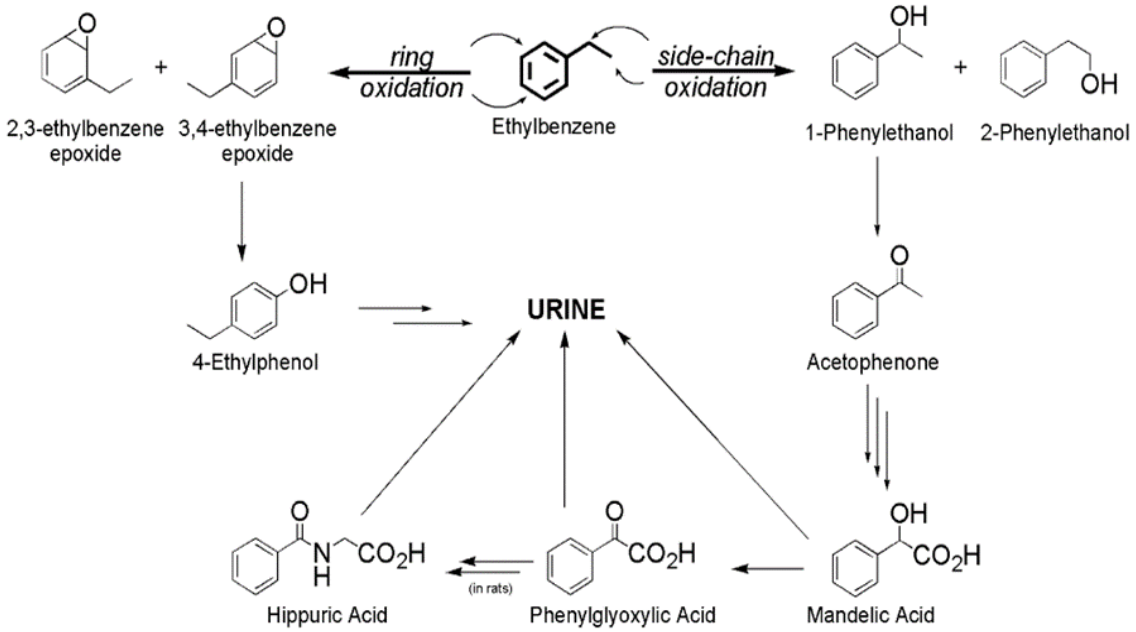

Figure 3-4: Simplified illustration of *ethylbenzene* detoxification (Cossec *et al.,* 2010).

There is discord amongst studies regarding the ratio of MA to PGA in urine. The details provided by a study which was conducted by Knecht *et al.* (2000) was relevant for this discussion. The study, in which 18 human subjects were exposed to 20 ppm and 100 ppm ethylbenzene respectively for a period of 8-hours provided details relevant for this study. The purpose was to evaluate the concentration and half-life of the metabolites found in urine. Ratios of MA/PGA were calculated to be 2.9 and 4.1, respectively.

This ratio was the most applicable since the 100 pm exposure to ethylbenzene for an 8-hour period in the study conducted by Knecht *et al.* (2000) corresponds to the OEL set by the HCSR for ethylbenzene. The 4.1 ratio derived at by Knecht *et al.* (2000) allowed for a conversion calculation for the ethylbenzene BGV found in the HCSR.

The original HCSR value accounts for MA exclusively, however, with the 4.1 ratio applied, a value for MA plus PGA could be obtained. In this manner, ethylbenzene was then considered in the calculations of the overall levels of BGVs between the HCSR and all other developed countries/organisations.

Recommendations

Based on the observation that leading developed countries/organisations in the establishment of BGVs favour the evaluation of MA plus PGA in the quantification of ethylbenzene exposure, efforts were made to gain insight into the reasoning supporting the notion.

Ethylbenzene is considered a major industrial solvent; used in products such as varnishes, printing agents as well as petroleum products including gasoline. Additionally, it is a primary intermediate in the production of styrene and constitutes approximately 20% of commercially available xylene. Exposure to ethylbenzene mainly occurs when making use of xylene and less so in the production of styrene. Hence, mixed exposure to ethylbenzene and xylene is most commonly encountered in the workplace (Korn *et al.,* 1992).

Notwithstanding the vast presence of ethylbenzene containing products, very little research had been conducted to investigate the health impacts of exposure to this HCS at the time the collection of BEIs were incorporated into the HCSR; i.e. 1995. Available scientific evidence was based on research mainly conducted in controlled environments with volunteers (Engstorm *et al.,* 1984). However, the actuality of occupational exposure to ethylbenzene is a great deal different than experimental conditions, taking into consideration mixed exposure to other aromatic solvents.

Further research has indicated that, at combined exposure to other aromatic solvents, the amount of MA formed is decreased due to the interactive inhabitation of the metabolism between ethylbenzene and xylene. The conclusion is that; at low exposures, MA may be used as an indicator of exposure to ethylbenzene. However, when seeking to determine over exposure, MA is not regarded a reliable indicator due to the saturation of the metabolite resulting from combined exposure to xylene. This may offer a possible explanation for developed countries/organisations in designating the sum of MA and PGA as the preferred biomarkers for total ethylbenzene exposure (Jang *et al.,* 2000; Marchand *et al.,* 2015).

Using the above mentioned as a basis for further investigations; in revising the HCSR, the South African Department of Employment and Labour should take into consideration the likelihood that applying MA as the single indicator of exposure to ethylbenzene no longer prevails as an applicable and most accurate approach. More suitable biomarkers should be explored that take into account recent scientific advancements.

3.6.2.6 n-Hexane

n-Hexane is a minor component of crude oil and is used commercially as a specialised solvent in oil extractions. When inhaled in excess, it may cause damage to the nerves of the arms and legs (ATSDR, 1998). It is common practice amongst developed countries/organisations to include context to the BGV set for n-Hexane describing the state of hydrolysis applied to the analytical chemistry processes used in its establishment. The condition will highlight whether the BGV is given with or without hydrolysis, in this manner giving indication to the laboratories on the analytical techniques required to extract the metabolites in the preferred biological matrices. The HCSR have, at present, chosen 2,5-Hexanedione (2,5-HD) in urine as the indicator used for occupational exposure to n-Hexane. No explanation is, however, offered as to the use of hydrolysis, or lack thereof, in extracting the metabolite during analysis. In order to effectively compare the 2,5-HD value designated by the HCSR with those of developed countries/organisations, it was necessary to postulate whether the said metabolite is given with or without hydrolysis. It is assumed that the BEI found in the HCSR correlates to total urinary 2,5-HD; i.e. after acid hydrolysis. This assumption is based on comparisons made with other countries/organisations which designated an equal level of the BEI as that set by South Africa and have distinguished it to relate to 2,5-HD post acid hydrolysis.

A study was conducted by Nolasco *et al.* (2007) which aimed at investigating the influence that acid hydrolysis has on 2,5-HD, the primary metabolite of n-Hexane exposure. It is the most commonly preferred metabolite amongst BGV establishing bodies due its high interconnection with environmental exposure to n-Hexane (Prieto *et al.,* 2003). Nolasco *et al.* (2007) found that the ratio of free to total 2,5-HD ranged from 0.10 to 0.30, with a mean value of 0.19.

In this present study, the mean ratio was used in order to calculate an assumed free 2,5-HD BEI; i.e. without acid hydrolysis. This ratio was also used to calculate either free or total 2,5-HD for developed countries/organisations in the database which did not cater for both free and total metabolite but only designated one value pertaining to only one analytical condition.

Recommendation

In 2003 the ACGIH advocated that 2,5-HD yields more accurate results of exposure to n-Hexane when determined without acid hydrolysis due to the fact that other minor n-Hexane metabolites such 5-hydroxy-2-hexanone and 4,5-dihydroxy-2-hexanone are transformed to 2,5-HD during hydrolysis (Manini *et al.,* 1999).

This demonstrates the possibility of an enormous margin of error in the case where the BEI limit does not give context to the hydrolysis applied. Laboratories responsible for analysing urine samples derived for the purpose of biologically monitoring n-Hexane are at liberty of applying their own discretion. Furthermore, the interpretation of those results with reference to a vague standard may lead to underestimating or overestimating the extent of occupational exposure to the HCS.

Based on the above, it may be concluded that a BEI that refers to free 2,5-HD without the urine being subjected to acid hydrolysis will offer a true reflection of worker exposure to n-Hexane. The ratio deduced by Nolasco *et al.* (2007) also indicates a significant difference between free and total 2,5-HD; which emphasises the need to revise the current HCSR to provide context to the metabolite regarding pre-treatment methods.

3.6.2.7 Methyl chloroform

Methyl chloroform, also referred to as 1,1,1-Trichloroethane, is an industrial solvent used for precise metal cleaning in mechanical assembly environments and less so in dry cleaning (McCulloch and Midgley, 2001). This HCS was disregarded in the sample database for the comparison between the HCSR and the DFG BAT value collection. The HCSR monitor methyl chloroform exposure through the following metabolites and matrices: methyl chloroform in end-exhaled air, trichloroacetic acid in urine, total trichloroethanol in urine and blood. The DFG on the other hand, examine the parent HCS in blood.

Only about 2% of the total inhaled methyl chloroform is metabolised in the human body, the remainder is exhaled again in the original state. The metabolised 2% is broken down into trichloroethanol and trichloroacetic acid and is excreted in urine (Figure 3-5).

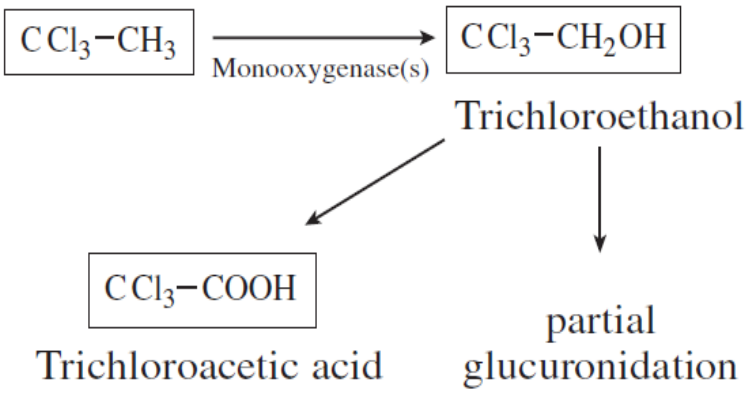

Figure 3-5: Simplified biotransformation of *methyl chloroform* (Bolt, 2012).

The DFG have ruled out the application of trichloroacetic acid as a biological indicator. Added to the low rate of methyl chloroform metabolism, trichloroacetic acid has an extensive biological half-life; making it unsuitable for effectively measuring occupational exposure to methyl chloroform. Trichloroethanol in urine and in blood correlates better to environmental exposure, the blood level concentration of the un-metabolised parent HCS itself is, however, the most efficient biomarker for exposure.

It is comprehensible, for the DFG especially, to prefer the extraction of the un-metabolised methyl chloroform from the blood as the concept application of the BAT values implicates that BAT values are directly linked to the expected health effects and are set as limits which may never be exceeded during any period of occupation. Critical toxicity studies undertaken by the DFG indicate that the ill health effects are caused by the parent chemical itself rather than by any resulting metabolites. The extraction of the un-metabolised HCS itself is hence preferred in the biomonitoring for BAT value application purposes (Bolt, 2012). In a country such as South Africa where BGVs are established for the primary purpose of detecting the body burden experienced as a result of inhalation exposure to the set OEL, the determination of un-metabolised methyl chloroform in exhaled air and trichloroethanol in urine will, however, serve as a practical and non-invasive approach.

3.6.2.8 Nitrobenzene

Nitrobenzene is mainly used as an intermediate product in the production of aniline. It is recognisable as a yellow oily substance with a distinct odour, similar to that of almonds. Intoxication occurs mainly through inhalation of the substance (ATSDR, 1999). It is a known methaemoglobin inducer and was disregarded in the data base collection when DFG and the HCSR were compared. The HCSR evaluate the level of the metabolite p-nitrophenol excreted in urine as well as the percentage induction of methaemoglobin.

When selecting indicators, the DFG acknowledge that the body burden resulting from exposure to nitrobenzene may be measured using a variety of bio-indicators, such as: nitrobenzene itself, aniline, aminophenol and p-nitrophenol either in whole blood or urine specimens. As it is a methaemoglobin inducer, the percentage increase in methaemoglobin formation may be used as measure to determine intoxication. When evaluating long term occupational exposure or nitrobenzene exposure according to the set MAK value of 1 ppm (which may be classified as low-level exposure), methaemoglobin formation does, however, not serve as a reliable bio-indicator. Methaemoglobin is quickly reversible in these circumstances; the time of sampling therefore greatly affects the results obtained. To alleviate underestimating the level resulting from delayed exposure, the DFG have settled on the sampling of the aniline which is released from the aniline-haemoglobin conjugate formed within the erythrocyte when nitrosobenzene interacts with haemoglobin, see Figure 3-6. This makes for a better sampling alternative as the aniline-haemoglobin adduct remains consistent regardless of sampling time (Lewalter, 2012b).

As illustrated, aniline is an essential intermediate in the metabolism of nitrobenzene, the account offered for aniline sampling measures mentioned in the beginning of this section applies herein as well.

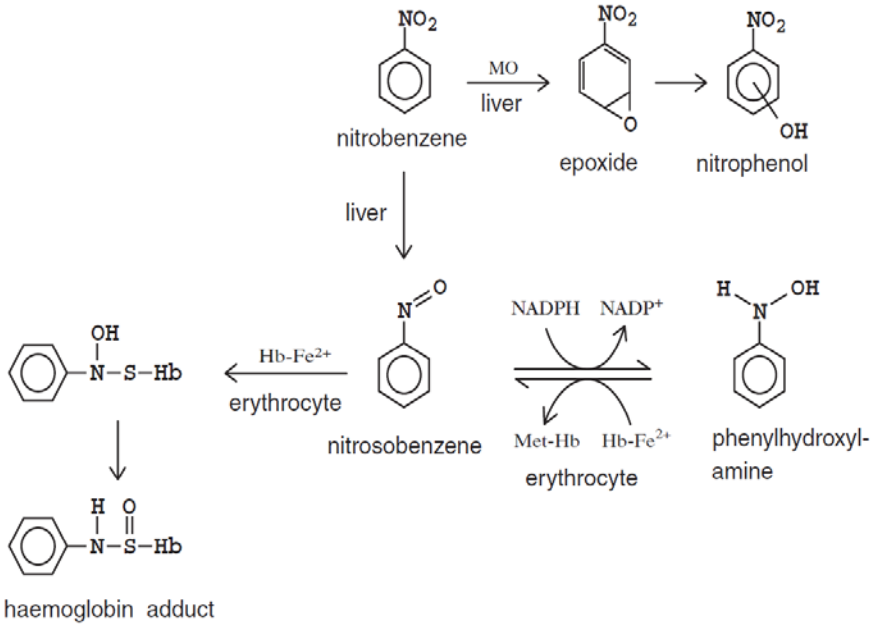

Figure 3-6: Simplified *nitrobenzene* metabolism in the liver as well as the red blood cells. Haemoglobin adduct = *aniline*-haemoglobin conjugate (Lewalter, 2012b).

3.7 Conclusion

From the results section, it is evident that HCSs covered within the HCSR are also included in the collection of BGVs for developed countries/organisations considered in this study. Three of the developed countries/organisations were found to have BGVs designated for all 30 HCSs covered in the HCSR; one showing a 97% overlap and only two of the considered countries/organisations showed a <75% overlap with the South African BEIs. However, over and above the HCSs which overlap with those found in the HCSR, the developed countries/organisations designate BGVs for a greater range of HCSs as compared to the South African legislation.

It is also evident from the GMs results that the developed countries/organisations have set their BGVs at far more stringent levels in comparison to the BEIs established by the South African legislations. This finding was also consistent when the interval method was applied, which indicated that a significant number of the BEIs found in the HSCR were above the 105th interval.

It may be concluded, based on the results of this study, that significant differences exist between the BEIs found in the HCSR and BGVs established by developed countries/organisations. These disparities are notable in both the levels at which the BEIs are set as well as the overall HCSs coverage. Referring to section 3.2 and the overall results, it may be said that the BEIs previously established by the South African legislation were not based on scientifically up to date data and interpretation to work place exposure of HCSs. The recent review of these BEIs is necessary.

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CHAPTER 4: CONCLUSION AND RECOMMENDATIONS

4.1 Conclusion

The aim of this study was to comparatively analyse South African BEIs with those established by developed countries/organisations to determine 1) the frequency of coverage of each BEI and 2) the overall level of the set concentrations of respective BEIs. This is a complimentary study to the studies conducted by Maponya (2016), Viljoen (2014) and Viljoen (2012); which focused on comparing South African occupational exposure limits (OELs) with those of either other developing countries or developed/organisations. In this study, only developed countries/organisations were considered on the basis that literature indicates that most developing countries/organisation face challenges with their occupational health and safety similar to those of South Africa (Nuwayhid, 2004; Wang *et al.,* 2011; Dubarev *et al.,* 2013). The above-mentioned studies which explored the relevance of the current South African OELs raised interest into the investigation of BEIs; with the understanding that BEIs are directly related to the set levels of corresponding OELs of the respective hazardous chemical substance (HCS) in question.

At the onset of this study, it was hypothesised that South African BEIs are set at levels which are significantly less stringent than those of developed countries/organisations i.e. <1 Geometric Means (GMs) ratio and/or <95 % interval of the compared HCSs level (hypothesis 1). Having applied the GMs method, the calculated ratios of the six developed countries/organisations considered in the study relative to the South African BEIs were all found to be below 1, indicating the overall higher levels of the South African BEIs.

In the interval method analysis, results indicated that a considerable portion of the BEIs found in the Hazardous Chemical Substances Regulations (HCSR) of South Africa are set at levels which are significantly higher than the comparing guidance values established by the respective developing countries/organisations. The hypothesis that states that the overall level at which South African BEIs is set, is less stringent than those of developed countries/organisations, is therefore accepted.

The second hypothesis, which states that there is less than 75% overlap between South African BEIs and those of developed countries, in other words, developed countries/organisations establish BEIs for a greater variety of substances, was tested by comparing the HCS coverage of the six developed countries/organisations relative to those found in the HCSR of South Africa.

The HCSs that appeared only in the HCSR, the HCSs that overlapped between the HCSR and the developed country/organisation in question as well as the HCSs that appeared only in the developed country/organisation were taken into consideration. It was found that four of the six developed countries indicate an >75% coverage overlap with the HCSR and only two of the developed countries/organisations have a <75% overlap. However, over and above the overlapping HCSs covered, developed countries/organisation have included more HCSs which are not found in the HCSR.

Therefore, the opening of hypothesis 2 is rejected; in that majority of the of the six developed countries/organisation show an overlap of above 75% while the latter part of the hypothesis is partially accepted as results show that developed countries/organisations indeed establish BEIs for a greater variety of substances than the HCSR.

Considering the results obtained from this study, particularly reflecting on discussions from the identical chemicals and their metabolites as well as the individual chemical discussion, it can be concluded that the current South African BEIs are not suitable and to some extent not scientifically up to date to serve as the reference guideline for industry to apply in protecting workers from developing occupationally related illnesses and diseases.

4.2 General Recommendations

Together with OELs, BEIs can be effective tools that will assist industry in preventing excessive exposure to HCSs that could potentially result in ill-health. Occupational hygiene as a profession seeks to anticipate, recognise, evaluate and control health hazards with the fundamental aim of protecting the health of workers. One of the ways in which BEIs may be considered to be reliable in supporting the prevention of work induced illnesses and diseases, is if they are recognised to be based on the most recent scientific data.

With the announcement by the South African Department of Employment and Labour that the HCSR is in revision, the following recommendations can be made as a contribution:

Recommendation 1

The South African Department of Employment and Labour should convene a functional Hazardous Chemicals Substances Regulations committee that is charged with maintaining the HCSR by incorporating scientifically sound occupational exposure limits (OELs) as well as BEIs. This committee should be responsible for implementing a strategy which ensures that all set levels of OELs and BEIs are allocated based on professional and knowledgeable judgement and are revised periodically such that they are in line with current scientific developments.

Recommendation 2

Various countries/organisations such as The American Conference of Governmental Industrial Hygienists (ACGIH) and Deutsche Forschungsgemeinschaft (DFG) invested considerable efforts in developing biological guidance values. It is therefore not obligatory for the Department of Employment and Labour to undergo similar processes but rather that BEIs for the HCSR are adopted from either one of these countries/organisations; taking care to note the feasibility of incorporating the said guidance values as well as context of application in relation to the industrial needs of the country as compared to the developed country/organisation in question. Furthermore, the HCSR BEI values should be accompanied by supporting documentation that provides guidance regarding the adaptation process as well as the interpretation of the values.

Recommendation 3

Following the latter part of recommendation 2, the supporting documentation that will accompany the HCSR BEI should include a list of all possible methaemoglobin inducers which are relevant to the South African industrial climate. Currently, a percentage of methaemoglobin in blood haemoglobin levels is present in the HSCR, however, it is re-iterated for substances such as Carbon Monoxide and Nitrobenzene as an individual matrix of measurement. Having a collective list of all possible methaemoglobin inducers will alleviate such repetition.

Recommendation 4

In the revision of the HCSR, precedent should be taken from the DFG regarding carcinogenic HCSs. Biological guidance values are not set for HCSs known to cause cancer or increase the risk of cancer development in humans. Carcinogens classified in categories 1, 2, 3 A and 3B should not be allocated BEIs as the implication is that the set BEI is indicative of a safe exposure level, whereas in reality it is not possible to allocate safe work levels to such HCSs as any amount of exposure inherently increases the risk of cancer development. However, the newly published regulations should include a disclaimer that the established values merely indicate the relationship between the workplace air concentration of carcinogenic substances and resulting body burden and that values are in no way meant to be applied in the same manner as BEIs.

While this study was in progress, the South African Department of Employment and Labour released a draft regulation for hazardous chemical agents, which is proposed to serve as a replacement for the current HCSR. A review of the newly proposed regulations indicates that a few additions have been made to the currently legislated BEIs, one of the most notable being the addition of CAS numbers for better identification of the HCSs. The newly proposed BEI list also includes a greater variety of HCSs coverage in comparison to the currently legislated list of BEIs.

Although no disclaimer is included in the proposed regulations, comparison with the ACGIH BEIs list of 2018 make it possible to hypothesise that the BEIs proposed by the South African Department of Employment and Labour have been adopted from the said organisation, as per recommendation 2. While a total of 22 new HCSs have been added to the proposed regulations, which have been adopted from the ACGIH, a few considerations should be taken into account.

The ACGIH is a private institution, having no regulatory authority. It is therefore comprehensible that the OELs, referred to as Threshold Limit Values (TLVs), together with the associated BEIs established by this institute are presented merely as recommendations for good practice (Morgan, 1997). In the TLV/BEI introduction section, the ACGIH outlines that the TLVs as well as the BEIs established consider health factors only and do not take into account the technical and economic feasibility. Therefore, the ACGIH encourages that regulatory bodies, such as the Department of Employment and Labour, should not come to the conclusion that it is practicable for industries to meet these as regulated requirements without conducting epidemiological studies. The ACGIH further outlines that although regulatory bodies looking to establish OELs as well as TLVs as legal standards should beforehand conduct analytical studies on the full spectrum of interrelated factors that affect industries within the intended enforcement landscape, these industries should consider the ACGIH's TLVs and BEIs as accurate scientific ground work (ACGIH, 2018).

Adopting standards from organisations such as the ACGIH is certainly a progressive change for the health and safety system in South Africa, as it is a known fact that setting BEIs as well as OELs is indeed a cumbersome and costly effort. Thus, leveraging off the ACGIH, an organisation renowned to invest vast amounts of resources in research is a commendable accomplishment for the Department of Employment and Labour. Considerations should, however, be made on the scope of application and the economic implications of legislating equivalent BEIs and OELs as those established by developed organisation/countries and the feasibility of industries meeting such stringent levels in a developing country such as South Africa. It is recommended that the Department of Employment and Labour conduct demographic studies on selected industries to fully comprehend the implications of the proposed regulations prior to regulating them.

4.3 Limitations

In retrospect, some limitations were encountered that are worth recognising in the appraisal of this study.

- Similar to prior studies that compared HCSs from the HCSR with those of developed countries/organisations, the lack of CAS numbers in the HCSR made it a challenge to match the correct HCSs in order to make accurate comparisons.

- In chapter 3, the discussion is divided into 2 subsections; one for identical chemicals with their metabolites and another for individual chemical substances. This was done due to the fact that a significant limitation was encountered. In the analyses of the data base, it was found that in some cases metabolites differed between the HCSR and the different developed countries/organisations. Since comparison could not be made on HCSR or metabolites that are indistinguishable, the sample size was affected. However; it should also be noted that some HCSs and metabolites were included in the analyses based on a literature framework.

- Biological guidance values from some developed countries/organisations were disregarded in this study due to a language barrier. The content was not available in English, which made it challenging to compare.

4.4 Future studies

This study, together with complimentary studies that investigated sections of the HCSR such as the OELs, short-term exposure limits (STELs) and ceiling exposure limits are all in consensus that the exposure limits and the index values are inadequate to assist industry in protecting workers from developing ill health as a result of over exposure to HCSs. The necessity to review the current HCSR is indisputable (Viljoen, 2012; Viljoen 2014; Maponya, 2012). In the review, especially for the BEIs, the following study should be considered:

An in-depth review can be carried out for each HCSs found in the collection of BEIs with the aim of obtaining the most recently available scientific data to understand why certain metabolites and biological matrices are ruled out or included over time. Such research may serve as supporting documentation for the HCSR that will guide industry with the intended application of the said exposure indices.

4.5 References

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ANNEXURE A – ETHICAL APPROVAL LETTER

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Mr CJ van der Merwe
Occupational hygiene
OHHRI

21 August 2019

Dear Mr van der Merwe

PROOF THAT THE FOLLOWING STUDY DOES NOT REQUIRE ETHICAL APPROVAL

Study title: Comparative analysis of South African BEIs with those of developed countries

Study leader: Mr CJ van der Merwe

Student: KR Sekhula - 26754568

Following review of a notification received from Higher Degrees Administration by the North-West University Health Research Ethics Committee (NWU-HREC), it was determined that no ethical approval was required as this study does not:

- Involve any human participants or their data/information that is not publicly available
- Involve any human samples
- Involve any animals
- Involve any animal samples
- Have any possible environmental impact

The study is an analysis of publicly available data.

Following review of this notification, the NWU-HREC is in agreement that the aforementioned study does not require ethical approval.

Yours sincerely

Digitally signed by Wayne Towers
Date: 2019.08.21 16:46:24 +02'00'

Prof Wayne Towers

NWU-HREC Chairperson

Digitally signed by Prof Minrie Greeff
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11 April 2019

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