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NEUROPSYCHOLOGICAL TOXICOLOGY: A THEORETICAL OVERVIEW OF NEUROPSYCHOLOGICAL ASSESSMENT

by

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Summary

Neuropsychological toxicology investigates the impact of chemical exposure on the structure and functioning of the nervous system and by implication the neuropsychological performance of affected individuals. As in mainstream neuropsychology, brain damage is assessed by measuring changes in the cognitive, psychomotor and emotional domains using diagnostic neuropsychological tests. The field of neuropsychological toxicology has undergone significant growth in the last 20 years, amongst growing concerns over people's potential everyday exposure to approximately 70 000 chemicals. Growing awareness of the possible dangers associated with neurotoxic exposure has lead to the increased regulation of exposure levels especially in industrial settings. This in turn has lead to a gradual shift in neuropsychological toxicology from the assessment of severe neurotoxic damage to the evaluation of subclinical signs, which may develop into disabling damage over many years of exposure. The assessment of these subclinical signs has proven to be tricky as they cannot always be measured through diagnostic tests and may be mimicked or hidden by numerous confounding variables.

The need for the effective assessment of these subclinical signs has created a need for more sensitive tests and improved research methodology. This paper uses evidence from cellular pathology and anatomical pathology (dynamic brain localisation theory) as a guide for the selection of neuropsychological tests. The purpose of the paper is to review the neuropsychological outcomes of toxic exposure, with an emphasis on test sensitivity (screening) and specificity (diagnostic) to carbon disulphide (solvent), manganese (metal) and organophosphate (pesticide) exposure.

Findings from this review point to the possible advantages of the continued use of standardised neuropsychological batteries that enable the assessment of global functions in addition to tests that measure deficits associated with the toxicodynamics of the neurotoxin under investigation. Methodological recommendations include the use of simultaneous cross-sectional and longitudinal designs to control for numerous confounding variables and correlation designs to determine dose-response relationships. Future studies need to address the sensitivity and specificity criteria of various neuropsychological measures utilising the principle of neurotoxicodynamics.

Key Words

Behavioural toxicology
Dynamic brain localisation theory
Carbon disulphide
Manganese
Methodology
Neurobehavioural toxicology
Neuropsychological toxicology
Neurotoxicodynamics
Neurotoxicology
Organophosphate
Psychological toxicology
Subclinical assessment
Theoretical review

Table of contents

Tables

Figures

CHAPTER 1: INTRODUCTION AND BACKGROUND

"Even small degrees of central nervous system dysfunction are not for moral, ethical, and health reasons to be tolerated. The loss of five points in I.Q., fatigability, irritability, or lethargy, or slowed reaction time are significant losses. These are areas of human functioning that make life enjoyable and worth living"
(Robins, Cullen & Welch, cited in Hartman, 1988 p.9)

1.1 Background to the Study

The global outcry over the potential damage caused by exposure to chemicals emphasises the need to evaluate the safety of the 70 000 chemicals to which we are all exposed in our daily lives (Rapp, 1996). Currently there are 85 000 industrial chemicals manufactured in the United States and 2000 to 3000 new chemicals are registered with the United States Environmental Protection Agency every year. Sixty-seven percent of these chemicals have not been tested for neurotoxicity and only seven percent have been tested for developmental neurotoxicity (Claudio, Kwa, Russell & Wallinga, 2000; Landrigan, 2001).

South Africans are as vulnerable, if not even more so, to exposure to neurotoxic chemicals than individuals living in First World countries for a number of reasons. Firstly, toxins that have been banned in other countries are still used in South Africa. One such example is DDT (Dichlorodiphenyltrichloroethane), a known neurotoxin that is widely used in South Africa to control malaria-spreading Anopheles mosquitoes. Another is Triflorine, a toxic chemical found in pesticides used in South Africa (Sukharaj, 2003). Secondly, even when toxic chemicals have been banned in South Africa, the bans might not be properly enforced. Thirdly, people who have not been educated about their dangers may use toxic chemicals, and this may result in accidental contamination. In a study conducted by Heeren, Tyler and Mandeya (2003) it was found that, due to their lack of knowledge concerning the correct safety precautions of pesticide use, rural women were exposed to dangerous toxins when they carried water in containers, previously used for pesticides. Furthermore, due to our strengthening economy, South Africa is one of the largest consumers of pesticides on the African continent (Heeren et al., 2003). The extensive mining industry is also a source of neurotoxic contamination (Stewart, 2002).

In South Africa the Department of Labour as well as the Department of Minerals and Energy enforce regulations regarding neurotoxic exposure. Acts such as the Occupational Health and Safety Act 35 of 1993 provide regulatory limits for exposure to these toxins. However, responsibility for ensuring the safety of manufactured chemicals rests with the manufacturer (Occupational Health and Safety Act 35 of 1993). In addition, due to South Africa's developing

nation status, the regulatory limits are often not as stringent as they are in more developed countries. New developments are in place to address this.

Toxic substances in the environment can have a profound impact on the physical and psychological health of an individual. Concerns about this impact have lead to the proliferation of research in the field of neuropsychological toxicology. Neuropsychological toxicology can be defined as a branch of neuropsychology that investigates the impact of brain damage, caused by chemical exposure, on the behaviour of affected individuals (Hartman, 1995). As in mainstream neuropsychology, brain damage is assessed by measuring changes in intellectual, emotional and control components in the behaviour of the affected individual (Lezak, Howieson & Loring, 2004). Changes in these components of behaviour are assessed with diagnostic neuropsychological tests, as well as tests that have specifically been adapted for the use of assessing brain lesions caused by toxic exposure.

In the 1980s institutions such as the World Health Organisation published standard neuropsychological toxicology batteries for the assessment of neurotoxic brain injury. These batteries are used to assess damage resulting from exposure to various different neurotoxins. Neuropsychological toxicology assessments are, however, not exclusively conducted with these standard batteries and numerous authors have compiled their own assessment batteries. However, an underpinning theory guiding the selection of these tests is lacking.

As our knowledge of neurotoxins increases and stricter regulations are introduced, the focus of neuropsychological toxicology investigations is moving away from the assessment of extensive damage resulting from high level exposure, to the assessment of subclinical signs, which may develop into disabling deficits over many years of exposure (Aaserud et al., 1990). The assessment of these subclinical changes, which may often go undetected, has lead to the need for the identification and development of more sensitive assessment methods. The need for more sensitive tests has been raised by a number of authors (Fiedler, 1996; Rohlman, Gimenes, Eckerman, Kang, Faarahat, & Anger, 2003; Stephens & Barker, 1998; Spurgeon, 1996)

1.2 Problem Statement

Neuropsychological toxicology assessments appear to be in a stage of transition. The rapid development of standard neuropsychological toxicology batteries, such as those published by the World Health Organisation, has answered the urgent need for the assessment of neurotoxic exposure in the last 20 years (Spurgeon, 1996). These assessments have in part contributed to our understanding of neurotoxic exposure and have indirectly contributed to the enforcement of lower exposure limits. This in turn has introduced a new era of neuropsychological toxicology, where assessments are not primarily focused on grievous

damage resulting from high-level neurotoxic exposure, but rather on subclinical signs resulting from low-level exposure. However, low-level exposure may be no less serious as the accumulation of effects over many years may result in the development of clinically significant and debilitating damage (Rosenberg, 1995).

The new role of neuropsychological toxicology is to find effective means of assessing this subtle and subclinical damage to assist in the development of more refined regulatory levels and prevent damage to exposed individuals. The assessment of subclinical damage poses another challenge in the form of assessment methodology. Subtle changes brought on by neurotoxic damage may easily be missed or mimicked by confounding variables (Stephens & Barker, 1998). This contributes to the often inconclusive nature of these findings.

There are therefore two problems addressed here: firstly, the selection of neuropsychological tests that are sensitive to subclinical neurotoxic damage; and secondly, methodological problems encountered in the evaluation of this damage.

1.3 The Aim of the Study

This study reviews current trends in the neuropsychological assessment of neurotoxic brain damage with regard to methodology, type of exposure assessed, test selection and rationale for test selection. In addition, the outcomes of specific neuropsychological tests predicted by dynamic brain localisation theory to be sensitive to deficits caused by the toxic mechanism (toxicodynamics) of three neurotoxtins are examined. This process addresses the two core aims of this review. Firstly, the use of dynamic brain localisation theory in guiding the selection of tests sensitive to subclinical neurotoxic damage is investigated. Secondly, a methodological best practice for the assessment of subclinical signs in this field is explored. These investigations are made possible by recent developments in the fields of neurotoxicology and neuropsychology. These developments are discussed below.

1.3.1 Advances in Neurotoxicology

Brain damage caused by exposure to neurotoxic chemicals is either diffuse (affects the whole brain) or bilateral (same damage to specific areas in both sides of the brain) (Rosenberg, 1995). To determine which brain structures will be affected by exposure to a specific neurotoxin, it is important to consider cell functioning and cytoarchitecture of the brain, as neurotoxins impact on a cellular level. The smallest unit of functioning in the brain is the synaptic junction between two neurons. Neurotoxic substances cross over the blood-brain barrier and influence neuron function at these sites. Synaptic junctions are the origin of all behavioural processes: intellect, emotionality and control are created by means of changes in

membrane receptors and neurotransmitters at synaptic junctions (Bray, Lewis & Walter, 1998).

These behavioural components may be altered in individuals exposed to neurotoxins, as these neurotoxins affect nerve conductivity and transmission at synaptic junctions (Bray et al., 1998). Neurotoxins can affect nerve conduction at synapses, may bind to receptors, competitively inhibit neurotransmitters, depolarise endplates in the peripheral nervous system, inhibit enzymes or destroy nervous tissue through enzymatic action, and may block or facilitate ion flow (Chubb & Geffen, 1979). Neurotoxins may also affect mental functioning by altering metabolic or circulatory processes (Jacobs, 1980). Such alteration will result in diffused or localised damage depending on the type of toxin (Rosenberg, 1995). Toxins that result in diffuse brain damage may cause changes in many behavioural outcomes, as many parts of the brain are affected. Exposure to these types of toxins may therefore best be assessed with global test batteries.

The majority of neurotoxins, however, affect specific brain areas more than others. These toxins selectively target cells with a specific morphology. Cell morphology is determined by cell functioning. Toxins that result in bilateral brain damage have toxic mechanisms that interfere with the proper functioning of these cells. As a result, certain toxic syndromes are associated with exposure to certain toxins.

Three neurotoxins are briefly discussed to illustrate the exposure-outcome specificity. These three neurotoxins represent one neurotoxin from each group (solvents, metals, and pesticides) in which neurotoxins are discussed in the literature. The three discussed here are carbon disulphide, manganese and organophosphate.

Carbon disulphide (a solvent) is a neurotoxin widely used in the rubber and rayon industries. Exposure to carbon disulphide leads to neuronal degeneration throughout the cerebral hemispheres. Maximum degeneration occurs in the frontal lobes resulting in psychiatric symptoms such as acute bipolar and psychotic symptoms, delirium, personality changes, impaired cognition and associated parkinsonism (Rosenberg, 1995). Carbon disulphide is also one of the few organic solvents clearly shown to cause damage through chronic exposure (Hartman, 1995; Rosenberg, 1995).

Occupational exposure to manganese occurs in mineworkers, welders and workers in dry cell battery plants (Hartman, 1995). Even though manganese is an essential trace element, occupational exposure to it is associated with neurotoxic effects. Manganese accumulates in the basal ganglia, and is associated with symptoms resembling those found in Parkinson's disease (Kaplan & Sadock, 1998; Lucchini, Albini, Placidi & Alessio, 2000)

Organophosphate (originally used as a nerve gas in World War Two, but which is now used as a pesticide) selectively targets acetylcholine cells. Organophosphate disrupts the enzyme cholinesterase, causing the accumulation of acetylcholine and a parasympathetic overload. This results in neuropsychological signs such as impaired concentration, reduced information processing and psychomotor speed, memory deficits, depression, anxiety and schizophrenia (Davis & Richardson, 1980; Eyer, 1995; Hartman, 1995).

It can be concluded that neurotoxins which cause bilateral damage affect specific areas of the brain: carbon disulphide affects the frontal areas (Rosenberg, 1995); manganese impacts the basal ganglia (Kaplan & Sadock, 1998; Lucchini et al., 2000) and organophosphate targets the acetylcholine system (Davis & Richardson, 1980; Hartman, 1995). These in turn result in specific neuropsychological effects.

1.3.2 Advances in Neuropsychology

The fundamental difference between psychometric assessment and neuropsychological assessment is “the conceptual framework of reference that takes brain functioning as its point of departure” (Lezak et al., 2004 p.16).

Dynamic brain localisation theory aims to explain the relationship between brain and behaviour. Alexander Luria is well known for supporting the dynamic localisation of functioning model. This model describes human mental activity as a complex functional system consisting of a combination of brain structures, each of which makes its own contribution to the functional system (Hartman, 1995). Behaviour is therefore the result of an innumerable amount of neurophysiological and biochemical reactions. These reactions may involve many neural networks in the brain (Lezak et al., 2004). Despite the overall integration of brain activity in the creation of behaviour, lesions involving the same anatomic structures can disrupt the same discrete psychological activities in most humans. The disruption of discrete psychological activities, which are integral to more complex behaviours, may result in neurobehavioral syndromes. Because certain lesions are so regularly associated with certain neurobehavioral syndromes, it is possible to predict the location of some lesions from the neurobehavioral syndrome presented (Lezak et al., 2004).

1.3.3 Interrelatedness of Concepts

Neurotoxicology has enabled the identification of specific brain areas damaged by exposure to certain toxins. Dynamic brain localisation theory indicates which behavioural outcomes will be affected by damage to these areas. Therefore, if the brain area affected by a specific toxin is known, this gives an indication of what behavioural outcomes may be affected by exposure to this toxin. This is illustrated in FIGURE 1-1.

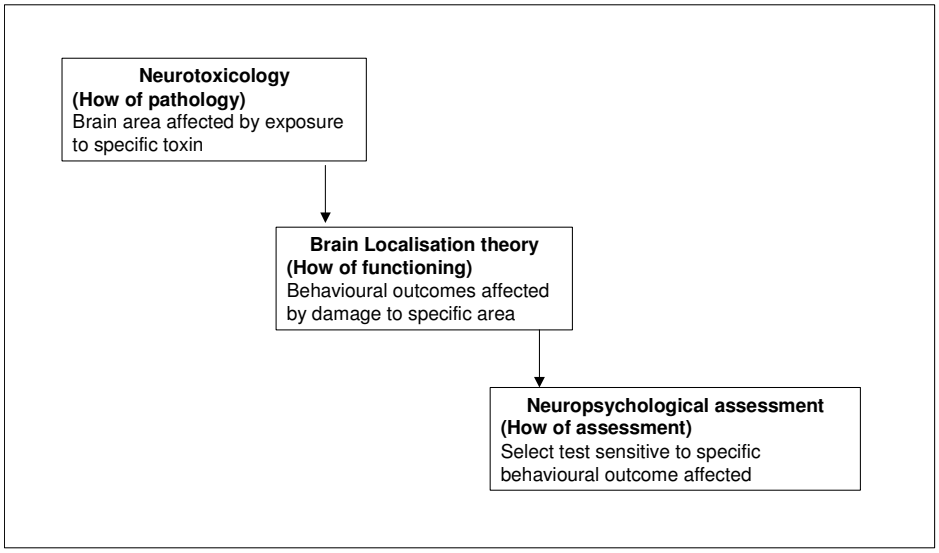

Figure 1-1: A conceptual model illustrating the interdisciplinary theoretical approach used in this dissertation

Neurotoxicology may therefore provide neuropsychologists with useful information regarding the mechanisms and location of damage caused by some neurotoxins. Neuropsychologists' knowledge of dynamic brain localisation theory may give them an indication of which outcomes will be affected by exposure to these toxins and should therefore be tested.

This study reviews neuropsychological studies to determine whether the rationale of brain theory is used to assist in guiding test selection. This study focuses on certain neurotoxins that cause bilateral damage. These are carbon disulphide (a solvent), manganese (a metal), and organophosphate (a pesticide). The decision to select specific neurotoxins and not to discuss all neurotoxins in a particular group is to facilitate the investigation of the relationship between chemical mechanisms and neuropsychological test sensitivity. Neurotoxins with the same chemical mechanisms were selected for these investigations. This review may contribute to understanding issues of criterion validity (the ability of the assessment to distinguish between exposed and non-exposed groups) of the neuropsychological tests used in assessing the impact of exposure to these toxins.

1.4 Format and Presentation of the Study

Chapter One explains the rationale behind this study, gives a brief overview of the relevant concepts as well as the approach followed in this research, and provides an overview of the contents of each chapter.

Chapter Two, entitled "A historical overview: The joining of neuropsychology and neurotoxicology and the birth of neuropsychological toxicology", encompasses an extensive review of the fields of neurotoxicology, neuropsychology and neuropsychological toxicology. Both general and specific information from each of these fields is presented. General, contextual and historical information is given as a means to gain perspective about where we have come from in the hope that this will provide insight into where we should be going. Specific information presented from each field provides the essential building blocks needed to unravel the components of the studies reviewed. This is done so as to obtain meaning from their findings. The ultimate objective of the literature review is to learn from other scholars in the field, as well as to gain an understanding of theories and methods used.

Chapter Three is the chapter that answers the question "how?" This chapter explains the methodology chosen and delineates the process followed in this dissertation.

Chapter Four entails an in-depth review of the neuropsychological studies published on carbon disulphide exposure. In this chapter, current trends in the methodology of carbon disulphide damage assessment are investigated. This contributes to the development of best practice framework for these evaluations. Special focus is given to the selection of neuropsychological tests and the rationale used by authors for the selection of these tests. In addition, the outcomes of frontal lobe tests is investigated as carbon disulphide is reported to cause maximum damage to this area (Rosenberg, 1995). The impact of the methodological issues, and the exposure levels assessed, are considered in the interpretation of the outcomes of these studies.

Chapter Five follows the same structure as chapter four. Current trends in the neuropsychological toxicology assessment of manganese is reviewed. The discussion covers the use of neuropsychological tests for these evaluations and the outcomes of these tests, as they relate to the pathology incurred by manganese exposure. Special focus is given to psychomotor deficits associated with basal ganglia pathology (Kaplan & Sadock, 1998, Lucchini et al., 2000)

Chapter six is structured identically to the previous two chapters, and explores issues relating to organophosphate toxicity and its assessment. Methodological issues are reviewed to provide an indication of current trends in this kind of assessment, and to contribute to the development of a best practice framework for such evaluations. In addition, these methodological issues are considered in the evaluation of the outcomes of these studies. Special focus is given to outcomes relating to acetylcholine-releasing neuron pathology induced by organophosphate exposure (Davis & Richardson, 1980; Hartman, 1995).

Chapter Seven presents a summary of the main thesis, as well as the conclusions and recommendations. Findings and arguments explored in previous chapters are summarised without the cumbersome but necessary details included in the review. In an attempt to contribute to the future direction of this vital field, these findings and recommendations are presented in consideration of the historical path of neuropsychological toxicology.

CHAPTER 2: A HISTORICAL OVERVIEW: THE JOINING OF NEUROPSYCHOLOGY AND NEUROTOXICOLOGY AND THE BIRTH OF NEUROPSYCHOLOGICAL TOXICOLOGY

2.1 Introduction

This dissertation is a compilation of interdisciplinary developments: chemical, physiological, anatomical, and neuropsychological perspectives, together with research methodology, are intertwined in unravelling studies and building meaning from these. Therefore, the purpose of this literature chapter is manifold. These may be outlined from the general to the more specific.

General and historical information regarding the main contributing disciplines provides a context for the reviews and recommendations. We start with the general where neurotoxicology, and neuropsychology, are introduced as the parent disciplines of neuropsychological toxicology.

Embedded in the general information are the specific contributions made to this review by each of these fields. Specific contributions from scholars in these fields form the map for the review process, the measuring stick against which studies are reviewed, as well as the foundation on which findings of this review are anchored.

Specific contributions include the understanding of the nature and chemical mechanism of neurotoxins uncovered in the field of neurotoxicology. This knowledge forms the first building block on which the investigation of this dissertation is built. Developments in neurotoxicology have made it possible to deduce which brain area incurred the maximum damage, or to infer the nature of the cellular pathology associated with exposure to a specific neurotoxin. For the purpose of this dissertation, we explore the pathology associated with carbon disulphide, manganese and organophosphate exposure.

The second building block is given by neuropsychology, where developments in dynamic brain localisation theory have enabled the creation of specific tests that are sensitive to damage in specific areas. This is investigated at length in the neuropsychology section of this chapter, with special focus on the functioning and assessment of the areas affected by the neurotoxins listed above.

With the knowledge from neurotoxicology of which brain areas are affected with exposure to specific neurotoxins, and with the knowledge from neuropsychology of which tests are sensitive to the assessment of these areas, we are equipped to investigate the sensitivity

of these tests to the neurotoxins in the review process. The functioning of these brain areas may also shed light on the psychological symptoms associated with exposure to specific neurotoxins.

Finally, we come to the birth of neuropsychological toxicology. We look closer at the special considerations and best practice of assessments in this field. This is the backbone of the review process and provides an indication of the extent to which the outcomes of the specific tests assessed in later discussions may have been influenced by confounding variables.

2.2 The Development of Neurotoxicology due to Concerns over an Increasingly Toxic Environment

> "Neurotoxicology is defined as the science that deals with the adverse effects of naturally occurring and synthetic chemicals (neurotoxins) on the structure and function of the nervous system" (Harris & Blain, 2004 p.29).

Since the start of civilisation people have been exposed to neurotoxins. Even in Roman times, lead, a well-known neurotoxin, was used as a sweetener, preservative and cosmetic (Hartman, 1995). However, exposure to neurotoxins began to increase dramatically after World War II, and with it arose the need to assess the impact of exposure to these neurotoxins (Zakrzewski, 1991).

After the war came an era that was referred to as *"Good life through chemistry"* (Zakrzewski, 1991). This was aptly named as it was the beginning of the rapid increase in the production of chemical fertilisers, insecticide and herbicides. This in turn, resulted in record high grain yields in countries all around the world. For the first time some Third World countries became self-sufficient due to their new high grain yields. Between 1965 and 1995 the world grain production doubled. This in turn led to a 5% yearly increase in the global economy as well as an exponential increase in the world's population. This increase in population has resulted in a global dependence on these chemicals to maintain food production (Zakrzewski, 1991).

This revolution in agriculture and industry led to the dumping of millions of tons of toxins into the environment, which has led to a decrease in water and air quality. As previously stated it is approximated that today we are exposed to 70 000 chemicals daily (Rapp, 1996). Most of these have not been tested for neurotoxicity (Claudio et al., 2000; Landrigan, 2001). Despite this overwhelming need for the evaluation of neurotoxic chemicals, the fields of neuropsychological toxicology, neurotoxicology and occupational medicine are still in their infancy (Tilson, 2000).

In 1800, studies were conducted on the neurotoxic damage caused by neurotoxins such as alcohol, paraldehyde, trionale, bromide of sodium and caffeine. However, the first neuropsychological toxicology study commenced only in 1963. The next paper was only published in the 1970s, marking the beginning of the growth period in this field (Anger, Sizemore, Grossmann, Glasser, Letz & Bolwer, 1997; Hartman, 1995). Events such as the Minamata methyl mercury poisoning disaster in the 1970s, in which many people lost their lives after mercuric chloride was discharged from an industrial plant and was converted to highly toxic methyl mercury by organisms living in the Minimata bay in Japan, sparked the rapid development of neurotoxicology and with it neuropsychological toxicology (Hartman, 1995).

Like neuropsychological toxicology, neurotoxicology is a young discipline that only experienced significant growth in the last 25 years. This development has been spurred on by the recent alarm in the international community over the large number of toxins to which we are exposed, and the relatively small number of these that have been tested for toxicity.

2.2.1 The Neurotoxicology Tool Box

Certain developments in the field of neurotoxicology are of key interest to this review. Firstly, this field has gained great insight into the nature of neurotoxins, so much so that the characteristics of neurotoxic exposure can be used to estimate the extent of damage sustained by individuals. Secondly, the field of neurotoxicology has enabled the identification of specific brain areas and cellular pathologies associated with exposure to specific neurotoxins. These are discussed below.

2.2.1.1 What is a Neurotoxin?

Neurotoxic substances cross over the blood-brain barrier and influence neuron function at specific sites depending on the chemical mechanism (toxicodynamics) of the neurotoxin. Neurotoxins may also affect mental functioning by altering metabolic or circulatory processes (Jacobs, 1980). As previously stated, the smallest unit of functioning in the brain that is affected by neurotoxins is the synaptic junction between two neurons. FIGURE 2-1 is an electron micrograph of multiple synapses. Neurotoxins can affect nerve conduction at synapses in a number of ways, including binding to receptors, competitively inhibiting neurotransmitters, depolarising endplates in the peripheral nervous system, inhibiting enzymes or destroying nervous tissue through enzymatic action, and blocking or facilitating ion flow (Chubb & Geffen, 1979).

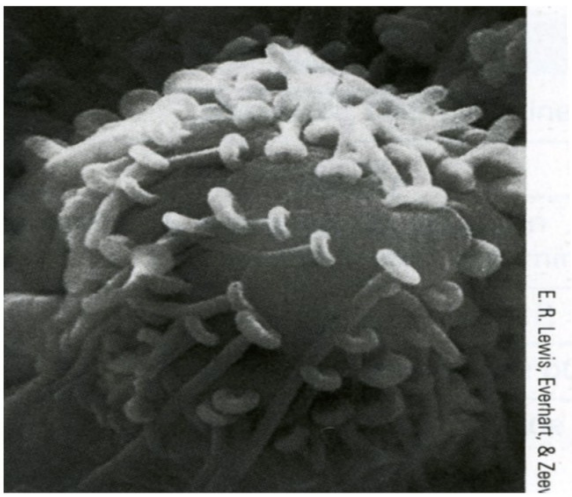

Figure 2-1 Electron micrograph of multiple synapses between axon terminals and the soma of a neuron (Lewis, Everhart & Zeevi, cited in Kalat, 2004 p.64).

Synaptic junctions are the origin of all behavioural processes. Intellect, emotions and control are created by means of changes in membrane receptors and neurotransmitters at synaptic junctions (Bray et al., 1998). These behavioural components may be altered in individuals exposed to neurotoxins, as these neurotoxins affect nerve conductivity and transition at synaptic junctions (Bray et al., 1998).

2.2.2 Factors Influencing the Nature and Extent of Neurotoxic Damage

The extent of damage that is caused by exposure to a specific neurotoxins is determined by a variety of factors. These include the route of absorption, in other words, whether it is ingested, through skin contact, inhaled or injected (Stellman et al., 1998). Individual susceptibility also plays a role in determining the extent of damage suffered by the exposed individual. These include the total volume and surface area of the individual, gender, hormonal status, genetic factors, life style and the use of drugs (Zakrzewski, 1991). Interaction of different toxins may also increase the effects of one neurotoxin on the central nervous system (Rosenberg, 1995).

Regardless of the above, symptoms experienced by individuals exposed to neurotoxic chemicals generally increase with the duration and the level of exposure (Rosenberg, 1995). With an increase in exposure level and increased duration of exposure, symptoms of the exposed individual increase and become less reversible (Rosenberg, 1995). For this and other reasons, studies on neurotoxic exposure are often divided into two groups: those conducted on chronic low-level exposure and acute high-level exposure. Chronic low-level exposure results in insidious nervous system changes whereas acute high-level exposure is often debilitating and irreversible (Stellman et al., 1998). Multiple incidences of exposure

result in progressive worsening of health. This may be due to sensitisation of the exposed individual, as in the case of multiple chemical sensitivity (discussed in a later section). This may also be due to the accumulation of cellular impairment and the accumulation of toxins in the body (Harris & Blain, 2004).

Symptoms at early stages of exposure may go unseen due to the reserve circuitry in the nervous system, and may not be accompanied by a functional disorder. However, as damage progresses, signs become apparent. In the early stages these may be slow changes in neuropsychological functions, changes in mood state, concentration, headaches, blurred vision and feelings of inebriation; however, these are often ignored. These early signs may later progress into apparent, progressive and irreversible syndromes (Stellman et al., 1998*).*

Acute symptoms are an immediate reaction to exposure to a neurotoxic chemical. These symptoms are directly proportional to the concentration of the chemical absorbed (Stellman et al. 1998*).* Low exposure levels often result in transient symptoms, which may disappear; whereas high-level exposure may result in death or debilitating symptoms (Stellman et al.1998*).* The chemical properties of the neurotoxin, such as its toxicity and the metabolic processes it affects, play a large role in determining the extent of damage suffered by the exposed individual either through low-level chronic exposure or during high-level acute exposure (Rosenberg, 1995)

2.2.3 Determining the Nature of Neurotoxic Damage

As previously stated, neurotoxic damage may be either diffused or localised, depending on the type of toxin (Rosenberg, 1995). Toxins that result in diffuse brain damage may cause changes in many behavioural outcomes, as many parts of the brain are affected. Exposure to these types of toxins may therefore best be assessed with global test batteries. The majority of neurotoxins, however, affect some specific brain areas more than others. These toxins selectively target cells with a specific morphology. Cell morphology is determined by cell functioning. Toxins that result in bilateral brain damage have toxic mechanisms that interfere with the proper functioning of these cells. As a result, certain toxic syndromes are associated with exposure to certain toxins.

Neurotoxicologists have developed a number of methods to determine the chemical mechanisms of neurotoxic chemicals, as well as to determine the nature of this damage. These include the following: neurological examinations, electromyography (EMG), nerve conduction studies (NCS), evoked potentials (EVP), electroencephalography (EEC), neurohistotology, physiology assessments, autopsies, and neuro-imaging techniques such as computer tomography (CT), magnetic resonance imaging (MRI), position emission tomography (PET) and single photon emissions (SPECT) (Rosenberg, 1995, Tilson, 2000).

These techniques have enabled neurotoxicologists to determine the brain areas and processes affected by specific neurotoxins as well as the chemical mechanisms of these toxins.

The use of behavioural and psychological assessment in both humans and animals is widely accepted in neurotoxicology assessment. Tilson (2000) argues that behavioural assessment represents the functional integration of the nervous system, which cannot be assessed through other neurotoxicological means. The use of animals in behavioural research is widespread in neurotoxicology. This enables neurotoxicologists to assess the effects of a neurotoxin on a living brain under controlled conditions, which would be unethical in human studies. However, despite the conservative nature of evolution it is nearly impossible to translate neurotoxic damage caused to higher cognitive functions from an animal model to a human. Changes in metabolic pathways between species may mean that exposure to a toxic substance in one species is fatal while other species may be resistant to it (Zakrzewski, 1991). Neuropsychological toxicology therefore plays a key role in providing a non-invasive method for assessing the impact of neurotoxins on the human brain.

The previously discussed techniques have enabled the identification of the nature of neurotoxic damage resulting from exposure to carbon disulphide, manganese and organophosphate. To briefly recap:

- Carbon disulphide leads to neuronal degeneration throughout the cerebral hemispheres. Maximum degeneration occurs in the frontal lobes resulting in psychiatric symptoms such as acute bipolar and psychotic symptoms, delirium, personality changes, impaired cognition and associated parkinsonism (Hartman, 1988; Rosenberg, 1995).
- Manganese accumulates in the basal ganglia, and is associated with symptoms resembling those found in Parkinson's disease (Lucchini et al., 2000)
- Organophosphate disrupts the enzyme cholinesterase, causing the accumulation of acetylcholine and a parasympathetic overload. This results in neuropsychological symptoms such as anxiety, decreased concentration, memory and decreased information processing ability (Davis & Richardson, 1980; Hartman, 1995).

2.3 The History and Origins of Neuropsychology

The origins of neuropsychology are as old as the earliest people who wondered about the behaviour of people. Early philosophers, physicians, scientists, and artists considered the possibility that the body plays a role in behaviour (Lezak et al., 2004). Records of these early beginnings date back to 2500BC. Papyrus documents dating back to these times have been found, which record various behavioural aberrations resulting from brain injury. Hippocrates (460-370BC) was the first to locate sensation, thought and emotions in the brain, as opposed to the heart (Smith, 2005).

Various philosophers, anatomists and physicians have contributed to our understanding of brain functioning and the development of neuropsychology through the centuries. The contribution of phrenology to neuropsychology cannot be ignored in the history of this field. Phrenology, the art or science of determining psychological attributes through evaluation of bumps on the skull, is today regarded as “preposterous” and “persistent nonsense” (Smith, 2005 p.3). However, some of their early findings are linked to theoretical models still used in neuropsychology today. The popularity of phrenology peaked around 1800. When Franz-Joseph Gall, an Austrian physician, lectured on phrenology in 1802, he concluded the following.

- Different parts of the brain have different functions
- Different people could be differently endowed with these abilities (Smith, 2005 p.3).

These concepts tie in closely with principles of modern brain localisation theory, which arose over concerns about the inaccuracy of phrenology (Mazziotta, Toga, Evans, Fox & Lanater, 1995). Brain localisation theory aims to explain the relationship between the brain and the behaviour that results from the innumerable numbers of neurophysiological and biochemical reactions that occur in the brain (Lezak et al., 2004). The localisation of functioning model was given further impetus by Broca, who showed that was possible to successfully and scientifically localise brain function (Smith, 2005).

The interest in brain functioning did not begin to take the shape of a scientific discipline until World War I produced a large number of traumatic brain injuries and the need for their assessment. This need was amplified with the start of World War II. The combination of these opportunities, combined with the development of psychometric testing, such as intelligence testing, provided the starting blocks for modern neuropsychology (Lezak et al., 2004)..

Although Broca had made progress on the concept of brain localisation, enthusiasm for this concept gradually diminished due to the lack of imaging techniques and the sheer complexity of the central nervous system. As a result, brain damage was treated as a unitary phenomenon in the 1930s and 1940s. Investigations often aimed to determine the organicity of patient deficits. This lead investigators to try to identify one central universal trait to characterise “organic” brain damage. This lead to the proliferation of single function tests based on how well they discriminated organic from psychiatric patients (Lezak et al., 2004). Predictably, this practice proved elusive as no single behavioural characteristic common to all brain-damaged patients could be found. Nonetheless, this one-dimensional approach to neuropsychology is still followed in some spheres today (Lezak et al., 2004).

The analysis of patients with localised gunshot wounds, and later improved neuroimaging techniques, promoted support for the localisation of functioning model. However, this model

was contested by a number of authors on the basis of its oversimplification and the tendency to note only the area of damage and not the underlying process and system of which local damage may be part (Long, n.d.).

2.3.1 Dynamic Localisation Theory as Theoretical Framework

"If our brains were so simple that we could understand them, we would be so simple that we could not" (Anonymous, cited in Lezak et al., 2004, p.15)

Giant leaps forward in contemporary neuroimaging techniques have provided support for the dynamic and connectionist approach to brain localisation. Early connectionist thinkers such as Norman Geschwind provided the foundation for modern dynamic brain localisation theory by identifying the importance of interconnections between primary motor, sensory and limbic areas. The importance of these connections was clearly demonstrated by the deficits incurred in patients with white matter lesions or lesions to association cortices. The identification of these disconnexion syndromes revolutionised the current understanding of the dynamic nature of brain functioning (Catani & Ffytche, 2005). Modern brain localisation theory, also referred to as "dynamic localisation of functioning model," no longer focuses exclusively on isolated brain regions but on the distribution of large-scale neural networks (Mazziotta et al., 1995). A functional brain system consists of a number of parts in the brain with interconnecting fibres between these parts. Damage to one part of the system will result in functional changes in the system. The nature and extent of the damage will depend on the part of this particular system that was damaged (Hartman, 1995; Lucchini et al., 2000; Spreen & Strauss, 1998). In other words, complex cognitive functions result from interconnections between several localised functional sites. By placing the principle of localised function within a connectionist framework, the idea of distributed or dynamic processing becomes central to the current understanding of brain function (Kandel, 2000).

Therefore, despite the overall integration of brain activity in the creation of behaviour, lesions involving the same anatomic structures can disrupt the same discrete psychological activities in most humans. The disruption of discrete psychological activities, which are integral to more complex behaviours, may result in neurobehavioral syndromes. As specific lesions are so regularly associated with specific neurobehavioural syndromes, it is possible to predict the location of some lesions from the neurobehavioural syndrome presented (Lezak et al., 2004). It is also possible to predict a behavioural outcome of a lesion to a particular brain structure.

The fundamental difference between psychometric assessment and neuropsychological assessment is "the conceptual framework of reference that takes brain functioning as its point of departure" (Lezak et al., 2004 p.16). As such, dynamic brain localisation theory is often

used as a rationale for test selection in the evaluation of traumatic brain injury. The purpose of this review is to investigate the use of this theory as a rationale for test selection in neuropsychological toxicology. The dynamic brain localisation theory is therefore adopted as the theoretical underpinning of this study. To provide a theoretical grounding for the review process, recent insights into brain functioning are considered. This inquiry covers aspects such as the independent functioning of one lobe as well as its functioning in relation of other brain areas. It focuses specifically on the roles of the frontal lobe and the basal ganglia, because these are the sites of maximum damage in carbon disulphide and manganese exposure (Hartman, 1988; Kaplan & Sadock, 1998, Lucchini et al., 2000; Rosenberg, 1995). Additional attention is given to cellular pathology, which is not associated with any one specific location, but is linked to the impact of organophosphate on cholinergic neurons that are dispersed throughout the cortex (Davis & Richardson, 1980; Hartman, 1995).

2.3.2 The Frontal Lobes

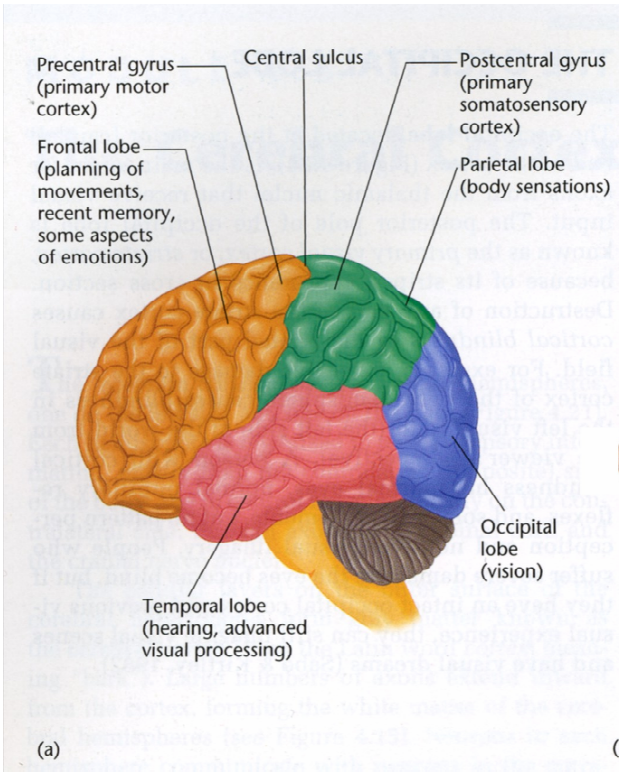

Figure 2-2: The location of the frontal lobes in relation to the parietal, temporal and occipital lobes (Kalat, 2004 p.96).

The frontal lobe is the site of maximum damage following carbon disulphide exposure (Rosenberg, 1995). Before we concern ourselves with its anatomy, psychology and assessment history, let us consider the case history of the first unlucky soul who unwittingly made a great contribution to our current understanding of this part of the brain.

Readers familiar with frontal lobe science will certainly be acquainted with the story of Phineas P. Gage. In 1848 Phineas Gage worked as the foreman in charge of group of men whose job it was to lay new tracks for the railroad expansion in Vermont. At this stage of his life Gage was described as a "most efficient and capable man" (Damasio, 1994, p.4). However, during an ill-fated working accident Gage was impaled by an iron rod, which entered his right cheek, pierced the base of his skull, traversed the front of his brain, and exited thought the top of his head. Remarkably, Gage survived the accident and appeared at first to be none the worst for it. This contributed to the belief of the time that the frontal lobes had little or no function. However, the accident left Gage

> Fitful, irreverent, indulgent at times in the grossest profanity which was not previously his custom, manifesting but little deference for his fellows, impatient of restraint or advice which it conflicts with his desires, at times pertinaciously obstinate, yet capricious and vacillating, devising many plans of further operation which are no sooner arranged that they are abandoned. A child in his intellectual capacity and manifestations he has the animal passions of a strong man (Damasio, 1994, p.8).

This poignant tale demonstrates two important things that must be considered in the investigation of frontal lobe injury, including exposure to sufficient amounts of carbon disulphide (Rosenberg, 1995). Firstly, survivors exhibit seemingly normal behaviour at a glance, such that this condition is recognised with great difficulty. Secondly, these injuries have potentially devastating consequences for the individual's functioning and quality of life (Brown, 2005).

2.3.2.1 Functional Anatomy of the Frontal Lobes

We turn our attention now to the relevant advances made in the understanding of this part of the brain.

The frontal lobes are situated in the anterior region of the brain and are separated from the temporal lobe by the central and lateral sulcus (Spreen & Strauss, 1998). The frontal lobes constitute a third of the human brain, making them the largest structure in the brain (Lezak et al., 2004; Walsh, 1987, Spreen & Strauss, 1998). The frontal lobes are characterised by the wide inter-distribution of cells with different morphology and functions (Passingham, 1995). Prefrontal neurons, specifically, are characterised by large dendrite branches enabling the integration of a large number of stimuli (Kalat, 2004).

The frontal lobe cortex can be further divided into four strips: motor cortex, premotor cortex, prefrontal cortex and the anterior cingulate. The motor cortex, premotor cortex and prefrontal cortex are located in strips arranged vertically, from posterior to anterior. The anterior cingulated lies horizontally (Passingham, 1995). These areas are distinguished according to differences in cytoarchitecture and function.

The motor cortex is specialised for movements of the limbs and face, but is not essential for non-learned movements such as walking. The motor cortex plays an important role in the "fine behavioural variants which are selected in voluntary action" (Passingham, 1995, p.37). The motor cortex is connected to other brain areas, which together form the motor system. These include the superior colliculus, the red nucleus, the pedunculopontine nucleus, reticular formation and the pontine nuclei. Lesions to the motor cortex in the frontal lobe result in paralysis or paresis (Lezak et al., 2004). However, it has been argued that the motor system works as an integrated whole, which may explain the remarkable degree of recovery after lesions to this area. For example, when the neocortex is removed from this system, there are still many motor pathways that remain intact (Passingham, 1995).

The premotor area receives sensory input from the parietal cortex, and this represents the decision for movement (Meyer, Meij & Meyer, 1997). The premotor region integrates motor skill and learned action sequences, and influences movement by providing sensory input into the primary motor area (Lezak et al., 2004). The medial and lateral premotor area is associated with the selection of movements. The lateral premotor cortex is associated with external cues, which are used to direct movements. The medial premotor cortex is associated with the planning of movements from internal cues such as memory (Passingham, 1995). Lesions to the premotor area results in disrupted or uncoordinated movements, as well as a decrease in limb strength and disrupted speech production (Lezak et al., 2004).

Luria (cited in Walsh, 1987) proposes a hierarchical system for the structures in the prefrontal cortex, motor area, premotor area and prefrontal area. Lesions to these areas demonstrate the development of this hierarchy. Lesions to the premotor area result in disorganisation of movement, while more anterior lesions result in disrupted comparisons of movement. Lesions to the prefrontal area result in an inability to plan and initiate movement (Spreen & Strauss, 1998). The prefrontal area is therefore credited with executive functioning.

The prefrontal area is located anterior to the premotor area and is the topic of much neuropsychological investigation (Kalat, 2004). Luria states that the prefrontal area serves as a tertiary integration zone for limbic as well motor areas. To enable the process of higher integration, the prefrontal area has rich connections to many other areas of the brain, including the upper parts of the brain stem, the thalamus, and all areas of the cortex, including all sensory and major motor systems. Information regarding the external environment is

carried to the prefrontal area by the heteromodal association cortex and secondary association areas. Information regarding internal states is transmitted via the limbic system (Lezak et al., 2004; Spreen & Strauss, 1998). Therefore, the prefrontal area receives an array of sensory and informational input, equipping it to conduct executive functioning.

The term 'executive functions' encapsulates a variety of operations performed by the prefrontal cortex. These include integrating and linking all components of behaviour, as well as linking all feedback loops to sensory and motor areas. The prefrontal area links all internal external conscious, unconscious memory and visceral information to attend to, monitor, plan, strategise, coordinate and adapt behaviour, as well as code representations in working memory (Lezak et al., 2004; Upton & Thomson, 1999). Damage to the prefrontal area results in the disruption of these processes and is associated with a range of pathological behaviour, including social disinhibition, profanity, impulsivity, tactlessness, loss of social responsibility, dysfunction of cognitive estimations, inability to utilise errors, inflexibility, difficulty suppressing inappropriate hypotheses, and difficulty in planning and executing actions (Dimitrov et al., 2003; Zalla, Plassiart, Pillon, Grafman, & Sirigu, 2001; Spreen & Strauss, 1998). Damage to the frontal lobes may also result in frontal amnesia; however, some authors maintain that there is no true frontal amnesia, but that frontal lobe patients are unable to plan the process of remembering and therefore appear to have memory deficits (Spreen & Strauss, 1998).

The abovementioned symptoms are associated with lesions to specific substructures in the prefrontal regions, namely, the dorsolateral, the orbitomedial and the orbital (basal) prefrontal areas. The dorsolateral prefrontal cortex is associated with control, regulation and integration of cognitive activities, the planning and adoption of appropriate strategies, as well as the evaluation of feedback (Gehring & Knight, 2002; Lezak et al., 2004; Upton & Thomson, 1999). The orbitomedial area is associated with social and emotional control (Lezak et al., 2004). Modern imaging studies have shown that social conduct regulation depends on the oribitofrontal cortex, and more specifically the ventromedial prefrontal cortex (Dimitrov et al., 2003). Damage to the ventromedial cortex is associated with difficulty in personal and social decision making (planning and choosing social acquaintances) (Bechara, 2004; Fellows & Farah, 2005). This is the basis of Bechara's (2004) somatic marker hypothesis, in which he proposes that decision making is in essence an emotionally guided process. Damage to the ventromedial area of the prefrontal lobes results in an inability to practise effective decision making due to deficits in emotional processing.

The orbital (or basal) prefrontal cortex is associated with impulse control and the regulation of ongoing behaviour. Damage to this area is therefore associated with disinhibited behaviour such as aggression and promiscuity (Lezak et al., 2004). Structures that are responsible for processing primary olfactory sensation are also situated at the base of the brain, and so damage to this region also results in impaired odour detection (Lezak et al., 2004).

Luria describes damage to the prefrontal lobes in two syndromes. The first syndrome is characterised by changes in personality and inhibitions and is associated with damage to the orbitomedial prefrontal cortex. The second prefrontal syndrome is characterised by impaired integration of behaviour over time, the inability to think abstractly, and plan and follow a course of action. This is associated with damage to the dorsolateral prefrontal cortex (Spreen & Strauss, 1998).

The anterior cingulate comprises the fourth subdivision of the frontal lobe. This area has been less extensively researched than the other areas of the frontal lobes. The anterior cingulate is located in the crease between the two cerebral hemispheres. The anterior cingulated is closely associated with the dorsolateral prefrontal cortex and work together in a dynamic negative feedback system to implement cognitive control. Experimental research with fMRI and conflict assessments, such as the stroop test, has identified the activity of the anterior cingulated during conditions in which errors may occur. The anterior cingulated appears to play an important role in evaluating processes and indicating when control needs to be applied, as well as monitoring conflicting information. The doroslateral prefrontal cortex provides top down support by implimenting control, to facilitate appropriate behaviour. (Carter, Braver, Barch, Botvinick, Noll, & Cohen, 1998; Botvinick, Nystrom, Fissell , Carter, & Cohen,. 1999; MacDonald, Cohen, Stenger, & Cater,. 2000). Therefore the anterior cingluate plays an important role in the feedback of errors to correct behaviour, as well the emotional reactions to behaviour (Miller, 2002). This may be in part due to the basal ganglia's major interactions with the limbic system (Morgane, Galler & Mokler, 2005). Damage to the anterior cingulate is associated with poor decision making, and is effectively measured using gambling tasks (Miller, 2002).

2.3.2.2 Neuropsychological Assessment of Frontal Lobe Damage

Damage to the prefrontal cortex has proven difficult to assess using traditional neuropsychological techniques. Patients with extensive damage to the frontal lobes may not show any significant changes in outcomes on a wide variety of neuropsychological tests (Spreen & Strauss, 1998). Upton and Thomson (1999, p.204) state that "there are few if any reliable measures for testing frontal lobe dysfunction". Patients with prefrontal cortical damage usually show normal IQ, long-term memory and perception on most psychological tests (Funahashi, 2001). One of the reasons for the elusive nature of this damage may be that the frontal lobes are primarily responsible for the executive functions discussed above, and that the other cognitive functions of frontal lobe patients remain for the most part intact. The presence of an evaluator in the testing situation compensates for the frontal lobe patient's lack of executive functions as the evaluator takes responsibility for the facilitation, planning and provision of a programme for the frontal lobe patient to follow (Spreen & Strauss, 1998).

In test situations where the evaluator plays a smaller role, the frontal lobe patient may perform less well on some cognitive tasks. This may be due to the decrease in this patient's test-wiseness (because of the frontal lobe damage) and not due to an actual decrease in their cognitive ability, as discussed in the case of frontal amnesia. This highlights the importance of the qualitative evaluation of these patients by a skilled neuropsychologist. The importance of a qualitative evaluation is discussed in the section pertaining to qualitative measurements and the use of computerised batteries.

The importance of qualitative evaluation is also demonstrated by the number of neuropsychological tests, which have been effective in evaluating frontal lobe damage when careful attention is paid to the qualitative changes in the executive behaviour of patients. The following neuropsychological assessment methods are effective in either quantitatively or qualitatively assessing patients with prefrontal damage:

- The **Wisconsin Card Sorting Test** is effective in assessing the ability of patients with dorsolateral prefrontal lesions to shift between tasks (Spreen & Strauss, 1998).
- The **Tower of London Test** effectively assesses changes in outcomes of planning in patients with left anterior frontal lobe damage (Spreen & Strauss, 1998; Upton & Thompson, 1999).
- To the skilled practitioner, the **Block Design Subtest** from the **Wechsler Adult Intelligence Scale** reveals qualitative differences in the manner in which frontal lobe patients reproduce this design. More specifically, the patient's ability or inability to monitor and adapt their behaviour during this process may be observed (Spreen & Strauss, 1998).
- Qualitative differences are also observable in the **WAIS Vocabulary Subtest** (Spreen & Strauss, 1998).
- The **Stroop Test** may also be used to demonstrate qualitative changes in frontal lobe patients' behaviour. Together with the WAIS Vocabulary Subtest, this test highlights the inability of some patients with frontal lobe damage to inhibit competing information (Spreen & Strauss, 1998).
- The **Wechsler Picture Arrangement Subtest** highlights the difficulties of some frontal lobe patients to plan sequences of behaviour (Spreen & Strauss, 1998).
- Bechara (2004) found significant changes in the outcomes of patients with frontal lobe damage when assessed on the **Cambridge Gamble Task**.
- Upton & Thomson (1999) found the **Twenty Questions** assessment effective for the qualitative assessment of frontal lobe damage.
- The **Minnesota Multiphasic Personality Inventory (MMPI**) showed marked alterations on the Depression, Hysteria, Psychasthenia and Schizophrenia scales in a study conducted on patients who had undergone psychosurgery (Spreen & Strauss, 1998).

- The **Delis-Kaplan Executive Function System (D-KEFS).** This set of nine tests is aimed specifically to be sensitive to many of the types of executive impairment. This selection is however no theory based. There is also no composite score (Lezak et al., 2004).

2.3.3 The Basal Ganglia

The basal ganglia are the primary area of damage associated with exposure to manganese (Kaplan & Sadock, 1998, Lucchini et al., 2000).

2.3.3.1 Functional Anatomy of the Basal Ganglia

FIGURE 2-3 below is a schematic representation of the basal ganglia. The basal ganglion comprises the striatum (consisting of the putamen, the caudate nucleus and the ventral striatum), the subthalamic nucleus, the pallidus and the substantia nigra. All these structures have interconnections with various cortical and thalamic areas. The basal ganglia receives inputs from most of the sensorimotor areas of the cerebral cortex, including the primary and secondary somatosensory areas, the premotor and primary motor areas and the cingulate motor area (Alexander, 1980).

The basal ganglia, the thalamus limbic system, the brain stem and the cerebellum form part of the association cortices. The main functions of the association cortices are to integrate information from the primary sensory cortices, to organise information required for reasoning and decision making, and then to formulate a motor response. The association cortex essentially links the sensory input areas and the main output area. Therefore, the basal ganglia assists in the integration of both innate and external knowledge regarding the body and the world for the production of mental and motor outputs. This highlights the interaction of brain areas and the importance of considering their dynamic nature in the interpretation of the brain localisation theory (Damasio, 1994). The role of the basal ganglia in the production of motor and mental outputs may provide an explanation for the motor and psychiatric deficits associated with damage to this structure in diseases such as Huntington's disease, and, as we will see in following chapters, exposure to manganese.

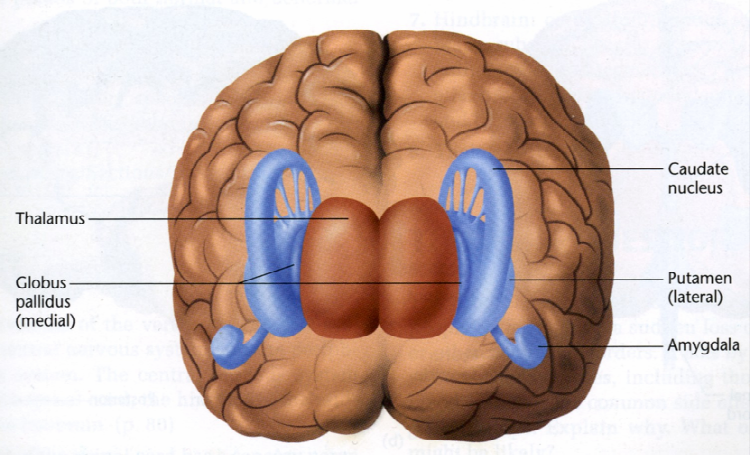

Figure 2-3: A schematic representation of the basal ganglia (Kalat, 2004, p.91)

Dopamine plays an important role in the proper functioning of the basal ganglia. This is demonstrated in pathologies in which normal dopamine metabolism is altered. Dopamine plays an important role in the way in which sensory inputs into the basal ganglia are handled (Bunney, Grace & Hommer, 1980). The putamen receives dopaminergic inputs from nigrostrial projections. The cortical motor and premotor areas also receive dopaminergic input from ventral tegmental projections. These projections are thought to influence the feedback given to the various cortical areas from the basal ganglia. Dopamine also plays a role in the synaptic plasticity of the striatum (Alexander, 1980).

The following functions have been attributed to the basal ganglia. The basal ganglia play a role in saccadic eye movements and movement control (Alexander, 1980). Damage to the basal ganglia may result in various degrees of disability. Wang and Cheng (2003) report acute onset movement disorders, Parkinsonism or dyskinesia, conscious disturbances, dysarthria, dysphagia or ataxia in patients who experienced bilateral basal ganglion lesions due to diabetic uremia. Damage to the basal ganglia is also associated with obsessive-compulsive disorder, Tourette's disorder and Huntington's disease (Kaplan & Sadock, 1998).

Unlike the frontal lobes, the basal ganglia are anatomically deep structures and are unlikely to be selectively damaged during traumatic brain injury. As much of what we know today is the result of the study of traumatic brain damage, this may have contributed to the relatively smaller amount of information available on basal ganglia functioning than on frontal lobe functioning. The study of manganese-induced damage may assist in rectifying this, as this area is predominantly affected by its exposure (Kaplan & Sadock, 1998, Lucchini et al., 2000). Much of what is known about the function of the basal ganglia is through the observation of patients with Parkinson's and Huntington's disease. These disorders are associated with cognitive and emotional disturbances resulting from changes in dopamine metabolism and

atrophy of the basal ganglia (Lezak et al., 2004). Insights gained from the assessment of Parkinson's and Huntington's disease may shed light on effective methods of assessing manganese neurotoxic damage due to the similar pathology. This is investigated in later chapters. The symptomatology and assessment strategies for these disorders are reviewed below for this purpose.

Huntington's disease is characterised by dramatic personality changes, cognitive impairment, and motor disturbances. Psychological changes, for example in personality, may become more disruptive as basal ganglia degeneration progresses. Characteristic of these patients are changes in executive functioning similar to that seen in frontal lobe patients, including diminished self-regulation, impaired behavioural regulation, and problems with planning and organising. Depression is common and is associated with increased suicide rates. The high rate of depression in these patients is associated with the neuropathology of the disease. Other psychiatric disturbances include mania and hypomania, schizophrenic delusions and hallucinations, obsessive-compulsive tendencies, irritability, anxiety, emotional liability, aggressive outbursts and sexual promiscuity (Lezak et al., 2004).

Parkinson's disease is a disease of the basal ganglia, which manifest clinical symptoms when the nigrostrial tract degenerates (Kaplan & Sadock, 1998). Normal motor functioning is dependent on the release of dopamine from projections in the substantia nigra to the striatum. Dopamine levels slowly decrease throughout a person's lifetime, and it is estimated that 5%-7% of nigral cell loss occurs per decade. However, a decrease of 80% in striatal dopamine is required for the onset of Parkinson's. It is suspected that neurotoxic exposure earlier in life may result in the loss of these cells, but that the effects only become apparent with increasing age as dopamine depletion reaches 80% (Hartman, 1995). Exposure to manganese is widely reported to result in the development of Parkinson's disease (Banta & Marksbery, 1977; Donaldson, McGregor, & LaBella, 1982; Gorell, Rybicki, Johnson & Peterson, 1999; Hageman et al., 1999). The neurodegenerative process that occurs in patients suffering from Parkinson's disease and those exposed to manganese is "remarkably similar" (Donaldson et al., 1982, p.1398). This includes degeneration of the melanin pigment in the substantia nigra, loss of dopamine in the caudate putamen and norepinephrine in the hypothalamus (Donaldson et al., 1982).

2.3.3.2 Neuropsychological Assessment of Basal Ganglia Damage

The cognitive deficits characteristic of Huntington's patients may provide an indication of tests sensitive to basal ganglia damage. These deficits are similar to the cognitive deficits experienced by frontal lobe patients and include difficulties on visual tracking tasks (effectively measured by the Weschler Intelligence Scale subtests such as Trail Making Test and Symbol Substitution) attention (Digit Recall) and memory. Thinking, reasoning, learning ability and

verbal tasks, such as those measured by WIS subtests; Similarities, Information, Comprehension and Vocabulary, are preserved. Performances on the Calculations, Digit Symbol, Comprehension, and Arithmetic tests generally deteriorate (Lezak et al., 2004).

Parkinson's disease is characterised by motor deficits, including involuntary tremors, decreased muscle power, bradykinesia and rigidity. Cognitive deficits which are often indistinguishable from those of prefrontal lobe patients may also occur. These include deterioration in executive and cognitive functions (attention span, memory, learning and visusospatial impairments), although vocabulary, grammar, and syntax scores may be normal. Digit Span (WIS) may also be normal. High incidences of depression are also associated with Parkinson's disease (Lezak et al., 2004).

2.3.4 Cholinergic Projections

As previously discussed, the smallest functional unit of the nervous system is the synaptic junction between two neurons. The entire nervous system, including the brain, is composed of neurons and supporting cells (Bray et al., 1998). The neurons of the central nervous system are differentiated in terms of morphology and function and result in the diverse cytoarchitechture of the brain (Spreen & Strauss, 1998). Because of differences in morphology as well as variations in blood-brain barrier and circulation within the brain, certain neurons are selectively targeted by certain neurotoxins (Davis & Richardson, 1980). For example, the metabolism of acetylcholine-releasing neurons is selectively targeted by organophosphate (Davis & Richardson, 1980; Hartman, 1995).

2.3.4.1 Functional Anatomy of Cholinergic Projections

Acetylcholine-releasing neurons are not limited to a particular macro-anatomic structure of the brain, but rather project to the entire cortex (Thiel, 2003). Of these projections, three cholinergic pathways are of particular importance in neuropsychology:

- The nucleus basilis of Meynert. These cell bodies are located at the basal forebrain, and project to the neocortex. They play a role in learning and memory. The medial septum also receives projections from the hippocampus. Degeneration of these nuclei is associated with Alzheimer's disease.
- Cholinergic fibres from the brainstem. These connect the midbrain and the thalamus, which is thought to play a role in the sleep awake cycle.
- Acetylcholinergic neurons in the basal ganglia. These play an important role in motoric learning (Schatz & Chute, 2000).

2.3.4.2 Neuropsychological Assessment of Cholinergic Projections

Similar to basal ganglia damage, cholinergic projections are not selectively damaged in cases of traumatic brain damage, as they are dispersed throughout the cortex. This may explain the lack of neuropsychological literature regarding the assessment of damage to this system. However, the assessment of disease processes characterised by damage to this system may provide some clues into the effective evaluation thereof.

Contrary to organophosphate neurotoxicity, which is characterised by increased cholinergic activity, Alzheimer's disease is associated with the depletion of this neurotransmitter. This is suspected to play an important role in memory deterioration. Curiously though, Alzheimer's patients may be treated with cholinesterase inhibitors due to the hypoactivity of acetylcholine, which has the same chemical effect as exposure to organophosphate (Kamel & Hoppin, 2004).

Memory deficits are the most obvious early signs of Alzheimer's disease although all areas of cognitive functioning are eventually affected. These deficits are effectively assessed using a number of memory assessments (Lezak et al., 2004). Although the pathology caused by Alzheimer's disease and organophosphate poisoning are the opposite of each other, they both represent pathology to the same neurological system, and may therefore provide clues to the assessment thereof.

2.4 The Birth of Neuropsychological Toxicology

The following discussion concerns the development of the new field of neuropsychological toxicology. Where did it come from and what is it doing? In addition, review articles that critically evaluate the field of neuropsychological toxicology are examined to provide an indication of factors which may influence the outcomes of neuropsychological toxicology assessments. These are considered in the interpretation of research outcomes in the following chapters.

2.4.1 Neuropsychological Toxicology Defined

The field of neuropsychological toxicology arose from the developments in neurotoxicology and neuropsychology. Neuropsychological toxicology investigates the impact of brain damage caused by chemical exposure on the behaviour of affected individuals (Hartman, 1995). As in other branches of neuropsychology, brain damage is assessed by measuring changes in intellectual, emotional and control components of the behaviour of the affected individual (Lezak et al., 2004). Changes in these components of behaviour are assessed with diagnostic neuropsychological tests as well as tests that have been specifically adapted for assessing

brain lesions caused by toxic exposure. Neuropsychological studies are conducted on patients exposed to neurotoxins in a variety of ways, stretching from patients who were exposed to neurotoxic chemicals in the form of prescribed medicines, substance abuse, environmental neurotoxins resulting from pollution, exposure to household chemicals as well as occupational and industrial exposure (Hartman, 1995).

Hartman (1995) gives the name "neuropsychological toxicology" to this field as this emphasises the unique contribution of neuropsychologists in it. However, a number of other names also exist, such as behavioural toxicology, neurobehavioural toxicology, psychological toxicology and neurotoxicology. Consensus surrounding the name of this young field has yet to be reached. Current trends in the literature indicate that "behavioural" refers to research conducted on animals where as "psychological" tends to refer to human investigations; "neurotoxicology" is seen to refer to medical research conducted by neurologists, while "psychological" refers to research conducted by neuropsychologists. These are merely trends, however, and are by no means laws of nomenclature.

2.4.2 A Very Short History of Neuropsychological Toxicology

Neuropsychological toxicology developed alongside neurotoxicology as events such as the Minamata methyl mercury poisoning disaster sparked an urgent need for neurotoxic assessment. Neuropsychology was identified as the only way to effectively assess the integrity of the whole central nervous system in humans (Tilson, 2000). Neuropsychological assessments are also often more sensitive than medical measures to damage sustained through neurotoxic exposure (Bolla, 1996; Lezak et al., 2004). The 1970s and 1980s saw a rapid increase in the number of 'behavioural' tests developed for workplace epidemiological research of neurotoxic exposure (Anger et al., 1997). Many of these neuropsychological toxicology tests were developed in Europe and Scandinavia. The tests listed below are some of the most popular standard neuropsychological toxicology assessment batteries.

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- 1983 WHO-NCTB: World Health Organisation- Neurobehavioural Health Core Test Batteries (Hartman, 1995)
- 1983 Neurobehavioural Test Battery (Lezak et al., 2004)
- 1984 TUFF Battery (Hartman, 1995).
- 1984 The London School of Hygiene Test Battery (Hartman, 1995; Lezak et al., 2004).
- 1985 NES: Neurobehavioural Evaluation System. (Anger et al., 1997).
- 1986 California Neuropsychological Screening Battery (Hartman, 1995)
- 1987 Pittsburgh Occupational Exposure Test (Hartman, 1995)
- 1990 Individual Neuropsychological Tests for Neurotoxicity (Lezak et al., 2004)
- 1992 ANBT: Adult Neurobehavioural Test Battery (Lezak et al. 2004)

- SPES: Swedish Performance Evaluation System Battery (Hartman, 1995)

*For more information on these batteries please refer to appendix A

The majority of these batteries have similar conceptual schemas and include the following functional areas: mental ability (usually verbal ability, which was previously considered to be fairly resistant to neurotoxic damage), memory, attention, motor speed, coordination, visual-spatial abilities and abstract reasoning (Lezak et al., 2004). However, other than the aim of assessing as wide a variety of mental functions as possible, there is no clear rationale for the inclusion of these subsets into these batteries. These batteries are also not specially designed for a particular neurotoxin, but are rather intended to assess brain damage caused by any neurotoxic exposure.

2.4.3 Current Trends in Neuropsychological Toxicology

This section examines past and current trends and practices in the field of neuropsychological toxicology. Firstly, we look at current rationales for test selection, with special focus on existing theoretical models. Then we move towards the practical implications of conducting assessments in the clinical, forensic and research arenas. Since the majority of publications in the remaining chapters were written for research purposes, special attention is given to the methodological best practices for these assessments, as recommended by other scholars in the field.

2.4.3.1 Current Trends in the Selection of Neuropsychological Toxicology Assessment Instruments

One of the primary aims of this dissertation is the investigation of theoretical underpinnings for neuropsychological toxicology assessments, and the selection of appropriate neuropsychological tests for these assessments. Consequently, this section gives some attention to the investigation of current trends in test selection and related theoretical models for this field.

Few of the research studies published in the field of neuropsychological toxicology make exclusive use of the standard batteries developed for neurotoxicology testing. Flexible batteries, in which researchers compile their own selection of tests, are often used in addition to standard batteries (Hartman, 1995). Of these subtests, the Wechsler Adult Intelligence Scales are by far the most popular. The need for standardisation, in addition to the familiarity of clinicians and researchers with the Wechsler Adult Intelligence Scales, may explain its frequent use in this field (Rabin, Barr & Burton, 2005). The need for replication as well as uncertainty as to which underlying functions standard tests measure, have resulted in the endorsement of these standard neuropsychological tests (Stephens & Barker 1998).

However, Stephens and Barker (1998) state that this has not been beneficial to the development of new, improved assessment methods. In addition, the majority of these tests were developed for diagnostic purposes and their roots lie in the assessment of psychopathology (Weiss & Elsner, 1996). Spurgeon (1996) questions the validity of using these tests as screening tools without the skill of a trained administrator.

Fielder (1996) published a review article evaluating these tests, and categorised them according to the various neuropsychological functions they assess. This is indicated in TABLE 2-1.

Table 2-1: Review of neuropsychological tests used to assess neurotoxic impairment of specific neuropsychological constructs (Fiedler, 1996 p. 240)

Function	Representative tests
Overall cognitive ability, verbal	• Vocabulary (WAIS-R) • National Adult Reading Test-Revised
Overall cognitive ability, spatial	• Block Design (WAIS-R) • Ravens Progressive Matrices
Concentration/attention	• Simple Reaction Time (NES) • Stroop Colour-Word Task • Continuous Performance Test (NES)
Motor skills and strength	• Grooved Pegboard • Finger Tapping • Dynamometer
Visual-motor coordination	• Hand-eye Coordination Test (NES) • Digit Symbol (WAIS-R)
Memory, verbal	• Logical Memory (WM-R) • Paired Associates (WMS-R) • California Verbal Learning Test • Digit Span (WAIS-R)
Visual	• Visual Reproduction (WMS-R) • Complex Figure Test
Sensory test – audition	• Audiometer • Seashore Rhythm
Sensory test – tactility	• Finger Agonise • Vibration
Sensory test – olfaction	• Universal Pennsylvanian Smell Indication Test • Olfactory Threshold Test
Affect/personality	• Profile of Mood State (POMS)

	• Minnesota Multiphasic Personality Inventory (MMPI)

Fielder (1996) concludes that batteries used for neuropsychological toxicology research usually consist of a combination of the above. However, even though the batteries vary in the specific tests used, the specific cognitive functions they assess are relatively consistent. As our review process unfolds in the following chapters, we discover that the studies that Fielder (1996) reviewed may have been too conservative in the use of different assessments for cognitive functioning.

2.4.3.2 And what of the Theory?

Although dynamic brain localisation theory is widely accepted as the rationale for test selection in cases of traumatic brain injury, a universal theoretical underpinning for the selection of tests in neurotoxicology investigation is almost entirely absent in the literature. Stollery (1996) made the only attempts for a theoretical foundation. Strollery proposes using theories from the field of cognitive neuropsychology to underpinning the examination and explication of toxic exposure injuries. Cognitive neuropsychology aims to classify psychological dysfunction into hypothetical cognitive systems so that future selection of tests may be facilitated by knowledge of the underlying pathology. For example, should a patient or research participant perform poorly on a memory task, the assessor would conduct further tests to determine which construct is affected: encoding, transfer of information to long-term storage, loss of stored information or problematic recall (Stollery, 1996). As we will see, London, Myers, Nell, Taylor, and Thompson (1997) made use of the cognitive information processing theory in an attempt to used culturally fair tests in investigating neuropsychological toxicology.

White, Feldman and Traver (1990) published an article which reviewed both the symptoms reported by patients, as well as the neuropsychological tests that were effective in evaluating the change of functioning of exposed patients. Exposure to a number of neurotoxic chemicals was reviewed, including inorganic lead, mercury, arsenic, manganese, carbon disulphide, trichloroethylene, toluene, perchloroethylene and chlordane. White et al. (1990) emphasises the need to differentiate specific patterns of dysfunction associated with different exposure and the importance of using tests that are sensitive to a particular neurotoxin. The most common criterion for the selection of these tests is the use of tests which measured deficits in exposed participants of previous research studies.

White et al. (1990) further recommend that tests selected for neurotoxic evaluations meet the following criteria:
1) They evaluate as broad a range of cognitive functions as possible.

2) They are ecologically valid.
3) They demonstrate "clinical utility," that is, they are familiar to the clinician.
4) They have been validated on patients with specific types of brain damage

Further recommendations for tests selection include Hartman's (1995) proposal that the neuropsychological test battery selected for neurotoxicology assessment should be comprehensive and adaptable to field conditions. Furthermore, confounding factors such as the age of participants should be factored out, at least for research purposes. Results should also be reproducible. Anger and Cassitto (cited in Hartman, 1995) recommend the use of computer-based tests for ease of administration and accuracy. Batteries should be experimentally and psychometrically valid. Tests should also measure functioning known to produce subclinical changes in neuropsychological functioning. These include reaction time/motor response; fine motor coordination, cognitive efficiency, attention and mood. Although these recommendations are valid, they do not point to a theoretical underpinning for the selection of these tests.

2.4.3.3 Current Trends in Assessment Methodology

Evaluations of neurotoxic damage are rarely done exclusively by neuropsychologists. Rather neuropsychologists form part of an interdisciplinary team that makes use of a variety of methods to assess the damage incurred (Hartman, 1995, Rosenberg, 1995). These professionals usually represent the following disciplines: neurotoxicology, occupational medicine, psychiatry, epidemiology, biology, industrial hygiene and pharmacology (Hartman, 1995). More and more neuropsychological methods are incorporated in these assessments (Tilson, 2000).

Neuropsychological toxicology assessments are employed in clinical, forensic and research arenas. Even though the focus of this dissertation is on the research context, both clinical and forensic assessments are briefly reviewed to provide a context for the interpretation of relevant studies reviewed in later chapters. Each of these contexts employ these assessments to meet different objectives. This influences the nature of assessments and the methodology employed. Of the publications reviewed in this dissertation, the majority are from the research context, a few comprise clinical case studies and one was conducted for forensic purposes. The following section is divided according to these contexts. This is done to facilitate the development of an understanding of the assessment process and the identification of methodological best practices. In addition, these factors are relevant to the review process of this dissertation. The extent to which the studies reviewed in the following chapters adhered to the methodological best practices identified here will determine the confidence with which findings from these studies can be interpreted.

2.4.3.3.1. Neuropsychological Toxicology in the Clinical Context

Clinical evaluations of individual patients who have been exposed to neurotoxic chemicals often occur only when symptoms are already apparent. In these cases, neuropsychological assessments form part of an interdisciplinary evaluation to determine the extent of damage suffered by the individual. Neuropsychologists may form part of an interdisciplinary team of neurologists, neurophysiologists, occupational physicians, psychiatrists, clinical psychologists and even ear, nose and throat specialists (Harris & Blain, 2004).

The role of the neuropsychologist in the evaluation of patients exposed to neurotoxic chemicals in the clinical setting is not exclusively diagnostic. Often neuropsychologists are called upon to determine the premorbid functioning of the affected individual (Stellman et al., 1998*)*. Neuropsychologists may also assist with the planning of rehabilitation and determining the impact of the neurological deficit on the patient's daily life (Sbordone & Long, 1996). FIGURE 2-4 delineates the role of the neuropsychologist as well as the management of a patient exposed to neurotoxic chemicals.

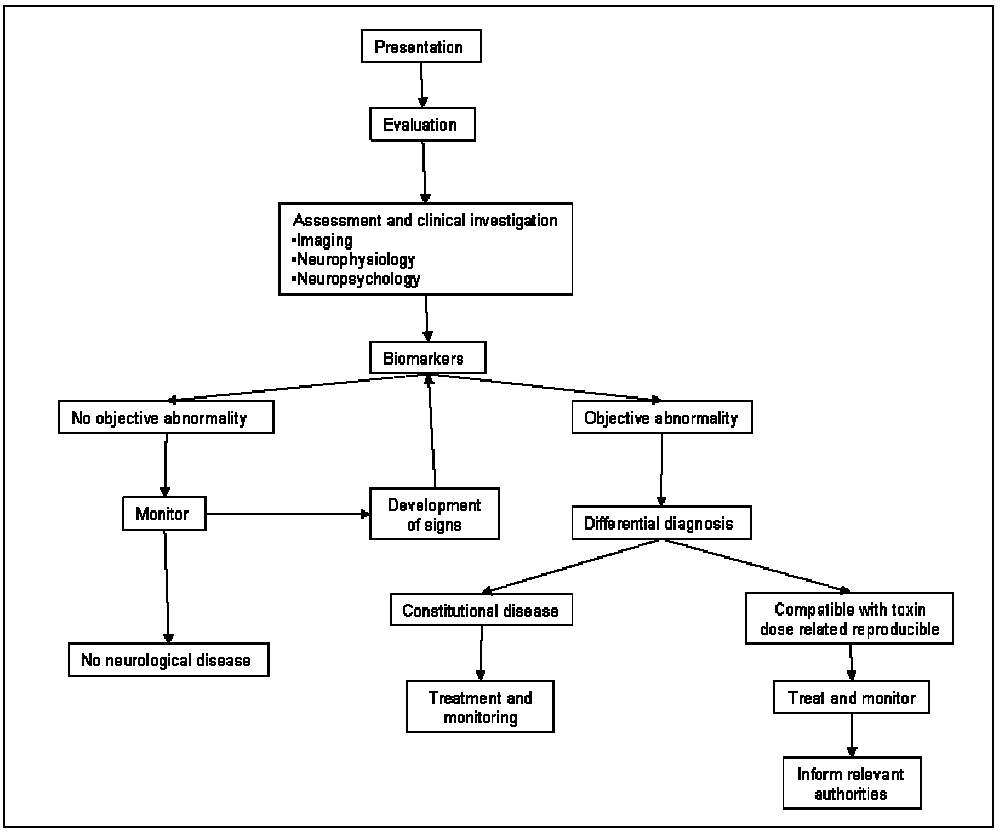

Figure 2-4: The role of neuropsychological evaluation in the assessment and management of patients' exposure to neurotoxic chemicals (adapted from Harris & Blain, 2004, p.32)

A number of case studies conducted on patients in the clinical setting are included in the following chapters. Although these studies usually make use of very small sample sizes, for example one patient, these small samples facilitate the use of in-depth investigations and may provide information that cannot be obtained during the evaluation of large research cohorts. Therefore, although these findings are not generalisable, they are included in the review for this purpose.

2.4.3.3.2. Neuropsychological Toxicology in the Forensic Context

Clinical neuropsychologists may also be called upon to conduct neuropsychological evaluations of patients exposed to neurotoxic chemicals for forensic purposes. In these cases, the psychologist may be required to provide their opinion on the nature and extent of the damage based on methods and techniques generally used and accepted by the scientific community (http://www.rvi.net/~fluoride/000102). The neuropsychologist may be asked to provide information on the following issues (Lees-Haley, 1995).

- the difference between the patient's functioning prior to and after exposure
- the nature and extent of the injury
- whether the injury may have been as a result of neurotoxic exposure
- the impact of the injury on the functioning of the patient
- the probability of remediation
- the prognosis

Due to the current political nature of neurotoxic exposure and the possibility of large compensations being granted to patients, neuropsychologists who conduct assessment for these purposes should be aware of the possibility of malingering, lack of motivation on tests, chemophobia, response bias and third party influence on assessments. Assessments could be further compromised by unreliable norms, or a complete absence of norms (Lees-Haley, 1995).

2.4.3.3.3. Neuropsychological Toxicology in the Research Context

Unlike the majority of clinical and forensic evaluations, evaluations for research purposes are conducted on many individuals at one time. Assessments may also be conducted on participants whose symptoms are not apparent, such as in the case of chronic low-level exposure (Stellman et al., 1998).

Neuropsychological toxicology research is conducted predominantly for two reasons. First, it may determine whether or not neuropsychological outcomes are altered by exposure to certain neurotoxins, as an indication of brain damage. Second, it may determine the exposure

levels at which symptoms of neurotoxic injury occur as an attempt to determine safe exposure levels (Lucchini et al., 2000; Stephens & Barker, 1998).

Currently no adverse effect levels (NOAEL) are calculated by determining the largest dose for which toxic effects are not observed and then dividing this number by an uncertainty number to provide an indication of a safe exposure level (Tilson & Mitchill, 1992). However, this does not consider members of the public who may be hypersensitive to exposure to certain neurotoxins. It also fails to take into consideration the long-term effects of neurotoxic exposure, as well as the fact that some damage from neurotoxins may only become apparent after many years (Zakrzewski, 1991). It is little wonder that authors such as Landrigan, Graham and Thomas (1994) identify this method as inadequate. Weiss and Elsner (1996) highlight the methodological difficulty of using this medical model to quantify more abstract and divergent behavioural processes.

In addition to the assessment of people who are accidentally poisoned or exposed to neurotoxins through occupational exposure, neuropsychological toxicological research has been conducted on volunteers who are exposed to neurotoxic chemicals in an ”exposure chamber”. This method of investigation is ethically questionable. A large portion of the neuropsychological toxicology research obtained for this review was conducted on industrial, mine and farm workers as well as members of the public who are exposed to these chemicals as they go about their daily lives. This type of research also makes it possible to assess the long-term effects of acute high-level exposure as well as the impact of chronic low-level exposure.

Neurotoxic exposure can be assessed using cross-sectional, longitudinal or correlation designs. As in the clinical and forensic assessment, the principles of test theory and proper research design are applicable to all research studies conducted in this field. However, the nature of neurotoxicology research requires a few additional considerations to ensure the reliability and validity of the research process. When using cross-sectional studies, Stephens and Barker (1998) recommend using matched controls rather than random controls to control for variables that cause changes in neuropsychological test outcomes that may mimic the effect of neurotoxic damage. These include gender, education, culture, language, age, sociodemographic factors and occupation. Anger et al. (1997) recommend that balanced control groups be considered when the percentage variance between groups is larger than 10%. Maurissen (1995) and Jamal, Hassen and Julu (2002) also recommend the use of a double blind methodology for these assessments. An additional consideration, which may not so easily be controlled for, is that there are approximately 70 000 chemicals found in our homes, school and offices (Rapp, 1996). Therefore, it is possible that control group participants are unknowingly exposed to neurotoxic chemicals along with experimental groups.

When conducting longitudinal studies, participants' pre- and post-exposure data form their own control group. This limits the number of possible confounding variables associated with a control group. However, researchers should control for the practice effect. The practice effect may be minimised by training participants on the assessment instrument to an optimal level before undertaking the initial assessment. Tests that are resistant to the practice effect may also be used (Anger, Rohlman, Sizemore, Kovera, Gibertini, & Ger, 1996; Stephens & Barker, 1998).

Confounding variables that mimic the effects of neurotoxic exposure should also be considered during the selection of control and experimental groups, as well as during interpretation of results (Hartman, 1995; Leez- Haley, 1995; Anger et al., 1997). Such confounding variables include medication use, psychoactive substances, alcohol abuse, other drug abuse, previous head injury, lack of sleep, tobacco, caffeine withdrawal, systemic illness and nutritional status.

The use of a correlational design is another way of controlling for the numerous confounding variables that may bias the findings of a neuropsychological toxicology study. This type of design is made possible through advances in quantitative measures of neurotoxic exposure levels, such as the use of occupational hygiene methods, or the analysis of neurotoxins or their metabolites in the body fluids of participants. However, correlational designs do not indicate causality but only relationship, which must be considered in the interpretation of results (Babbie & Mouton, 2001).

2.4.3.4 Interpreting Results and Drawing Conclusions from Neuropsychological Toxicology Assessments

Due to the vast number of confounding factors that could bias neuropsychological toxicology studies and the often subtle nature of deficits, the interpretation of neuropsychological toxicology assessments can only be described as tricky. As previously discussed, neuropsychologists in clinical, forensic or research settings often need to draw certain conclusions regarding the neurotoxic damage sustained by the patient. These may include determining premorbid functioning, the probability that a specific toxin resulted in the presenting lesion, the severity of deficits and contributing to the development of NOAEL.

2.4.3.4.1. Determining Premorbid Functioning

Neuropsychologists in clinical and especially forensic settings are often required to determine premorbid functioning. In the past neuropsychological findings were compared against so-called "hold functions," which are neuropsychological constructs such as vocabulary (that may

be measured with the Vocabulary subtest of the WAIS-R/III) (Lezak et al., 2004). This form of crystallized intelligence is presumably resistant to neurotoxic and many other forms of brain damage and may be used to give an indication of premorbid functioning and the extent or progression of neurotoxic damage. This practice is, however, questionable (Stephens & Barker, 1998). The use of previous records, such as educational or occupational achievement and a complete history, or measures such as the Barona index or National Adult Reading Test may prove more useful in determining premorbid functioning (Lezak et al., 2004). The National Adult Reading Test has also been used in South Africa to determine premorbid functioning.

2.4.3.4.2. Determining Toxin-Lesion Causality

Neuropsychologists in clinical, forensic or research settings may need to draw conclusions as to the probability that a specific toxin resulted in the presenting lesion. In these cases, Stephens & Barker (1998) recommend that the Brandford-Hill criterion be used. In this method, six indications of causality are considered (Stephens & Barker, 1998):

1. Temporal relationship: this holds that exposure to the neurotoxin must occur before the onset of symptoms.
2. Biological gradient: symptoms are proportional to exposure intensity and duration.
3. Specificity and consistency: the association between exposure and symptoms is confirmed by different researchers investigating different populations and using different methods. The neurotoxin is also shown to produce specific symptoms when isolated from other neurotoxins.
4. Biological plausibility: the mechanism of damage must be plausible.
5. Strength of association: there is a strong association between the disease and the toxin.
6. Coherence: data regarding the effects of exposure to a particular neurotoxin are consistent across different disciplines.

2.4.3.4.3. Determining the Severity of Deficits

Once causality has been determined, the severity of the changes in neuropsychological outcomes should be assessed. There are two conflicting discourses surrounding these interpretations. The first position holds that slight changes in neuropsychological outcomes should not be cause for alarm as long as they fall 'within normal limits' and do not constitute a disease that will require a participant or patient to receive clinical attention (Bellinger, 2004). The second position states that slight changes in neuropsychological outcomes merely reflect the tip of the iceberg and may be indicative of even more worrisome signs that have gone undetected (Bellinger, 2004). It also states that small changes in the whole population may have a large effect, for example, a global decrease in two IQ points may impact significantly

on the economy. Furthermore, small changes may have a severe impact in a critical area, for example, a temperament change in an employee in a nuclear generator may have disastrous consequences (Stephens & Barker, 1998).

2.4.3.4.4. Risk Assessment and Determining NOAEL

The primary objective of neuropsychological toxicology is formulating risk. This is often done by determining NOAEL. As previously stated, the current methods of determining NOAEL may require revision (Weiss & Elsner, 1996). The development of improved NOAEL, which provide an effective evaluation of risk, is a formidable challenge and a working process. This is augmented by the possible subclinical nature or absence of symptoms resulting from low-level exposure, which may nonetheless accumulate into clinical deficits over many years of exposure (Stellman et al., 1998). NOAEL may be determined by data collected by members of the interdisciplinary team, such as biomarkers of concentrations of toxic substances in body fluids or tissues, or changes in biochemical processes due to neurotoxic exposure. These may be correlated with changes in neuropsychological outcomes to determine if a dose-response relationship exists (Landrigan et al., 1994). In addition to the development of NOAEL, neuropsychological toxicology research contributes to the understanding of the brain-behaviour relationship, and the impact of neurotoxins on this (Weiss & Elsner, 1996). The understanding of these neurotoxic mechanisms will assist in these calculations and in the development of new improved NOAEL that incorporate the diverse susceptibility of different individuals and the impact of long-term exposure (Landrigan et al., 1994).

Ideally, no individual should ever be exposed to neurotoxic chemicals, due to the uncertainty of the long-term impact of exposure. However, due to our general dependence on chemicals such as pesticides, this option (at least in the foreseeable future) does not seem possible. Therefore, the quagmire of interpretation of neurotoxic results lies in setting standards that are too restrictive, and not providing the public with adequate protection.

2.4.4 Further Considerations in Neuropsychological Toxicology Assessments

The following considerations are relevant to the neuropsychologist conducting an evaluation on a participant or patient with neurotoxic brain injury in the clinical, forensic or research arenas. These factors are reviewed here to provide insight into the impact of these on the findings of various studies reviewed, and may thus render these studies more meaningful.

2.4.4.1 Assessment Considerations for Chronic Low Level and Acute High Level Exposed Subject

For an in-depth explanation on the difference between chronic low-level exposure an acute high-level exposure please refer to the section on factors influencing the extent of neurotoxic damage. In the following section methodological considerations for the evaluation of these type of exposure will be reviewed.

2.4.4.1.1. Chronic Low-Level Exposure

Chronic low-level exposure to neurotoxins often causes insidious and progressive damage. The neuropsychologist should be aware that during the early stages of exposure symptoms may easily go undetected. The signs of neurotoxic exposure may only become apparent after many years, rendering biological monitoring ineffective (Stellman et al., 1998). In addition, due to the possibility that symptoms may only become apparent in later life, neurological signs resulting from toxic exposure must be discriminated from changes in neuropsychological outcomes due the normal ageing process or due to the onset of neurodegenerative disease resulting from other causes. This is discussed further in the section on individual differences.

Secondly, the study of chronic neurotoxin exposure is complicated by the fact that it is almost impossible to determine if the neurotoxin under investigation is the only one to which the patient or research participant was exposed (Stellman et al., 1998). It is also quite likely that the individual was exposed to more than one neurotoxin over an extended period of time. It is generally accepted that the interaction of neurotoxins within an individual may increase the damage they cause (Rosenberg, 1995). It is therefore important that researchers keep this in mind during the design of the study as well as when interpreting results, especially when causality is to be determined.

2.4.4.1.2. Acute High Level Exposure - Clinical Poisoning

The study of acute symptoms poses fewer methodological challenges than does the study of chronic low-level exposure. For one, symptoms have a rapid onset and it may therefore be easier to identify the responsible neurotoxin through biological monitoring (Stellman et al., 1998). Symptoms are also more likely to be apparent and less likely to go undetected during psychological testing. The influence of multiple chemical exposure should, however, also be considered.

A single high-level exposure may result in permanent damage, which may only become apparent many years after exposure. This is discussed further in the section dealing with the association between degenerative disease and exposure to neurotoxins. However, it is important for neuropsychologists wishing to investigate such symptoms to ensure that sufficient time is allowed for acute effects to subside after exposure and before assessment.

This is to ensure that the effects measured are chronic and not acute effects, to prevent false positive findings (Stephens & Barker, 1998).

2.4.4.2 Qualitative and Quantitative Considerations for Test Selection

Computerised batteries are increasingly being used in research, while traditional pen and paper methods may be more widely practised in the clinical setting. The use of either computer assessments or pen and paper methods may influence the findings of a study. Computer-based research provides a number of advantages over the pen and paper method with regard to objectivity and increased sample size (Bolla, 1996; Strollery, 1996). However, computerised batteries minimise the availability of a qualitative assessment by a skilled practitioner, who may notice deficits in a patient while taking a patient history or conducting an assessment that may not be assessed in the computerised battery. For example, as previously mentioned, frontal lobe damage is not easily assessed in a structured assessment. These issues led Spurgeon (1996) to question the use of these diagnostic tests for research purposes. It also highlights the importance of taking a complete patient history, the omission of which Sbordane and Long (1996) refer to as a "grave error" (p.29). Also important is verifying data with the findings produced by assessments by other members of the interdisciplinary team.

2.4.4.3 Sample Characteristics

A number of participant characteristics may determine the outcomes on neuropsychological assessments. It is therefore recommended that matched controls are used. These characteristics include gender, education, culture, language, age, occupation, and sociodemographic and cultural factors (Lezak et al., 2004; Stephens & Barker, 1998). As neuropsychological toxicology investigations are conducted around the world, it is especially important to consider the cultural validity of these assessments to allow the valid comparison of findings. Culture may impact on neuropsychological test outcomes as it determines which cognitive abilities are learned, what is situationally relevant, what mode of thinking is used, as well as how people act, feel and understand (Ardila, 1996; Flaskerud, 2000; Kennepohl, 1999; Péreze- Arce, 1999).

2.4.4.3.1. Individual Sensitivity to Neurotoxic Exposure

In addition to the impact of individual differences on the outcomes of neuropsychological tests, individual differences also determine the nature and extent of the damage sustained by exposed individuals. Possible factors that could cause individual sensitivity include gender, genetic influences, familial sensitivity, co-exposure, nutritive deficiency, pathology of respiration, hepatic biliary excretion system and alcoholism (Bouchard, Mergler, Baldwin,

Sassine, Bowler & MacGibbon, 2003). Members of the population range from those who are less sensitive to neurotoxic exposure to those who are hypersensitive. The sensitivity of a population to a particular neurotoxin may be represented in a dose-response curve. This is a graphic representation of the number of people in a normal distrubtion who show signs after exposure to a neurotoxin, with increases in dose. Hypersensitive individuals form the very long tail that approaches zero on this normal distribution (Winder, 2002). As these are the individuals most likely to be affected by exposure to neurotoxic chemicals, they are most likely to resign their jobs due to these effects and therefore never form part of cross-sectional studies.

A large number of studies have been published on multiple chemical sensitivity, also known as idiopathic environmental disease. Multiple chemical sensitivity is a debilitating disorder in which the patient reacts in a hypersensitive way when exposed to multiple chemicals (Bailer, Rist, Withöft, Paul & Bayer, 2004; Caress, Steinemann & Waddick, 2002; Haumann, Kiesswetter, van Thriel, Blaszkewiez, Golka & Seeber, 2003, Kreutzer, 2002; Miller & Mitzel, 1995). Many theories have been developed to explain the disease process of multiple chemical sensitivity. These include immunological, psychological, neurological and toxicological theories (Winder, 2002, Miller, Ashford, et al., 1997). However, two poles have developed in the current research on multiple chemical sensitivity: those supporting a toxicological aetiology of multiple chemical sensitivity and those who support the position that multiple chemical sensitivity is psychological in origin and is closely associated with somatoform disorder (Bailer et al., 2004). Some researchers have adopted an intermediary position, suggesting that multiple chemical sensitivity symptoms are due both to environmental and psychological factors (Klopper & Fahron, 1995; Lehrer, 1997; Herr et al., 2004). Despite this inconclusiveness, the increasing number of sufferers as well as the severity of the disease makes this disorder an important consideration in any toxicological research. The current estimated incidence of multiple chemical sensitivity is between 12.6% and 15.9%, with up to 30% less severe cases (Haumann et al., 2003).

The age of participants also greatly impacts their sensitivity to neurotoxins and their outcomes on neuropsychological assessments. These are now reviewed in more detail.

2.4.4.3.2. Developmental Neuropsychological Toxicology

The susceptibility of people to neurotoxins runs in a u-shaped curve. The very old and the very young are the most at risk due to the physiological differences of these groups compared to the young adult and middle-aged population (Dietert et al., 2000; Hartman 1995).

2.4.4.3.2.1. Paediatric assessment and exposure

Foetuses and young children are more sensitive to neurotoxic exposure for a number of reasons. Firstly, the brain of foetuses and young children are less protected from neurotoxic chemicals due to absence of a fully developed blood-brain barrier, which prevents most neurotoxins from reaching the brain in adulthood. The placenta provides some measure of protection to the developing foetus; however, this is far more permeable than a mature blood-brain barrier. Secondly, developmental processes (in children) and the basic structure of the brain (in foetuses) occur in stages, and the successful completion of all previous stages is a prerequisite for the successful completion of later stages. This is of particular concern in prenatal exposure, as toxic insult that occurs before active cell division causes the death of precursor cells, greatly diminishing the number of cells that may now be generated from these cells. Thirdly, immature biochemical systems may be more sensitive to neurotoxins. Fourthly, babies and children are expected to live for a longer period of time, leaving more years for potential exposure. Finally, children may be exposed to toxins more often that adults as they are closer to the ground, are less likely to wash their hands and more likely to put things in their mouths. Relative to their body size, children also eat, drink and breathe more than adults (Harris & Blain, 2004; Hartman, 1995; Levitt, Doyle, MacIsaac, Grava-Gubins, Ramsay, & Rosser, 1997; Goldman & Koduru, 2000; May, 2000; Weiss, 2000; Rohlman, Anger, Tamulinas, Philips, Bailey & McCauley, 2001; Weiss & Elsner, 1996). It is not surprising that even though children are not directly exposed to neurotoxic chemicals in industry, they still carry 43% of the world's environmental disease (Crain, 2000).

Early exposure to neurotoxins is associated with disease and mental retardation (Claudio et al., 2000). This incidence is increasing in countries such as the United States (Goldman & Koduru, 2000; Landrigan, 2001). Although the aetiology of many of these disorders is not fully understood, there is rising concern about the potential role of environmental neurotoxins in the development of these disorders (Goldman & Koduru, 2000, May 2000). We may expect to find neurotoxin exposure-induced developmental disorder among the other developmental disorders in a population. This poses additional challenges for the neuropsychological toxicology assessment of children, as it may be difficult to determine the aetiology of the deficits assessed. In addition, the natural developmental process occurring in children should be considered for the effective assessment of this group (Costa, Azambuka, Portuguez & Costa, 2004; Temple, 1997, Weiss, 2000; Yeates, Ris & Taylor, 2000). Further neurotoxicology research into the interaction of these developmental processes with neurotoxic exposure is needed, especially given that factors such as an enriched environment appear to provide some measure of protection against neurotoxic damage (Schneider, Lee, Anderson, Zuck & Lidsky, 2001).

2.4.4.3.2.2. Geriatric assessment and exposure

Geriatrics represent the second high risk developmental group. Physiological factors that increase the vulnerability of this group include decreased ability of the kidneys and liver to filter and metabolise neurotoxins, and decreased neurotransmitter reserves. In addition, due to their older age, this population group has been exposed to neurotoxic chemicals for a longer time. A lifetime of subclinical exposure may either develop into a clinical syndrome or may exasperate the normal ageing process (Rosenberg, 1995).

As in the assessment of children, it may be difficult to distinguish between neurotoxin-induced developmental disorders and other degenerative disorders. The difficulty in distinguishing between neurotoxin-induced degenerative disorders and those with other causes hinders the assessment of geriatric neuropsychological toxicology. The neurodegenerative disorders that are commonly associated with neurotoxic insult are Parkinson's, Alzheimer's, and vascular dementia (Rosenberg, 1995). TABLE 2-2 indicates the neurodegenerative disorders associated with exposure to the neurotoxins reviewed here.

Table 2-2: Neurodegenerative diseases associated with neurotoxic exposure

	Alzheimer's disease	**Parkinson's disease**	**Vascular dementia**
Carbon disulphide	x	√ (Hageman et al., 1999; Rosenberg, 1995	√ (Lacunar infarction) (Cha, Kim, Han, Kim, Yim & Kim, 2002)
Manganese	√ (Srivastava & Jain, 2002).	√ (Aschner, 2000).	x
Organophosphate	x	√ (Kamel & Hoppin, 2004).	√ (Kamel & Hoppin, 2004).

√ Association between neurotoxin and neurodegenerative disease reported in the literature
X No association between neurotoxin and neurodegenerative disease found in the literature.

When assessing elderly patients exposed to neurotoxins neuropsychologists should not only be aware of the possible role of neurotoxins in neurodegenerative disease, but should also consider the impact of the natural ageing process on the results. However, as none of the studies reviewed in the following chapters selected geriatric samples, this is beyond the scope of this review. Readers who are interested in further information on this topic are referred to Albert (1981) and Lindeboom and Weinstein (2004).

2.5 Summary

This chapter reviewed the history and origins of neuropsychological toxicology, together with the contributing disciplines of neuropsychology and neurotoxicology. This provided a context for the field in terms of past, current and future practices. Additionally, key information from these disciplines was investigated in order to better understand the findings of the publications reviewed in the following chapters. The next chapter delineates the process followed for the review of these publications and the process by which meaning is derived from them.

CHAPTER 3: METHODOLOGY

3.1 Introduction

The two key objectives of this study are, firstly, to investigate the role of dynamic brain localisation theory in neuropsychological toxicology, and secondly, to investigate methodological best practice for assessments in this field. These objectives are addressed in the form of a review of studies conducted in this field. More specifically, the review focuses on neuropsychological studies that assess damage caused by three neurotoxins: carbon disulphide, manganese and organophosphate. These three neurotoxins were chosen as representatives of solvents, metals and pesticides, respectively. Additionally, their selection was motivated by the relatively large numbers of neuropsychological toxicology studies that have been published on these. This facilitated a review. The studies discussed above therefore constitute the data for these investigations. This chapter elucidates how these publications were obtained and reviewed.

3.2 Step 1. Delineation of the Field

The literature chapter serves two purposes. Firstly, the nature and history of neuropsychological toxicology is investigated to provide a context for all future recommendations. Secondly, pertinent information such as findings published by other scholars regarding neuropsychological toxicology assessment methodology are combined with information elucidated by the current review, to establish recommendations for methodological best practice in the field. These are presented in the final chapter. Relevant information for this chapter was obtained from a number of fields such as neurology, neurotoxicology, occupational medicine, psychiatry, public health administration, pharmacology, cross-cultural psychology and agriculture (Hartman, 1995). Information was also gathered from appropriate organisations such as the American Board of Neuropsychological Toxicology, the World Health Organisation and South African Government websites such as the Department of Labour and the Occupational Health and Safety Act. Dr Claassen of the Department of Physiology at the University of Pretoria also provided additional information regarding occupational hygiene in South Africa.

3.3 Step 2. Hunting for Data

The collection of studies reviewed in this dissertation was as systematic and complete as time and resources permitted. This process is discussed below. The following databases were searched for relevant publications: EBSCO, SABINET, PsycINFO, PUBMED, and Science Direct.

The following keywords were used to search the databases listed above:

Neuropsycholog* toxicology
Behaviour* toxicology
Psychiat* toxicology

Neuropsycholog* and Carbon Disulphide
Behaviour* and Carbon Disulphide
Psychiat* and Carbon Disulphide
Alzheimer's and Carbon Disulphide
Neuro degenerative and Carbon Disulphide
Parkinson's and Carbon Disulphide
Neuropsycholog* and Carbon Disulfide
Behaviour* and Carbon Disulfide
Psychiat* and Carbon Disulfide
Alzheimer's and Carbon Disulfide
Neuro degenerative and Carbon Disulfide
Parkinson's and Carbon Disulfide

Neuropsycholog* and Manganese
Behaviour* and Manganese
Psychiat* and Manganese
Alzheimer's and Manganese
Neuro degenerative and Manganese
Parkinson's and Manganese

Neuropsycholog* and Organophosphate
Behaviour* and Organophosphate
Psychiat* and Organophosphate
Alzheimer's and Organophosphate

Where possible, information that has not been reported in the literature was obtained by direct correspondence with authors. No unpublished studies were used. Authors were merely contacted, when nessessary, to clarify points regarding studies which had already been published.

3.4 Step 3. Review of Relevant Publications

The research process is seldom linear. This was the case the current study. Once the review process had commenced it became clear that an objective method of determining the extent

to which methodological factors and confounding variables influence the outcomes of these studies would be required, if any valid conclusions were to be drawn from the findings of these studies. The methodologies used by the various authors reviewed alluded to problems in the investigation of neurotoxins as well as solutions to these problems. This information was combined with recommendations published by other authors conducting neuropsychological toxicology evaluations. In addition, certain criteria were adapted from a review study conducted by Jamal, Hansen and Julu (2002) in which only cross-sectional studies were conducted (presumably because of their prevalence) on both medical zoological and neuropsychological evaluations of organophosphate exposure.

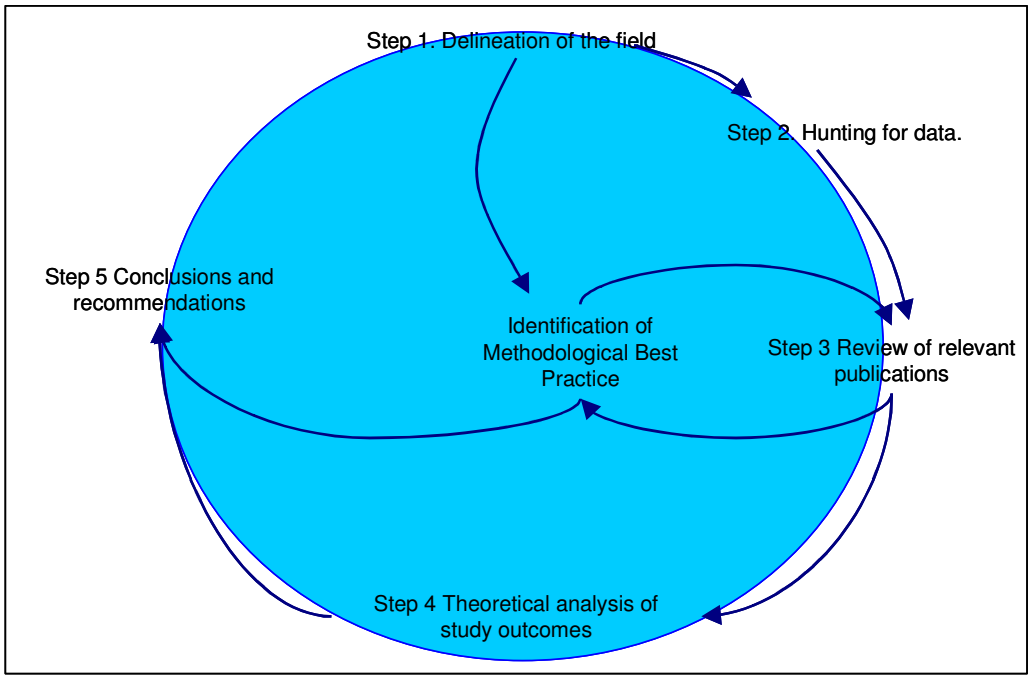

Figure 3-1: The methodological process

Numerous confounding variables may bias the findings of neuropsychological toxicology investigation. The various studies reviewed here controlled for a number of different factors. These confounders ranged widely and included the following; age, alcohol consumption, caffeine, central nervous system pathology not due to exposure, computer familiarity, depression, diabetes mellitus, systemic disease, drugs, education, ethnic group, eye disease, hearing loss, lack of sleep, language, nutritional status, occupation, other neurotoxic exposure, peripheral nervous system pathology, gender, sleep, smoking and socioeconomic status. Maurissen (1995) further identifies work environment, experimenter effect, expectancy, placebo effect and malingering as possible confounding factors in neurotoxicology research. The type of research design employed may determine how these confounding variables are controlled for, and may influence findings. Aspects of the assessments that are considered in the review process are outlined below.

3.4.1 Longitudinal Studies

The use of a longitudinal design controls for a number of the confounding variables discussed above, as each participants becomes their own control group. However, longitudinal studies may still be biased by the impact of natural ageing on participant results, as well as the practice effect (Stephens & Barker, 1998).

3.4.2 Correlation Studies

Correlational designs are also able to control for a number of these confounding variables. This method may provide a good indication of test sensitivity as exposure level (an indication of damage sustained) is correlated against neuropsychological test outcomes. However, correlation designs do not provide an indication of causality and interpretations may be hindered by the effect of third variables (Babbie & Mouton, 1998). In the case of neuropsychological toxicology, age may act as a third variable as older participants are likely to have been exposed for longer periods of time and have declining neuropsychological outputs due to the natural ageing process.

3.4.3 Cross-sectional Studies

The majority of studies sourced for this review were true experimental design, cross-sectional studies in which the results of an experimental group (exposed group) are compared to those of a control group (unexposed group). Due to the numerous confounding variables listed above which may mimic or hide the deficits arising from neurotoxic damage, Stephens and Barker (1998) recommend using matched controls in neuropsychological toxicology. Anger et al. (1997) conducted a study to investigate the influence of subjective variables on 18 tests widely used for neuropsychological toxicology assessments. Anger et al. (1997) conclude that education, cultural group, age and gender all significantly influence performance on these tests and should be controlled for.

Another factor to consider in the interpretation of cross-sectional studies is that some of the studies reviewed here used control groups that were also exposed to the neurotoxin under investigation. This practice may reflect an attempt to find participants with similar demographics, in which workers from the same factory are often used. The use of a control group that is exposed to the neurotoxin in question can limit the findings of the study, as this group may have sustained damage due to the exposure to the neurotoxin. Therefore, comparisons between the experimental and exposed control groups may result in false negative findings.

Jamal, Hansen and Julu (2002) and Maurissen (1995) recommend using a double-blind study to prevent purposeful or accidental interpretation of participant symptoms in line with the hypothesis of the study. The use of a double blind method was often not reported in the studies reviewed. The effect of not using a double-blind methodology may be minimised by using a computerised assessment. Computer assessments are gaining in popularity, although this has some disadvantages with respect to the exclusion of the expertise of a skilled practitioner. These assessments are widely acclaimed for increasing the standardisation of the assessment process (Bolla, 1996; Strollery, 1996).

3.4.4 Case Studies

The case studies reviewed in this study often provide valuable in-depth information about psychological symptoms reported by family members, which is often not possible in quantitative studies with larger cohorts. Although these studies were conducted on very small samples and are therefore not generalisable, these small sample sizes often facilitated the use of a number of assessment instruments not used in large cohorts (Banister, Burman, Parker, Taylor & Tindall, 1999). In addition, assessments were often conducted by skilled administrators who provided insight through qualitative findings.

3.5 Step 4. Theoretical Analyses of Study Outcomes

The primary aim of this study is the investigation of dynamic brain localisation theory as a theoretical guide in the selection of neuropsychological tests for neurotoxic studies. This was accomplished by considering both test specificity and test sensitivity.

“Specificity refers to the probability of correctly identifying a normal individual or an individual from another clinical population intact with respect to the test under construction” (Lezak et al., 2004, p.149).

“Sensitivity refers to the probability of correctly detecting abnormal functioning in an impaired individual” (Lezak et al., 2004, p.149).

I investigate sensitivity of neuropsychological tests that measure deficits associated with the specific pathology induced by the chemical mechanism of the neurotoxins reviewed here. As stated previously, in addition to the intrinsic nature of the neuropsychological tests, the impact of exogenous and methodological facts on their outcomes is considered. Furthermore, as the level and duration of neurotoxic exposure provides an indication of the nature of brain damage sustained by participants, and hence their performance in neuropsychological tests, this is also reviewed.

3.6 Step 5. Conclusions and Recommendations

Finally, conclusions and recommendations are presented, together with answers to the main questions posed in the objectives of the study. These include a summary of the findings regarding the use of dynamic brain localisation theory in neuropsychological toxicology investigations, and recommendations for best practice methodology for these investigations.

CHAPTER 4: CARBON DISULPHIDE

4.1 Introduction

Carbon disulphide is one of the few organic solvents clearly shown to cause damage through chronic exposure (Rosenberg, 1995). The danger it poses as a neurotoxin was noted immediately after it was introduced into industry around the 1900s. Workers from carbon disulphide factories were frequently reported to suffer from “acute insanity” and displayed a “violent manical condition” (Hartman, 1995 p.192). It was also not uncommon for workers to commit suicide by jumping from the top factory rooms. Unfortunately, factories remedied this by placing bars on the windows rather than introducing safety measures (Hartman, 1995). Carbon disulphide is still widely used in the rubber and rayon industries, and is also used in the production of carbon tetrachloride, allphane films and pharmaceuticals. Carbon disulphide is used in the grain industry to control pests, as well as a solvent for wax, fats and oils (Canadian Centre for Occupational Health and Safety, 2004; Chapman, Stauter, Henning, Levine, Matthews & Peters, 1991; WHO, 2002). Currently the internationally accepted exposure limit for carbon disulphide is <10ppm (Gobba & Cavalleri, 2003). However, an increase in subjective symptoms, as well as changes in neuropsychological outcomes, have been reported at concentrations lower than 10ppm (Takebayashi, Omae, Ishizuka, Nomiyama & Sakarai, 1998). Although the increase in knowledge regarding carbon disulphide has lead to a decrease in exposure, high exposure levels are still seen in developing countries (Rosenberg, 1995; Rounds, 1998).

Carbon disulphide exposure results in damage to the cardiovascular, reproductive and ophthalmologic systems. The main target of damage, however, is the nervous system (Rounds, 1998). Exposure to carbon disulphide leads to neuronal degeneration throughout the cerebral hemispheres, although maximum degeneration occurs in the frontal region (Rosenberg, 1995). Damage has been reported to the globus pallidus, and Purkinje cells, cerebral cortex and the basal ganglia (Rosenberg, 1995; Huang, Chu, Chen, Lin & Shih, 1996). Cha et al. (2002) conducted MRI evaluations on 91 patients suffering from carbon disulphide poisoning to determine the extent of white matter hyperintensity and lacunar infarction. Of the lacunar infarcts found, 39.6% were basal ganglia, and 25.7% were frontal white matter. Cha et al. (2002) reported that this incidence of cerebral lacunae was high, as the expected incidence in the generic population is 7.8% for individuals who do not suffer from cardiovascular disease.

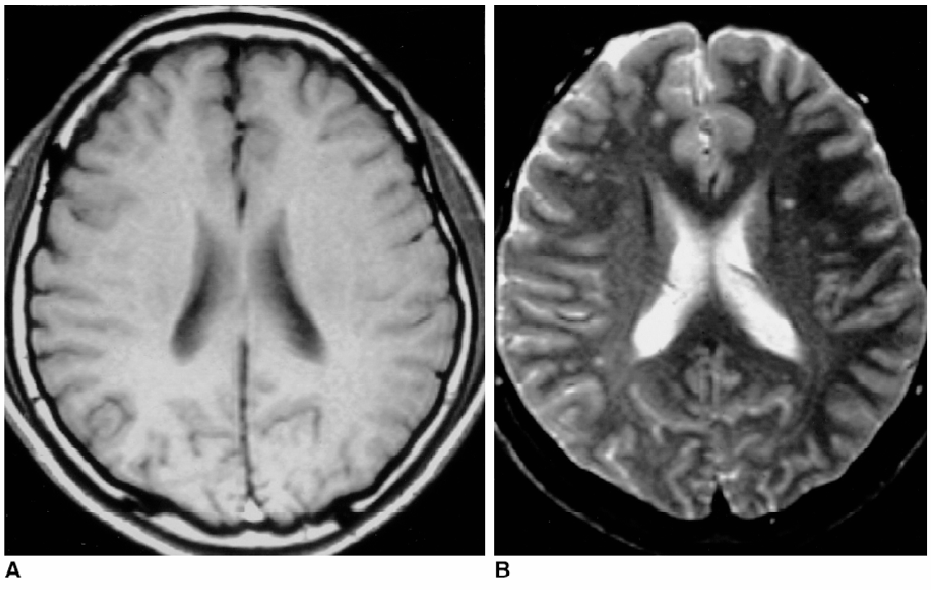

Figure 4-1: MRI depicting between ten and twenty focal white matter lesions of the frontal lobes in a thirty-four year old participant exposed to carbon disulphide for nine years (A= T1 weighted, B =T2 weighted) (Cha et al., 2002 p.158)

Central nervous system damage from carbon disulphide causes prominent psychiatric symptoms such as acute bipolar and psychotic symptoms, delirium, personality changes, impaired cognition, decreased memory and associated parkinsonism (Feldman, Ricks & Baker, 1980; Hartman, 1995; Rosenberg, 1995). Cases of Parkinson's disease have been reported in more than 60% of viscous rayon factory workers, but the level and duration of exposure that result in the development of associated Parkinson's has not been determined (Cho, Kim, Yim, Tak, Lee & Son, 2002; Gobba & Cavalleri, 2003; Rosenberg, 1995).

Symptoms associated with chronic exposure tend to have an insidious onset. Patients may present with tremors, which may develop into ataxia after a few years (Chapman et al., 1991). Other symptoms associated with chronic exposure include loss of colour vision, peripheral nervous system loss of sensation, tingling in the arms and feet, insomnia, depressed mood, mild motor impairment, intellectual impairment, behavioural abnormalities and irritability (Canadian Centre for Occupational Health and Safety, 2004; Gobba & Cavalleri, 2003; Hannu, Tosikalal, Tuomi & Sainio, 2005; Rosenberg, 1995).

Acute exposure is associated with confusion, delirium and serious psychological disturbances including excitability, irritability, uncontrollable anger, emotional instability, nightmares and depression (Canadian Centre for Occupational Health and Safety, 2004; Huang et al., 1996). Exposure to more than 500 ppm or ingestion of 18g will result in psychosis (Takebayashi et al., 1998). This may also result in seizures and may be fatal (Huang et al., 1996; Rosenberg, 1995). Acute damage is usually permanent (Huang, Cheu, Wu, Shih & Chu, 2002)

Seven neuropsychological toxicology studies, conducted on participants exposed to various levels of carbon disulphide, are reviewed in this chapter. This includes all the articles found on this topic during a systematic search of all available databases. (This process is delineated in the methodology chapter). The review of these articles is integrated in the following discussion to expedite the review process and to support the arguments presented. The simultaneous presentation of various aspects of these studies enables the comparison between methods and findings.

The remainder of this chapter is divided into two sections. In the first section, current trends in the neuropsychological assessment of carbon disulphide exposure are reviewed. This not only provides insight into current trends in this assessment but also provides insight into best practices methods. This information is used as the basis for further discussions in the second section of this chapter. The main purpose of the second section is to investigate the reported sensitivity of different neuropsychological tests to damage sustained through carbon disulphide exposure. More specifically, the sensitivity of frontal lobe tests is investigated, as these areas are reportedly affected by carbon disulphide neurotoxicity (Huang et al., 1996; Rosenberg, 1995). In addition, the level and duration of carbon disulphide exposure is considered in the interpretation of test sensitivity. The nature and extent of exposure determines the brain damage sustained by participants (Rosenberg, 1995). This in turn determines participants' neuropsychological test outcomes. Therefore, the test outcomes are interpreted with respect to the extent of damage sustained by participants, as indicated by the nature of their exposure. The choice of methodology, as well as possible confounding variables which may impact study outcomes, are also considered.

Table 4-1 Summary of carbon disulphide studies reviewed.

Authors	Country	Design	Double blind	Sample size	Description of participants	Sex	Age (years)
Aaserud et al. (1990)	Norway	Cross Sectional (clinical investigations)	Not reported	n=16	Viscous rayon workers	Male	Mean age: 56 years Range: 43-65 years
Cho et al. (2002)	South Korea	Cross Sectional (Quasi experimental design)	Double blind	High exposure group n=37 Low exposure group n=37.	Viscous rayon workers	Male	High exposure: Mean age: 55.4 years Low exposure: Mean age: 5.6 years Range not reported
Feldman et al. (1980)	Not reported	Cross Sectional (Case study)	Not double blind	n=1	Worker in viscous rayon	Male	28 years

Authors	Country	Design	Double blind	Sample size	Description of participants	Sex	Age (years)
					factory		
Hanninen, cited in Feldman et al. (1980)	Not reported	Cross sectional design (experimental group and control group)	Double blind	Not reported	Viscous rayon workers	Male	Not reported
Krstev et al., (2003)*	Serbia	Cross sectional design (experimental group and control group)	Not double blind	High level exposure group: n=97 Control group: n=38	Viscous rayon workers	Male	High exposure group: mean age: 41.7 years/ range 26-59 Intermediate exposure group: Mean age 44.2 years/ range 26-61 Control group: Mean age 42.3 years/ range 27-63
Reinhardt et al. (1997)	Germany	Cross sectional design (experimental group and control group)	Double blind	Experimental group: n=222 Control group: n=191	Viscous rayon workers	Male	Experimental group: Mean age: 35 years/ Range 23-59 years Control group: Mean age 33 years/ Range 21-58 years
Takebayashi et al. (1998)	Japan	Cross sectional design (experimental group and control group)	Double blind	High exposure group:: n=309 Low exposure group: n=123 Control group: n=402	Viscous rayon workers	Male	Age not reported

*Krstev, Perunicic, Farkic and Banicevic (2003

4.2 Current Trends in the Neuropsychological Toxicology Investigation of Carbon Disulphide Exposure

This section reviews current trends in the neuropsychological toxicology assessment of carbon disulphide. The review process is structured according to the research process and entails the following. Firstly, the aims of the various studies are reviewed. The questions which are asked in scientific investigations are often more important than the answers which are found. Secondly, the nature of the neurotoxic exposure investigated in the studies reviewed here is discussed to facilitate the comparison of these outcomes relative to exposure level in the second section of this chapter. Thirdly, methodologies employed for these investigations are considered. Different methodologies are vulnerable to the effects of different confounding variables. The extent to which authors control for these variable is considered, since this is an important aspect of the discussion section of this chapter.

Fourthly, the sample characteristics will be summarised. Finally, the rationale for the selection of assessment instruments is considered; and medical, neuropsychological and psychological tests employed in these studies are reviewed. As the rationale for neuropsychological toxicology test selection lies at the crux of this dissertation, a closer look is taken at how this was done. Dynamic brain localisation theory as a tool for test selection is also investigated.

4.2.1 Neuropsychological Toxicology Study Aims as an Indication of the Direction of the Field

The majority of the studies reviewed here, in both clinical and research investigations, had similar aims. The studies were conducted either to characterise the effects of carbon disulphide exposure on participants, and/or to determine whether or not carbon disulphide exposure results in changed neuropsychological outcomes and medical measures, which may be indicative of neurotoxic brain damage. The study aim in Krstev et al. (2003) is an example of a typical objective of these studies: "The aim of our study was to establish the central nervous system dysfunction in workers exposed to different levels of carbon disulphide by neuropsychiatric check-ups and questionnaire 16 (Q16)" (p.81).

The aims of the studies reviewed here are analogous to other neuropsychological toxicology studies. The predominant aim of these studies is firstly, to determine whether neuropsychological outcomes are altered by exposure to certain neurotoxins, as an indication of brain damage; and secondly, to determine at which exposure levels symptoms of neurotoxic injury occur, in an attempt to determine “safe” exposure levels (Stephens & Barker 1998).

4.2.2 The Continuum of Exposure Concentrations and Durations Assessed by Various Studies

The duration and concentration of carbon disulphide exposure determines the extent of damage incurred (Rosenberg, 1995). This in turn impacts on the participants’ performance on neuropsychological assessments. Therefore, neuropsychological assessments are more likely to measure deficits in participants exposed to higher levels and duration of carbon disulphide. It can be concluded that neuropsychological tests that detect deficits in participants exposed to lower levels and duration of carbon disulphide are more sensitive than those that measure deficits at higher levels and duration of exposure. To make these comparisons, the relative exposure levels of each study must be interpreted and converted to the same unit of measure. The following discussion pertains to these calculations. In addition, where possible, a cumulative exposure index is calculated, which combines duration and level of exposure to provide an indication of total exposure.

The measurement of carbon disulphide exposure levels has evolved along with the knowledge of its neurotoxic effects and resultant safety measures. In some of the older studies reviewed, the researchers were unable to determine the level of exposure to participants. Exposure levels in these studies could only be estimated by the analysis of the damage sustained by these participants and their reported subjective symptoms. For example, in the studies conducted by Feldman et al. (1980), the authors speculate that the patient was exposed to a single episode of very high levels of carbon disulphide, as the exposure was sufficient to disintegrate his t-shirt and cause severe disability.

Studies conducted more recently, after 1990, make use of a variety of methods to determine the exposure levels of participants. The concentration of 2-thio-1,3-thiazolid-4-carboxylic acid (TTCA) in urine is measured as a carbon disulphide metabolite to give an indication of exposure level. TTCA levels report, range from 1.28mg/g creatinine (Takebayashi et al., 1998) (low exposure group) to 17.8mg/g creatinine (Krstev et al., 2003) (high exposure group). Occupational hygiene methods of personal air sampling, using methods such as diffusive charcoal badges, were also used to determine exposure levels. Carbon disulphide exposure levels reported by authors varied from 4.02 ppm (Reinhardt, et al., 1997) to 320ppm (Aaserud et al., 1990).

Currently, the internationally accepted exposure limit for carbon disulphide is <10ppm (Gobba & Cavalleri, 2003). Therefore, it is evident that despite the increase in knowledge and regulation of carbon disulphide exposure, the participants in some of the studies reviewed here were exposed to very high concentrations of carbon disulphide. In the study conducted by Aaserud et al. (1990), high levels of carbon disulphide exposure resulted in loss of consciousness in some workers. The patient examined by Feldman et al. (1980) was exposed to sufficiently high levels of carbon disulphide to dissolve his shirt. The participants in the studies by Krstev et al. 2003 and Reinhardt et al. (1997) were occasionally exposed to carbon disulphide levels above Yugoslav and German maximum allowable concentrations, respectively. This is cause for concern because carbon disulphide is one of the few organic solvents clearly shown to cause damage (Rosenberg, 1995).

In addition, the majority of authors report long durations of exposure, ranging from six months (Hanninen, cited in Feldman et al., 1980) (latent group) to 23 years (Aaserud et al., 1990). It can be expected that the extremely high and long duration of exposure of participants in the Aaserud study will result in severe deficits in the participants. Cho et al. (2002) combined the duration and level of carbon disulphide exposure and reported exposure level as a cumulative exposure index. This was calculated as follows:

Σmonths x exposure level ppm

This index can be calculated for most of the studies reviewed here, allowing a comparison between the exposure of participants across studies. Authors reported exposure level in either ppm or $mg/m^{3;}$ it is therefore necessary to use the conversion factor below to calculate a cumulative exposure index (United States Environmental Protection Agency, 1994).

1 mg/m3 = 0.32 ppm

The calculation of the cumulative exposure indices provides a comparison of participants across studies from least exposed to most exposed. The lowest cumulative exposure level is found in the low exposure group in Cho et al. (2002) (198.48 months-ppm), followed by Reinhardt et al. (1997) (289.44 months-ppm). The intermediate group studied by Krstev et al. (2003) had a cumulative exposure index of 855.36 months-ppm. This is followed by the higher exposure group of Cho et al. (2002) (1069.74 months-ppm) and Krstev et al. (2003) (3747.74 months-ppm) respectively. Aaserud, et al. (1990) report the highest cumulative exposure levels; however, the level of exposure varied greatly over time (2944-88320 months-ppm).

Takebayashi et al. (1998) only report on TTCA levels, and so it is not possible to calculate a cumulative exposure index for this study. However, as Reinhardt et al. (1997) also used these measurements, it is possible to place the Takebayashi study relative to that of Reinhardt et al. The low exposure group in the Takebayashi study (1.28mg/g creatinine TTCA) was exposed to slightly lower levels of carbon disulphide than in Reinhardt's study (1.43mg/g creatinine), while Takebayashi's high exposure group was exposed to slightly higher levels (3.13 mg/g creatinine TTCA). The duration of exposure by participants in the Takebayashi study was longer than that of Reinhardt (approximately 13 years and 6 years, respectively).

The exposure levels and duration assessed by the studies reviewed here form a continuum. This facilitates the comparison of the results with respect to their relative exposure levels. This is discussed in depth in the following sections of this chapter. Unfortunately the studies conducted by Hanninen, cited in Feldman et al. (1980) and Feldman et al. (1980) did not report on quantitative measures of exposure levels and the relative exposure of these participants can therefore only be estimated. Quantitative measurements of exposure level only give an indication of current exposure levels and cannot account for possible previous high-level exposure that may have resulted in permanent damage, which may therefore bias results. The comparison of study outcomes with respect to their relative exposure levels may ultimately facilitate the future development of more sophisticated means of determining NOAEL. This may be done by plotting study outcomes against exposure levels to determine dose-response relationships across studies. This is discussed in the second section of this chapter.

4.2.3 Current Trends in Carbon Disulphide Assessment Methodology

Due to the limited available research conducted in this field, a variety of studies was included for this review. Studies that use different methodologies and therefore reveal different findings are discussed below. The review of studies with different methodologies and epistemologies has enabled the collection of diverse information, which has contributed to the depth of this review. The different methodologies employed by these studies are discussed below.

Neuropsychological toxicology investigations comprising both clinical and research investigations have been published on carbon disulphide exposure. Reinhardt et al. (1997), Hanninen, cited in Feldman et al. (1980), Krstev et al. (2003) Cho et al. (2002) and Takebayashi et al. (1998) all conducted epidemiology research studies to achieve the aims discussed at the beginning of this chapter. This has implications for the choice of methodology as well as the nature of their findings. Aaserud et al. (1990) conducted a clinical investigation to determine the absence or presence of pathology in exposed patients. Feldman et al. (1980) conducted a qualitative case study. The results from this study cannot be generalised as the investigation was conducted with only one participant. However, the use of a qualitative methodology enabled the collection of more in-depth information. In addition, information about the patient's behaviour could be collected from his family, which is seldom possible in large epidemiological studies with hundreds of participants. It was also possible to conduct a number of neuropsychological evaluations and medical evaluations on this participant. Frontal lobe damage is widely reported as being difficult to assess using neuropsychological measures, and since carbon disulphide exposure is associated with damage to this area, this damage may be overlooked. The use of a qualitative methodology for the investigation of this phenomenon should therefore not be underestimated.

All the publications reviewed here utilised a cross-sectional design for their investigations. Cross-sectional designs measure some phenomenon at one cross-section in time (Babbie & Mouton, 1998). With the exception of Aaserud et al. (1990) and Feldman et al. (1980), all the studies employed true experimental designs which compared the results of the exposed participants with those of a matched control group to determine if behavioural changes had occurred.

The use of a control group that has also been exposed to the neurotoxin under investigation is a confounding factor in many neuropsychological toxicology investigations. The use of a control group that has been exposed to the neurotoxin under investigation may confound a study because it is unknown whether the exposed control group participants also experienced brain damage as a result of their exposure. Therefore, the use of an exposed control group as

a normal comparison results in an increase in false negative errors. This is demonstrated by the study conducted by Cho et al. (2002). Participants diagnosed with carbon disulphide poisoning at the Wonjin Green Hospital were divided into four quartiles according to exposure level. The researchers then compared the outcomes of the fourth quartile of high exposure participants with the first quartile of low exposure participants. They failed to find statistically significant differences in neuropsychological outcomes between these two groups. This may have been due to a number of factors, including the possibility of false negative findings because a cohort of low exposure participants were compared to the high exposure group, instead of a control group which had not been exposed. It is quite likely that both the low exposure group and the high exposure group had sustained significant damage prior to the assessment as the participants from both these groups had been diagnosed with carbon disulphide poisoning and admitted to hospital. Damage sustained by both these groups was confirmed with MRI. Acute exposure to carbon disulphide is usually permanent (Huang et al., 2002). This may account for the similarity of these participants' outcomes. Krstev et al. (2003) and Takebayashi et al. (1998) conducted medical monitoring on control group participants to ensure that these groups had not been exposed to carbon disulphide. This demonstrates another advantage of quantitatively evaluating the exposure levels of participants.

Another possible confounding variable associated with cross-sectional studies is the evaluator effect. The use of a double-blind methodology is recommended for cross-sectional studies as this eliminates bias that may creep in due to the expectations of the evaluator (Babbie & Mouton, 1998). Of the studies reviewed here, only 57% made use of this method.

Due to the often subclinical nature of neurotoxic brain damage, small differences between experimental and control groups may hide the impact of neurotoxic damage. For this reason, it is recommended that matched controls are used (Stephens & Barker 1998). In the studies reviewed here, confounding variables were compensated for through the selection of matched controls or through statistical means such as multiple linear regression, in adjusting findings and excluding participants who did not meet the criteria. Although excluding participants may eliminate confounding variables, this may also bias findings. In the study conducted by Cho et al. (2002), two participants from each group were excluded from the study due to "poor cooperation"(p.270) Prominent psychiatric symptoms are associated with carbon disulphide exposure and are readily associated with frontal lobe pathology (Rosenberg, 1995; Spreen & Strauss, 1998). It is therefore possible that the "poor cooperation" of these two participants was due to the damage they had sustained. This was not considered in this study and the exclusion of these participants may have skewed the findings. These participants may have represented a more sensitive group of the population.

TABLE 4-2 indicates confounding factors that were considered in each of the studies reviewed here. It may be possible that the authors did take other factors into consideration,

but that these were not reported. The confounding variables reported for Cho et al. (2002) represent consideration for possible differences between high and low exposure groups, whereas variables reported by other authors are indicative of possible differences between the experimental and control groups. Possible confounding variables were not reported in the publications of Hanninen, cited in Feldman et al. (1980) and Feldman et al. (1980). Aaserud et al. (1990) considered the following confounding factors: alcohol use, cardiovascular disease, diabetes mellitus, and cerebral concussion. These were not excluded from the analysis as in the other studies reviewed; however, as Aaserud et al. (1990) reported on clinical aspects it is likely that these factors were considered in the diagnostic process.

Table 4-2: Confounding variables considered during neuropsychological toxicology investigation of carbon disulphide exposure

Confounding variables	Cho et al. (2002)	Krstev et al. (2003)	Reinhardt et al. (1997)	Takebayashi et al. (1998)
Age	√	√	√	√
Alcohol consumption		√	√	√
Depression	√			
Diabetes mellitus	√		√	
Education	√	√		√
Eye disease	√			
Hearing loss	√			
Hypertention	√			
Other neurotoxic exposure			√	
PNS pathology			√	
CNS pathology not resulting from carbon disulphide	√ Brain infarction		√	
Sex	√	√	√	√
Smoking	√		√	√
Weight or BMI			√	√

√ *Confounding variables reported*

Blank: confounding variable not reported

Although the authors of the studies reviewed here went to great lengths to account for as many confounding variables as possible, it seems impossible to control for all possible confounding variables that may bias results between control and experimental groups. This is a large drawback in the selection of cross-sectional designs for neuropsychological toxicology

investigations. As a result, findings from cross-sectional studies should be interpreted with caution.

4.2.4 Sample Characteristics

Sample size and participant characteristics have an impact both on the validity of the findings as well as their generalisability. These will now be reviewed.

The sample size employed by the studies under review are dependent on the methodology used. The qualitative case study conducted by Feldman et al. (1980) included a single participant. However, cross-sectional studies employed larger samples, the smallest of which was Cho et al. (2002) and the largest Takebayashi et al. (1998). The range was as follows:

- Experimental group n=37 to n=309
- Control group n=37 to n=402

These studies were conducted around the world on participants from various cultures, often with the same neuropsychological batteries. The distribution by country is as follows:
Reinhardt et al. (1997) – Germany
Aaserud et al. (1990) – Norway
Krstev et al. (2003) – Serbia
Cho et al. (2002) - South Korea
Takebayashi et al. (1998) – Japan

The participants of the studies reviewed were all male, middle-aged, viscous rayon workers. The findings of these studies may not be generalisable to women, as women may have a different level of sensitivity to carbon disulphide. In addition, the lack of research on prenatal, paediatric and geriatric exposure is of concern as these represent groups with increased sensitivity (Hartman, 1995). More research is required to investigate the impact of carbon disulphide exposure on these groups and to ensure their safety.

Overall, in the studies reviewed, the presence of varied levels of sensitivity among members of the public were not considered. Reinhardt et al. (1997) do raise concerns that it is difficult to control for the effect of sensitive workers who become ill and leave the work environment, and are therefore not included in cross-sectional studies. This may be exactly what happened in the study conducted by Aaserud et al. (1990), whose sample consisted of workers who had worked at a factory for many years and were still working at the factory when it closed.

4.2.5 Trends in the Assessment of Neurotoxic Brain Injury due to Carbon Disulphide Exposure

Neurotoxicology research and clinical evaluations are generally conducted by different members of the medical team. The majority of studies reviewed here used medical, psychological as well as neuropsychological evaluations. This review focuses on both the neuropsychological and psychological assessments of participants who were exposed to neurotoxic chemicals. For this reason, both neuropsychological and psychological assessments are reviewed. In addition, medical measures are discussed, but only in their relation to psychological and neuropsychological findings.

4.2.5.1 Medical Assessment

Twenty-three medical measures were administered in the various studies reviewed here. The most popular of these measurements were TTCA levels, discussed previously in the section of exposure levels. TTCA levels were used to provide an indication of carbon disulphide exposure. Additional medical measurements include neurological measurements (electroencephalogram, median nerve conduction velocity, regional cerebral blood flow, magnetic resonance imaging, etc), immunological measurements (antinuclear antibodies) and endocrine measurements (thyroid functioning). Unfortunately none of these measures, including TTCA measures, were directly correlated with neuropsychological outcomes. These measures were either reported separately or combined with neuropsychological findings to make a clinical diagnosis. The results of these assessments are discussed in the next section with regard to how they relate to psychological and neuropsychological measures.

4.2.5.2 Neuropsychological and Psychological Assessment

TABLE 4-3 lists the neuropsychological tests employed by the studies reviewed to assess the possible brain damage resulting from carbon disulphide exposure. These are discussed at length in the following sections.

Table 4-3: Review of neuropsychological and psychological tests used to assess damage due to carbon disulphide exposure

Authors	Neuropsychological tests used
Reinhardt et al. (1997)	• Benton Test • d2 Test
Hanninen, cited in Feldman et al. (1980)	• Benton Visual Retention Test • Bourdon-Wiersman Vigilance Test • Mira Test • Rorschach • Santa Anna Dexterity Test • Symmetry Drawing

	• Wechsler Adult Intelligence Scales (WAIS) subtests
Aaserud et al. (1990)	• Halstead-Reitan Test Battery with supplements for memory and motor tests • Wechsler Adult Intelligence Scales (WAIS)
Krstev et al. (2003)	• Coblentz Rating Scale for Dementia • Benton's Visual Retention Test • Hamilton Rating Scale for Depression • Swedish Questionnaire 16 (Q16)
Cho et al. (2002)	• Wechsler Adult Intelligence Scales (WAIS) (Korean version)
Takebayashi et al. (1998)	• Wechsler Adult Intelligence Scales (WAIS) subtests • Benton Visual Retention Test • Manifest Anxiety Scale • Self-rating Depression Scale
Feldman et al. (1980)	• Memory testing (not specified) • Psychometric evaluation of verbal IQ, performance IQ not specified • Shipley-Hartford Conceptional Quotient • Smith's Digit Modalities Test • Vigilance Test • WAIS subtest

The table above shows that no standard neuropsychological toxicology batteries such as WHO, NCTB or the other batteries discussed in the literature chapter were used in the studies reviewed here. Two rationales were noted for test selection. Reinhardt et al. (1997) state that the Benton test and d2 Test were selected "for reasons of practicability and the avoidance of language difficulties" (p.334). In correspondence with Dr Takebayashi, he mentioned that all neuropsychological tests selected in his study are derived from the publications of previous studies.

The Wechsler Adult Intelligence Scale subtests were used widely in the assessments reviewed here. Another popular test for the evaluation of carbon disulphide-induced neurotoxic brain damage was the Benton Visual Retention Test. The frequent use of these tests may be due to practitioners' familiarity with them, and also due to the prevalence of these tests in standard neuropsychological toxicology batteries published by organisations such as the World Health Organisation. The Wechsler Adult Intelligence Scale subtest are used in the following standard neuropsychological toxicology batteries:

- 1983 World Health Organisation - Neurobehavioural Health Core Test Batteries (WHO-NCTB)
- 1984 Tuff Battery
- 1984 the London School of Hygiene Test Battery
- 1986 California Neuropsychological Screening Battery
- 1987 Pittsburgh Occupational Exposure Test
- 1990 Individual Neuropsychological Tests for Neurotoxicity
- SPES (Swedish Performance Evaluation System) Battery

The Benton Visual Retention Test is also a common component of standard neuropsychological toxicology batteries such as the WHO-NCTB and the Tuff Battery.

Notwithstanding the popularity of the above measures, a wide variety of tests was used in the studies reviewed here. The abovementioned tests measure a variety of cognitive functions, which are explored in the next section. This characterises two tensions that occur in test selection in neurotoxicology: firstly, the need to use standard tests so that these will be comparable, and secondly, to test global functioning in a variety of areas. These functions are not limited to cognitive and motor abilities, but include a number of psychological functions measured by, for example, the Hamilton Rating Scale for Depression, the Manifest Anxiety Scale, the Rorschach and a Self-rating Depression Scale. Subjective complaints were recorded using Swedish Questionnaire 16 as well as a subjective symptoms questionnaire.

Findings from the neuropsychological evaluations were often integrated with the medical results for diagnostic purposes. For this reason, the individual neuropsychological outcomes were not reported in all the articles. Achievement on individual neuropsychological assessments, as well as the constructs measured by some of the lesser-known tests, were requested from authors who did not originally publish this information. These findings are discussed in the next section. However, not all authors could be reached (especially those who conducted their research a number of years ago). It was nevertheless decided to include these studies as their methodological processes and test selection still contribute to the findings of this review.

4.2.5.3 Collection of Additional Information

Information regarding patients' medical and occupational history are usually taken by means of questionnaires. Factors that may aggravate neurotoxic exposure, such as smoking or alcohol consumption, are often measured by these questionnaires. Aaserud et al. (1990), Cho et al. (2002), and Reinhardt et al. (1997) reported using these types of questionnaires to obtain background information, while Takebayashi et al. (1998) analysed company records to obtain background information.

Both qualitative and quantitative means of test administration were used. Despite the increasing use of computerised batteries for neuropsychological toxicology research, only

Takebayashi et al. (1998) made use of this method. The other researchers conducted assessments with the assistance of skilled clinicians.

4.3 Discussion

In the remaining sections of this chapter, the information presented so far is integrated and synthesised in such as way as to derive meaning from the studies reviewed here. Tests, which are specific to the damage caused by the toxicodynamics of carbon disulphide, will be examined. These tests, which are associated with frontal lobe functioning and motor functioning, are examined in terms of their sensitivity to carbon disulphide-induced damage. It is expected that these functions may be damaged through carbon disulphide exposure, as this is associated with damage to the frontal lobe and the basal ganglia (Rosenberg, 1995). In this case, "sensitivity" can be defined as the intrinsic ability of the test to discriminate between participants who were exposed to neurotoxic chemical and participants who are not exposed. Therefore, a sensitive neuropsychological test is one that measures the deficits resulting from damage incurred through neurotoxic exposure. For the purposes of the following discussions, an indication of test sensitivity in cross-sectional studies is the ability of a test to measure significant differences in outcomes between experimental and control groups. In the case of studies where clinical investigations were conducted and no control groups were used (i.e. the Aaserud and Feldman studies), tests which measure outcomes which differ significantly from appropriate norms are considered sensitive to damage incurred by patients. In addition, the quantitative evaluation of carbon disulphide exposure levels has enabled the evaluation of these outcomes relative to the expected level of damage incurred by these participants. The implication of this damage for the outcomes of neuropsychological assessments is also investigated.

4.3.1 Neuropsychological Outcomes Relative to Exposure Level and Duration: A Dose-Responses Relationship

The quantitative measurement of exposure levels makes it possible to estimate the relative exposure levels of different studies in relation to one another. This was not possible in previous review articles as the use of quantitative exposure measures appears to be a relatively new process that was not observed in articles published before 1980. Information regarding relative exposure levels will now be used in the interpretation and comparison of the findings reported in the studies reviewed.

Damage sustained by neurotoxic damage can be represented in a dose-response curve. This may either depict the number of individuals affected at a specific exposure level, or (for our

purposes) the deficits incurred at a specific exposure level. Therefore dose (exposure level) and response (neuropsychological deficits) are represented on the x- and y-axes respectively. This curve usually has a positive gradient as increased exposure is associated with increased deficits. Both duration and concentration of exposure determine damage in the occupational setting. For the purpose of this discussion, the cumulative exposure index, in which both concentration and duration of exposure is considered, is used for the x-axis. The calculation of this index is discussed at length earlier in this chapter. The various studies reviewed here are combined in a review schematic dose-response curve in FIGURE 4-2.

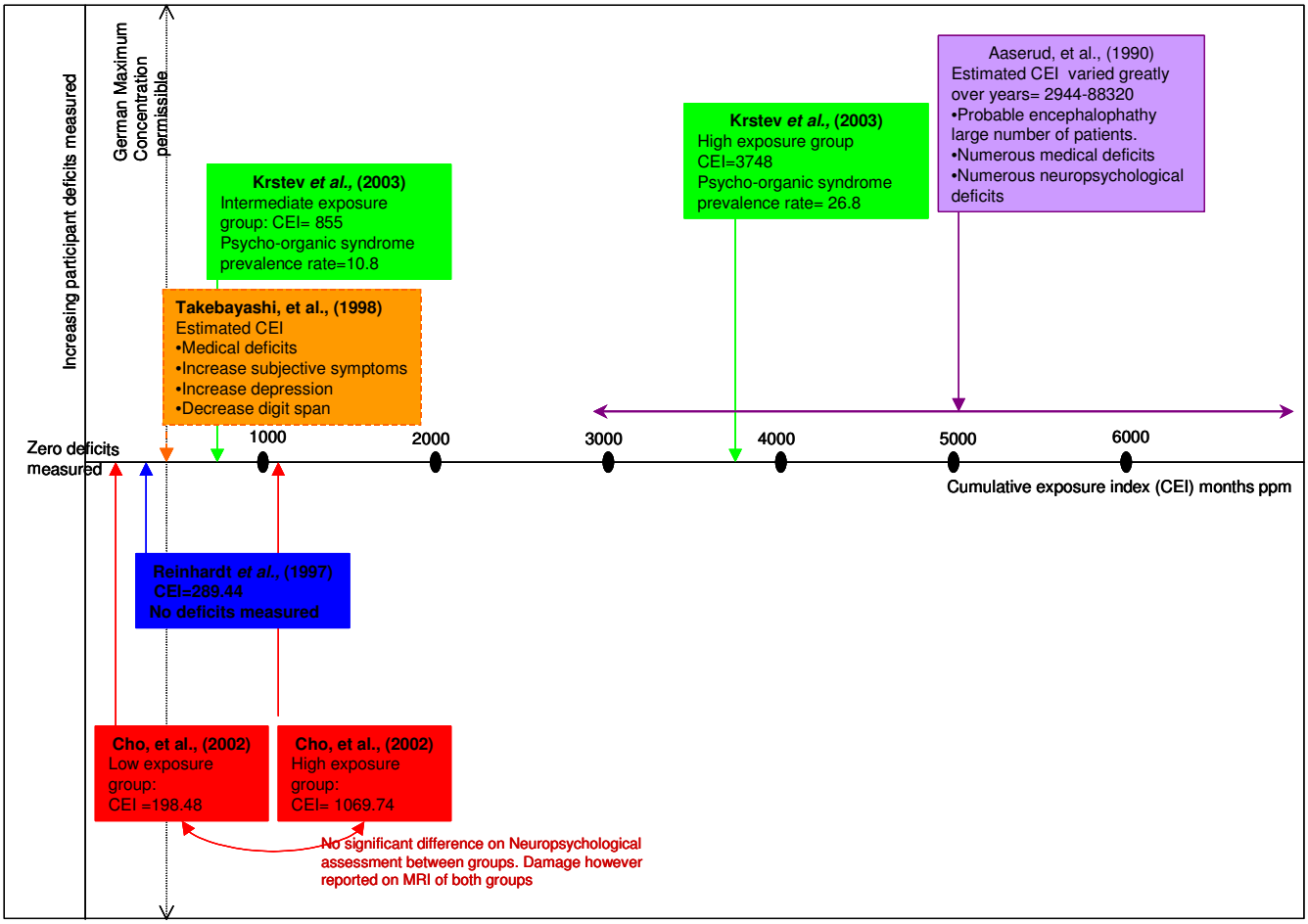

Figure 4-2: A schematic representation of a review dose-response curve of carbon disulphide neurotoxicity

Reinhardt et al. (1997) evaluated participants with the lowest carbon disulphide exposure level and duration of exposure (TTCA 1.43.mg/g creatinine for 6 years). It is therefore not surprising that Reinhardt et al. (1997) did not find any significant differences between the control and experimental group in neuropsychological measures, subjective complaints reported, laboratory parameters and neurological examination (except in the ability to walk

with eyes closed). This was despite the fact that 10% of participants were exposed to above-minimum neurotoxic levels.

The lack of positive findings in the Reinhardt study may have been further influenced by the lack of instruments sensitive to frontal lobe damage. Reinhardt et al. (1997) selected the Benton Visual Retention Test and the d2 test for this study. The Benton Visual Retention Test is essentially a memory test reported to assess visuospatial perception, visual and verbal conceptualisation and immediate memory span. It has been found to be effective in assessing damage to both left and right hemispheres (Lezak et al., 2004), although the literature does not report it to be sensitive to frontal lobe damage. We will return to the Benton Visual retention test in the chapter on organophosphate. The d2 test is used as an assessment of attention (Brickenkamp & Zillmer, 2002).

Fears that the negative results of the Reinhardt study are due to the presence of subtle subclinical damage are raised by an analysis of the findings of the Takebayashi study. Takebayashi et al. (1998) evaluated two cohorts of participants: a low-level and a high-level exposure group. The participants in the Takebayashi low-level exposure group (TTCA) 1.28 mg/g creatinine for 12 years) were exposed to levels comparable to those in the Reinhardt sample (TTCA) 1.43.mg/g creatinine, for 6 years) while the participants in the Takebayashi high-level group (3.13g/mg creatinine for 13 years), were exposed for approximately twice as long as those in the Reinhardt study. Takebayashi et al. (1998) measured changes in behavioural outcomes for these participants. In comparison with controls, the experimental group participants had the following deficits:

- medical deficits (decreased in median nerve conduction velocity and changes in insulin and haemoglobin)
- neuropsychological deficits (Digit Span backwards)
- psychological deficits (increase in self-reported depression scale)
- increase in subjective symptoms (increase of tremors, decreased grasp strength, decreased sexual desire, dullness in limbs, fainting when suddenly standing upright, headaches, heavy feeling in head, rough skin and sensitivity of skin on extremities)

As the instruments discussed above were sensitive to the damage sustained by these participants at low exposure levels, these tests may warrant further attention as effective means of assessing carbon disulphide-induced damage. However, the potential impact of previous high-level exposure cannot be accounted for in this study.

Krstev et al.'s (2003) intermediate group of participants were exposed to levels of carbon disulphide comparable with Reinhardt's and Takebayashi's participants. However, due to the longer exposure time, this group's cumulative exposure index is much higher (855.36months ppm compared to that of Reinhardt et al.'s 289.44months ppm). Unfortunately, Krstev and colleagues did not report on the neuropsychological outcomes of particular tests but used

these findings for diagnostic purposes. Krstev *et al.,* (2003) diagnosed psycho-organic syndrome diagnosed significantly more frequently among the high-exposure group (3747.744 months ppm) than other two groups.This demonstrates that increased damage is associated with increased duration and concentration of exposure.

Aaserud et al. (1990) conducted evaluations on participants who had been exposed to very high levels of carbon disulphide. The authors measured neuropsychological deficits on a number of motor and frontal lobe tests, and diagnosed encephalopathy probably due to carbon disulphide exposure in a large proportion of participants. Abnormalities were also found in EEG, EMG, Neurography, AER, VER, SER, Doppler examination and rCBF. The sensitivity of the neuropsychological tests employed by Aaserud et al. (1990) may be attributed to the extensive damage sustained by participants at these exposure levels. With sufficient exposure, brain damage will become so extensive that participants will perform poorly on all neuropsychological assessments and eventually die.

The outcomes of the studies discussed above demonstrate the relationship between increased exposure and the resultant increase in deficits. The only study whose findings contradict this is Cho et al. (2002). This may be because the authors reported on the differences between the high-exposure group (1069.74 months ppm) and low-exposure group (cumulative exposure index 198.4 months ppm), both of which had been diagnosed with acute poisoning and may have suffered permanent damage from this. Cho et al. (2002) did not measure any differences between groups with any of the neuropsychological tests employed, despite a MRI indicating that brain damage had occurred in both groups. This suggests that these are false negative findings. This is further supported by the authors' choice of assessment instrument, since overall Wechsler Adult Intelligence Scales have not been found to be sensitive to frontal lobe damage (Nell, 2000). However, individual subtests within the battery may be sensitive to specific kinds of frontal deficits.

The dose-response curve demonstrates the increased sensitivity of neuropsychological tests to increased exposure to neurotoxic chemicals. Together with the results of Cho et al. (2002), it demonstrates the effect that methodological issues may have on the findings from these neuropsychological tests. In addition, a pattern appears to be emerging in which tests such as the Digit Span (which is sensitive to damage to frontal lobe functioning) are more sensitive than tests which are not associated with these areas, such as the Benton Visual Retention Test, which is primarily a memory test (Lezak et al., 2004; Rosenberg, 1995). However, this requires further investigation. The sensitivity of these tests will now be discussed further.

4.3.2 Review of Neuropsychological Outcomes of Frontal Assessments

Carbon disulphide toxicodynamics have a vascular component (Tan et al., 2004). The high prevalence of damage to the frontal lobes resulting from carbon disulphide exposure, and the associated symptoms resulting from this damage, raises questions regarding the similarities in aetiology of carbon disulphide neurotoxic damage and other neurological damage caused by cardiovascular disease such as multiple infarct dementia. Cardiovascular disease seems to particularly affect the frontal lobes, and is characterised by dysexecutive syndrome (Lezak et al., 2004). The sensitivity of frontal lobe tests will now be investigated.

Tests that the literature reports to be sensitive to frontal lobe functioning were selected for further scrutiny from the 47 tests and subtests used in the studies reviewed here. The following assessments are reported to be sensitive to frontal lobe damage in the literature (Lezak et al., 2004; Spreen & Strauss, 1998). These WAIS-R/III assessments were employed by the authors reviewed here to assess carbon disulphide exposure:

- Block Design
- Digit Span
- Similarities
- Trail Making A and B
- Vocabulary
- Picture Arrangement

4.3.2.1 Block Design

Inter-neurotoxin comparison

The popularity of the Wechsler subtests enables the comparison of its outcomes across studies. The Block Design appears to be equally effective in assessing damage sustained from carbon disulphide exposure and damage due to organophosphate exposure. This may be because acetlycholine neurons are found throughout the cerebral hemispheres (Schatz & Chute, 2000; Thiel, 2003), and the Block Design subtest has been found effective in assessing many areas of the cortex. Another explanation is that Block Design scores also tend to be lower with any type of brain damage (Lezak et al., 2004).

Table 4-4: Inter-study comparison of the Block Design

	Carbon disulphide			**Organophosphate**				
Study	Aaserud et al. (1990)	Cho et al. (2002)	Feldman et al. (1980)	Rosenstock et al. (1991)*	Richter et al. (1992)*	Farahat et al. (2003)*	Reidy et al. (1992)*	Savage et al. (1988)*
Block Design	√	x	√	√	√	√	x	x

√ Test measured deficits in participants

X Test did not measure deficits in participants

*Farahat, Abdelrasoul, Amr, Shebl, Farahat and Anger (2003).

*Reidy, Bowler, Rauch and Pedroza (1992)

*Richter, et al. (1992).

*Rosenstock, Keifer, Daniell, McConnell and Claypoole (1991)

*Savage, Keefe, Mounce, Heaton, Lewis and Burcar (1988)

Intra-neurotoxin comparison

Block Design is effective in assessing damage to the right parietal lobe, prefrontal cortex and left hemisphere (Lezak et al., 2004). This assessment was employed by Aaserud et al. (1990), Cho et al. (2002) and Feldman et al. (1980) to assess carbon disulphide-induced damage. Both Aaserud et al. (1990) and Feldman et al. (1980) found this assessment to be effective in assessing behavioural changes resulting from carbon disulphide exposure; however, in the study conducted by Cho et al. (2002) this assessment was not effective in distinguishing between groups. As previously stated, the outcomes of Cho et al.'s (2002) study may have been influenced by the use of a low-exposure group, which had been diagnosed with carbon disulphide poisoning, rather than a non-exposed control group. The findings may also be influenced by the different methodologies used by authors.

4.3.2.2 Digit Span

As previously discussed exposed participants in the study conducted by Takebayashi et al. (1998) performed significantly poorer than control subjects on this assessment, at very low levels of carbon disulphide exposure. This assessment will now be reviewed in more detail as possible tool for assessment of this type of exposure.

Inter neurotoxin comparison

As with the Block Design test, Digit Span is not primarily a frontal lobe assessment. The Digit Span test has, however, been found to be effective in the assessment of frontal lobe damage when special attention is paid to the qualitative errors made by these patients during this assessment. Frontal lobe patients make characteristic errors, such as the substitution of bits of learned sequenced strings from previous series (Lezak et al., 2004). The extent to which qualitative errors were assessed was not reported in all the articles reviewed. Together with other factors, this may have contributed to the difference in outcomes. Digit Span appears to be more effective in assessing damage sustained by organophosphate exposure. This may be because short-term memory functioning is essential for the successful completion of this assessment (Lezak et al., 2004). Organophosphate exposure is associated with the disruption of the acetylcholine system, which plays an important role in memory (Daniell et al., 1992;

Eyer, 1995). This is discussed in detail in the chapter pertaining to organophosphate exposure.

Table 4-5: Inter-study comparison of the Digit Span

	Carbon Disulphide			Manganese				Organophosphate							
Study	Takebayashi et al. (1998)	Aaserud et al. (1990)	Cho et al. (2002)	Brown et al. (1991)*	Deschamps et al. (2001)*	Myers et al. (2003)*	Sjögren et al. (1996)*	London et al. (1997)	Rosenstock, et al. (1991)	Richter et al. (1992)	Savage et al. (1988)	Stephens et al. (1995)	Farahat et al. (2003)	Fiedler et al. (1997)*	Reidy et al. (1992)
Digit span	√	x	X	x	X	x	x	x	√	√	√	x	√	x	X

√ Test measured deficits in participants

X Test did not measure deficits in participants

* Brown, Wills, Yousefi and Nell (1991)

* Deschamps, Guillaumot. and Raux (2001)

*Fiedler, Kipen, Kelly-McNiel and Fenske (1997).

*Myers, et al. (2003)

*Sjögren, et al. (1996).

*Stephens, Surgeon, Clavert, Beach, Levy and Bery (1995)

*Stephens, Spurgeon and Berry (1996)

Intra neurotoxin comparison

Digit Span was effective in measuring change in behavioural outcomes in the study conducted by Takebayashi et al. (1998) but not in the studies conducted by Aaserud et al. (1990) and Cho et al. (2002). The participants of the Takebayashi study were exposed to lower levels of carbon disulphide than those in the Aaserud sample. If Digit Span were sensitive to the damage sustained by participants in the Takebayashi study, we may expect that it would also be sensitive to the damage sustained by participants with higher exposure, such as those found in Aaserud et al.'s (1990) study. This was not the case, however. No clear explanation can be found for this; although possibly these findings were influenced by confounding factors which have not been considered. In addition, the fact that none of the neuropsychological tests employed by Cho et al. (2002) measured deficits in exposed participants may be due to methodological factors.

Digit Span performance is reportedly reduced in participants with long-term solvent exposure (Lezak et al., 2004). However, Digit Span was not sensitive to the damage sustained by

participants in the majority of studies reviewed here. This highlights the role of chemical structure and mechanisms on the damage sustained by participants, and the use of unique tests to assess specific compounds. We will return to this concept in the chapter on organophosphate, where we will see the differences in severity of damage associated with different organophosphate compounds.

4.3.2.3 Similarities

This subtest is reported to be sensitive to brain damage regardless of the location of the damage. It is involved in left temporal and frontal functions (Lezak et al., 2004). This may explain the absence of a clear pattern of sensitivity of this subtest. The Similarities subtest was not sensitive to behavioural change in either the study conducted by Aaserud et al. (1990) or Cho et al. (2002). This assessment was used only by Deschamps et al. (2001) to assess manganese exposure, and did not measure any change in these participants. Farahat et al. (2003) and Savage et al. (1988) were successful in measuring organophosphate-induced deficits with this measurement.

4.3.2.4 Trail Making A and B

The Trail Making subtest is reported to be effective in measuring behavioural changes in traumatic brain injury and frontal lobe damage (Lezak et al., 2004). The Trail Making Part B subtest was sensitive the deficits in the study conducted by Aaserud et al. (1990), although Part A was not. Deficits are reported to correlate highly with caudate atrophy in patients with Huntington's disease (Lezak et al., 2004). Similarities between the pathology of Huntington's disease and manganese neurotoxicity may be cause for further investigation. However, none of the studies reviewed on manganese neurotoxicity made use of this assessment for this purpose.

Table 4-6: Inter-study comparison of the Trail making A and B subtest

Neurotoxin	**Carbon disulphide**	**Organophosphate**					
Study	Aaserud et al. (1990)	Rosenstock et al. (1991)	Richter et al. (1992)	Savage et al. (1988)	Farahat et al. (2003)	Fiedler et al. (1997)	Reidy et al. (1992)
Trail Making AB	A√ B X	√	√	x	√	x	X

√ Test measured deficits in participants

X Test did not measure deficits in participants

4.3.2.5 Vocabulary

Qualitative differences are also observable in the WAIS Vocabulary subtest in patients with frontal lobe damage (Spreen & Strauss, 1998). However, this subtest did not measure any significant deficits in the Aaserud and Cho studies. As previously mentioned, however, the outcomes of Cho et al. (2002) may be explained by methodological issues. This assessment did not measure deficits in manganese neurotoxicity in the studies conducted by Sjögren et al. (1996) and Deschamps et al. (2001). However, deficits were measured in the studies conducted by Rosenstock et al. (1991) and Savage et al. (1988), who used it to measure the effects of acute organophosphate poisoning.

4.3.2.6 Picture Arrangement

This subtest highlights the difficulties of some frontal lobe patients in planning sequences of behaviour (Spreen & Strauss, 1998). As with Vocabulary (WAIS-R/III), the emphasis is on the qualitative nature of the assessment and the ability of the psychologist to recognise patterns in patients that are characteristic of frontal lobe dysfunction. The extent to which this was done in the studies reviewed here is difficult to determine. This assessment was utilised only by Cho et al. (2002).

4.3.2.7 Summary of findings

Of the tests that are sensitive to frontal lobe functioning, and that were employed by the studies reviewed here, not all were used by a sufficient number of authors to draw conclusions regarding their sensitivity. In addition, a large number of tests require interpretation of qualitative response patterns by a skilled practitioner to identify frontal lobe pathology in test takers. It is not possible to determine the extent to which this was done in the studies reviewed here. These include the Picture Arrangement, Vocabulary, and Trail Making A and B subtests. Further research is required to investigate the efficacy of other tests of frontal lobe functioning, such as the Block Design, the Digit Span and other tests of frontal functioning not used in these studies such as Tower of London, Stroop Test and gambling tasks.

4.3.3 Other Tests

Some neuropsychological tests that are not sensitive to frontal lobe damage pick up changes in behavioural outcomes. These include the following motor tests:

- Grooved Pegboard (both hands) (Aaserud et al., 1990)

- Mira Test (Hanninen, cited in Feldman et al., 1980)
- Santa Ana Dexterity Test (Hanninen, cited in Feldman et al., 1980)
- Smith's Digit Modalities Test (Feldman et al., 1980)
- Steadiness Test (both hands) (Aaserud et al., 1990)

The sensitivity of these tests may be attributed to the damage to motor functions of the frontal lobes and basal ganglia resulting from carbon disulphide exposure.
However, some motor tests employed were not sensitive to the damage sustained by participants. These include the following:

- Choice reaction time (Takebayashi et al., 1998)
- Finger Tapping (Aaserud et al., 1990)
- Simple reaction time (Takebayashi et al., 1998; Cho et al., 2002; Aaserud et al., 1990)

A number of neuropsychological measures which are not associated with frontal lobe or motor functioning were reportedly effective in assessing behavioural change in exposed participants:

- Memory testing (Feldman et al., 1980)
- Pictorial Puzzle (Feldman et al., 1980)
- Shipley-Hartford Conceptional Quotient (Feldman et al., 1980)
- Verbal IQ performance (Feldman et al., 1980)
- Vigilance Test (Feldman et al., 1980)

It is interesting to note that these tests were all employed by Feldman et al. (1980) in a case study methodology. It is likely that the participant of the case study conducted by Feldman et al. (1980) was exposed to extremely high levels of carbon disulphide. The positive results of the abovementioned tests may be explained by widespread brain damage resulting from high-level exposure. Feldman et al. (1980) also collected information from the patient's family. The authors composed the following qualitative description of the patient's behaviour: personality changes, irritability, forgetfulness, depression, decreased memory, decreased attention, decreased interest in favourite activities and tremors. It is notable that most of these symptoms are associated with frontal lobe damage.

Changes in neuropsychological outcomes were also measured with the Digit Symbol subtest in the studies conducted by Aaserud et al. (1990) and (Hanninen, cited in Feldman et al., 1980). Lezak et al. (2004) describes the Digit Symbol subtest as a highly sensitive test, which can measure even slight differences in functioning. This test is therefore also recommended for screening purposes. However, this test may also result in false positive findings. The sensitivity of this test may explain its effectiveness in measuring behavioural changes in the studies reviewed here.

In sum, although authors such as Aaserud et al. (1998) conclude that "the typical neuropsychological findings were psychomotor retardation combined with slight signs of frontal lobe dysfunction" (p.280), not all the tests which are sensitive to frontal lobe functioning were sensitive to the damage sustained by these participants. In addition, tests that were not expected to be sensitive to this damage did measure neuropsychological change. Furthermore, the Digit Span subtest was sensitive to damage sustained by participants in the Takebayashi but not in the Aaserud research, despite the latter participants' higher level of exposure. Therefore, no clear pattern of test sensitivity could be concluded. When the number of a specific type of tests (for example tests reported as measuring frontal lobe function) which measure a deficit in participants is calculated as a percentage of the number of these type of tests employed, the probability of measuring a change in outcomes of participants with specific types of instruments can be broadly calculated. For example the probability of measuring deficits in individuals with carbon disulphide-induced damage with a frontal lobe test in the studies reviewed here is P=0.33, when methodology and exposure are not considered. The probability of doing so when using a motor test is P=0.71. However, when using a neuropsychological test that does not measure either motor or frontal lobe functioning, and that does not use the Digit Symbol subtest, the probability decreases to P=0.27.

Numerous reports point to the difficulty of measuring frontal lobe deficits with cognitive assessments such as those discussed above. Although the frontal lobes may be involved with cognitive tasks such a reasoning and planning, they play an important role in personality, temperament, social functioning, flexibility, emotional processing and a number of executive functioning tasks (Spreen & Strauss, 1998; Dimitrov et al., 2003). These psychological attributes are examined below as effective tools for measuring these deficits.

4.3.4 Psychological Assessment

Psychological deficits experienced by participants were most frequently measured using a subjective symptoms questionnaire and a number of psychological assessment instruments. Psychological symptoms reported by patients and their families were also included in case studies. These symptoms are summarised in TABLE 4-7 below. A number of authors merely reported on significant symptoms and did not list all the symptoms measured. Since the latter may have an impact on these findings, this should be considered in their interpretation.

Table 4-7: Psychological symptoms measured in carbon disulphide-exposure participants

Psychological symptoms	Aaserud et al. (1990)	Feldman et al. (1980)	Hanninen*	Krstev et al. (2003)	Reinhardt et al. (1997)	Takebayashi et al. (1998)
Absentmindedness		√		√		
Anxiety						X
Affect lability				√		
Attention		√				
Concentration problems	√	√		√	X	X
Decreased sexual desire				√		√
Depression	√	√	√			√
Disorganisation		√				
Dizziness	√					X
Fainting						√
Feeling of inebriation	√					
Forgetfulness		√		√		
Headaches	√			√	X	X
Irritability	√	√		√	X	
Light headaches						√
Loss of initiative/ spontaneity	√		√			
Loss of interest		√				
Memory difficulty	√				X	
Obtaining meaning when reading				√		
Personality changes		√	√			
Sleep disturbances	√				X	X
Speech difficulty						X
Tiredness	√			√		
Visualisation			√			

√ Symptom measured in or reported by participants

X Symptom measured but not significant

Blank - symptom not measured or reported

Cho et al. (2002) did not measure any psychological constructs.

** Hanninen, cited in Feldman et al. (1980)*

Deficits such as absentmindedness, concentration problems, disorganisation, forgetfulness, irritability, loss of initiative and spontaneity, loss of interest and personality changes are reported in studies assessing high-level exposure. These include Aaserud et al. (1990), Krstev et al. (2003) and Feldman et al. (1980). These symptoms are associated with frontal lobe damage and dysexecutive syndrome, and may be an indication of the carbon disulphide damage to this area.

A number of studies also noted a high incidence of depression. For example, Takebayashi et al.'s (1998) Self-rating Depression Scale measured a significant increase in the rate of depression amongst exposed participants. The Manifest Anxiety Scale used by the same author did not discriminate between groups. Aaserud et al. (1990) reported depression among 44% of participants. Krstev et al. (2003) reported depression rates of 30% in the high-exposure group, 35% in the intermediate-exposure group, and 15% of the control group (not exposed). Feldman et al. (1980) and Hanninen, cited in Feldman et al. (1980) also reported incidences of depression in their samples. The incidence of depression is raised in patients with Parkinson's disease. This is attributed to the disease process and is not merely the psychological consequence of being diagnosed with a serious illness (Lezak et al., 2004). The similarity between carbon disulphide-induced parkinsonism and idiopathic Parkinson's raises suspicions that the depression reported in these participants may be due to the physiological process of the damage sustained.

In addition to the assessment of psychological symptoms, general system questionnaires measured somatic complaints. The studies reviewed here reported a high incidence of nausea, tremors and other psychomotor complaints. Carbon disulphide exposure is readily associated with Parkinson's disease (Cho et al., 2002; Gobba & Cavalleri, 2003; Rosenberg, 1995). The increased self-reported tremor may be an indication of this. Both Takebayashi et al. (1998) and Feldman et al. (1980) reported tremors. The suspected acute damage that Feldman's patient sustained would explain the rapid onset of a tremor. Reports of these symptoms may be due to an increase in testing for this symptom, although it may also be associated with carbon disulphide exposure. Further research is needed to determine this. The reports of tremors in the Takebayashi study at relatively low exposure levels may indicate that this is an effective monitoring tool; however, this requires further investigation.

4.4 Conclusion

The studies reviewed in this chapter are representative of the historical way of assessing neurotoxic exposure, and generally aimed merely to characterise or determine whether damage had been sustained. Exposure levels assessed included both low-level and extremely high-level exposure, which was associated with serious deficits in participants.

Exclusively cross-sectional studies and case studies were employed, leaving the findings from these studies open to the impact of confounding variables. All the studies were conducted on middle-aged men working in an industrial setting. Although a wide range of neuropsychological tests was employed, the researchers did not consider the toxicodynamics of this neurotoxin, namely, damage to the frontal lobes, and the intricacies of assessing this damage. The discrepancies in assessment instruments employed by these authors as well as methodological issues may have contributed to the inconclusiveness of these findings. This review highlights the need for further research into the neuropsychological assessment of carbon disulphide damage. Special attention should be given to the investigation of methodological issues, and the assessment of women, children and older adults. A further focus should be the efficacy of tests shown to be effective in assessing deficits associated with frontal lobe damage such as personality changes, dysinhibition and dysexecutive syndrome.

CHAPTER 5: MANGANESE

5.1 Introduction

Exposure to manganese does not only occur in the industrial setting, as manganese is ubiquitous to the environment. The urgency for the study of manganese neurotoxicity has been augmented by the introduction of methylcyclopentadienyl manganese tricarbonyl (MMT) as an antiknock in petrol. MMT releases salts of manganese upon combustion, increasing environmental exposure (Gwiazda, Lee, Sheridan & Smith, 2002). A recent South African study conducted by Rollin, Mathee, Levin, Theodorou and Wewers (2005), measured the blood manganese of Grade 1 learners in Johannesburg (where MMT had been introduced) and in Cape Town (where MMT had not been introduced). Rollin et al. (2005) found that Johannesburg children had significantly higher levels of blood manganese than children living in Cape Town.

People at risk for occupational exposure to manganese include manganese miners, dry cell battery plant workers, steel alloy plant workers, ceramic factory workers, workers involved in the production of matches, glass, dyes, fertilizers, welding rods, oxidizing solutions, animal food additives, germicides and antiseptics (Hartman, 1995). The American Conference of Governmental Industrial Hygienists determined a threshold limit value (ACGIH TLV) for manganese of 0.2mg/m^3 (Myers et al., 2003). Exposure to high levels of manganese, which may occur in these industrial settings, is associated with neurotoxicity. Despite the neurotoxicity of manganese at high concentrations, manganese is an essential trace element, which is used by the body in many enzymes and in neuromuscular function. Manganese deficiency is associated with infantile death, psychological changes, personality change, apathy and psychosis (Linter, 1985).

At concentrations higher than what is required for nutritional purposes, neurotoxic mechanism of manganese results in damage to the basal ganglia (Lucchini et al., 2000). Disruption of the dopamine and catecholamine systems has also been reported (Hartman, 1995). The basal ganglia are closely associated with the frontal lobes, and together with some other subcortical structures, forms the part of the association cortices. The main function of these structures is to integrate information and to deploy motor and mental outputs (Damasio, 1994; Gwiazda et al., 2002). It is therefore not surprising that basal ganglia damage is associated with a wide range of motor and emotional disturbances (Kaplan & Sadock, 1998; Lucchini et al., 2000). It has also been suggested that manganese exposure may be associated with criminal and violent behaviour (Finley, Penland, Pettit & Davis 2003). Emotional disturbances associated with basal ganglia pathology are demonstrated in diseases such as Parkinson's and Huntington's disease, which affects these areas of the brain (Lezak et al., 2004). The similarities between the extensive personality changes associated with Huntington's disease

and the changes brought about during “manganese mania” raises questions about a similar mechanism of damage. The relationship between manganese-induced damage and idiopathic Parkinson’s disease has long been recognised; however, there are differences between the two. The role of manganese in the aetiology of Parkinson’s disease remains to be determined (Aschner, 2000).

Manganese neurotoxicity is a progressive process, which can be described in three phases (Hartman, 1995). These phases are characterised by extra-pyramidal and neuropsychiatric symptoms (Zatta, Lucchini, van Rensburg & Taylor, 2003), presenting as a schizophrenia-like psychosis (Banta & Markesbery, 1977). The first stage of manganese neurotoxicity is characterised by behavioural changes (Zatta et al., 2003). These behavioural changes were previously referred to as “manganese mania.” These include months of sleeplessness, asthenia, anorexia, compulsive laughter, insomnia, hallucinations, aggression, memory and judgement deficits, emotional lability, delusions and hallucinations. Patients may also present with poor coordination, ataxia and impaired speech (Aschner, 2000; Donaldson et al., 1982; Hartman, 1995; Lucchini et al., 2000; Zatta et al., 2003). The second stage is characterised by Parkinsonian features (Zatt et al., 2003). These include an increase in neurological symptoms, abnormal gait, expressionless face, speech impediments, clumsiness, and sleepiness (Hartman, 1995). The final stage, also known as manganism, is a Parkinsonian-like state characterised by dystonia, tremors, staggering gait, hypokineasia as well as emotional lability and dementia disturbances (Hartman, 1995; Zatt et al., 2003).

This chapter reviews nine neuropsychological toxicology studies conducted on participants exposed to various level of manganese. Interestingly, the majority of these studies were conducted in the last five years. The sudden proliferation of these studies attests to the rapid growth of the field of neuropsychological toxicology. As in previous chapters, the publications reviewed are all those which could be sourced during a systematic search of available databases, as delineated in the methodology chapter. In this chapter, current trends in the neuropsychological toxicology assessment of manganese are reviewed. These efforts are geared towards the investigation of the application and use of dynamic brain localisation theory in the field. In addition, test sensitivity is discussed in relation to neurotoxic mechanisms. In the case of manganese exposure this entails the investigation of psychomotor assessments speculated to be sensitive to the basal ganglia damage incurred. The structure of this chapter is identical to that of the previous chapter.

Table 5-1 Summary of manganese studies reviewed

Authors	Country	Design	Double Blind	Sample size	Sample characteristics	Sex	Age- Mean
Banta and Markesbery (1977)	USA	Case study	Not double blind	n=1	Patients	Male	55 years
Bouchard et al. (2003)	not reported	Cross Sectional (Quasi experimental design)	Not double blind	n=75	Plant workers	Not reported	43.8 years -5.3 Range 35-59 years
Brown et al. (1991)	South Africa	Cross sectional design (experimental group and control group) as well as co relational design	Double blind	High n=19 Low n=20	Refinery workers	Male	High41.4 -10.34 Low40.5 -8.19 Range not reported
Deschamps et al. (2001)	not reported	Cross sectional design (experimental group and control group)	Not double blind	Experimental n=138 Control n=137	Enamel production workers	Male and female	40 years (Exp=11 Con t=10)
Finley et al. 2003	North Dakota USA	Cross Sectional (Quasi experimental design)	Not double blind	n=17	Not reported	Female	35.7 years -8 Range 21-46 years
Myers et al. (2003)	South Africa	Correlation designs	Not double blind	n=480	Blue and white collar workers	Not reported	39.3 years -8.7 Range 21-61
Santos-Burgoa et al. (2001)	Mexico	Correlation designs	Not double blind	n=73	Community members living in mining region	Male and female	43.3 years -17.43 Range 14-93 years
Sjögren et al. (1996)	Not reported	Cross sectional design (experimental group and control group)	Not double blind	Experimental n=12 Control n=44	Railroad welders	Not reported	40.4 years Range 27-61 yea
Takser et al. (2003)*	Paris France	Longitudinal	Not double blind	Examined at 6 months n=195 Examined at 3 years n=126 Examined at 6 years n=100	Healthy pregnant woman and babies	Male and female	6months 3 years 6years

*Takser, Mergler, Hellier, Sahuquillo and Huel (2003)

5.2 A Review of Neuropsychological Toxicology Investigations of Manganese

The following section considers methodological issues in the studies reviewed here. This includes a review of current study aims, the type of manganese exposure assessed, methodologies employed, participant characteristics and the medical, psychological and neuropsychological tests employed in the evaluations. This will not only provide us with an

indication of current trends in this research, but will also facilitate the discussion in the second section of this chapter. The discussion considers the impact of methodological issues on the outcomes of the neuropsychological assessments used. In addition, this information will also indirectly contribute to the development of recommendations for best practice in this field.

5.2.1 Neuropsychological Toxicology Study Aims as an Indication of the Direction of the Field

A wider variety was noted in the study aims of research conducted for the assessment of manganese neurotoxicity than those assessing carbon disulphide. This may be attributed to the contemporary nature of these studies. The publications demonstrate a shift towards more focused study aims, presumably due to the increased understanding of the neurotoxic mechanism of manganese.

Manganese exposure is known to be associated with motor deficits, therefore authors such as Takser, et al. (2003) and Banta and Markesbery (1977) aimed to specifically assess psychomotor development and extrapyramidal signs respectively. Takser et al. (2003) aimed to investigate the effect of prenatal manganese exposure on the motor development of children.

Bouchard et al. (2003) conducted a study to determine the impact of alcohol and blood manganese exposure on mood. Psychological and emotional changes are also associated with damage to the basal ganglia as well as manganese neurotoxicity (Zatta et al., 2003).

Finley et al. (2003) investigated the relationship between dietary manganese, fats and neuropsychological outcomes. This demonstrates a wider application of neuropsychological toxicology assessment than the more typical determination of NOAEL.

Myers et al. (2003), Banta and Markesbery (1977), Deschamps et al. (2001) and Sjögren et al. (1996) conducted studies to investigate the general effect of manganese exposure, which is much the same aim as the majority of studies conducted on carbon disulphide exposure. Similarly Brown et al. (1991) a South African study, conducted neuropsychological evaluations on participants exposed to higher levels of manganese. This investigation was primarily exploratory concerned with the neuropsychological sequelae of manganese exposure.

The trend towards increased specificity in the aims of the majority of these studies indicate an increased understanding of the toxic mechanisms and related symptoms of this neurotoxin. It also demonstrates an understanding of the variability in the damage sustained from exposure to different neurotoxins as well as a shift away from the tendency to treat neurotoxic damage

as a unitary phenomenon (a tendency to handle all neurotoxins as if they all resulted in the same damage). This tendency is reminiscent of the historical origins of the neuropsychology of traumatic brain injury, when investigations primarily aimed to determine the "organicity" of damage.

5.2.2 A Move Away from High Exposure Assessments to the Assessment of NOAEL

The extent of neurotoxic exposure determines the extent of brain damage sustained (Rosenberg, 1995). The extent of brain damage will determine the participant's outcomes on a neuropsychological test. Thus, neuropsychological tests that are sensitive to the neurological damage sustained at exposure to low levels of manganese are more sensitive than tests able to detect damage sustained at higher levels of exposure. Quantitative exposure measurements provide a scale for comparison with the outcomes of various neuropsychological tests. In the following discussion, the level and duration of exposure assessed by these studies is analysed to lay the foundation for the comparison of the neuropsychological outcomes of these studies in the next section. As the majority of studies assessed exposure levels approximate to regulatory levels, a cumulative exposure index was not calculated. This facilitated an investigation of current regulatory levels.

The source of manganese exposure may impact on the type of damage sustained (Stellman et al., 1998). In addition, the nature and extent of damage sustained may be influenced by exposure to different manganese-containing compounds. Studies conducted on manganese neurotoxicity addressed exposure from various sources, although more than half of the studies reviewed here investigated occupational exposure. Santos-Burgoa et al. (2001) investigated environmental exposure, Takser et al. (2003) examined prenatal exposure and Finley et al. (2003) studied dietary exposure. Three authors (33%) reported on the type of compound to which participants were exposed, which included manganese oxide, ferro-manganese, silicon-manganese, and manganese dioxide. The type of exposure assessed by Banta and Markesbery (1977) is unknown.

Exposure to more than one neurotoxin results in increased damage (Rosenberg, 1995). Three authors (33%) considered the impact of additional neurotoxins, such as aluminium and lead, on the outcomes of their studies. Lead has become ubiquitous to the environment since the introduction of tetraethyl lead as an antiknock in petrol in 1921 (Bryson, 2005). It is therefore likely that all participants were also exposure to lead. Although it is seemingly impossible to control for exposure to other neurotoxins, Myers et al. (2003) took special care to measure possible exposure through a questionnaire, and controlled for the results in their data analysis.

The majority of studies (67%) assessed long-term manganese exposure, ranging from 11.2 years (Brown et al., 1991) to 20.4 years (Bouchard et al., 2003). One short-term exposure study (Finley et al., 2003) considered women who were exposed to dietary manganese for eight weeks. Levels of manganese exposure were quantitatively determined in 67% of studies using blood manganese levels. Forty-four percent used air sampling (personal sampling, stationary sampling and high volume filtration suction pump). The larger percentage of studies utilising quantitative measurements of manganese exposure relative to carbon disulphide studies may be attributed to the contemporary nature of these studies. The evaluation of these measurements reveals that the majority of studies reviewed assessed participants who had been exposed to manganese levels within the American Conference of Governmental Industrial Hygienists Threshold Limit Value of 0.21mg/m^3. Studies that assessed exposure to manganese at levels lower than regulatory standards include Bouchard et al. (2003), Deschamps et al. (2001) and Myers et al. (2003). Sjögren et al. (1996) reported blood manganese levels lower than *The Agency of Toxic Substances Disease Registry of* 14 µg/L. Brown et al. (1991), Takser et al. (2003) and Santos-Burgoa et al. (2001) conducted assessments on participants exposed to manganese levels higher than regulatory levels. Finley et al. (2003) and Banta and Markesbery (1977) did not make use of either blood manganese or air sampling measurements and it is therefore not possible to compare the exposure of these participants with those of the other studies reviewed here.

5.2.3 Current Trends in Manganese Assessment Methodology

The studies under review used a variety of methodologies to achieve the aims. These methodologies include longitudinal designs (Takser et al. 2003), cross-sectional experimental designs with control groups (Deschamps et al. 2001; Sjögren et al., 1996) as well as correlational designs (Myers et al., 2003; Santos-Burgoa et al., 2001) and a case study (Banta & Markesbery, 1977). Brown et al. (1991) conducted a cross-sectional study but also correlated neuropsychological outcomes with manganese exposure levels. Finley et al. (2003) compared the outcomes of women given different combinations of manganese-supplemented diets in a quasi-experimental design. Bouchard et al. (2003) conducted a quasi-experimental design in which they compared outcomes of participants with different levels of alcohol consumption and different levels of manganese exposures. Of all the studies reviewed here, only Brown et al. (1991) used a double-blind methodology.

As with the studies on carbon disulphide neurotoxicity, the studies reviewed here encountered many possible confounding variables. The authors employed statistical measures such as multiple linear regression and matched control groups to counteract these influences. The confounding variables accounted for in the various studies are indicated in TABLE 5-2. Since many studies used correlation and longitudinal designs, few control groups were used. The use of an exposed control group in a cross-sectional experimental design may result in false

negative findings. This should be considered in the findings of the study by Brown et al. (1991), in which the outcomes of a high and low exposure group were compared. In addition, Sjögren et al.'s (1996) findings may be biased by the use of control groups potentially exposed to steel lead or aluminium, which may have neurotoxic effects.

Table 5-2: Confounding variables considered during neuropsychological toxicology investigation of manganese exposure

Confounding variables	Bouchard et al. (2003)	Brown et al. (1991)	Deschamps et al. (2001),	Myers et al. (2003)	Santos-Burgoa et al. (2001)	Sjögren et al. (1996)	Takser et al. (2003)
Age	√	√	√	√		√	√
Alcohol use						√	
Birth weight							√
Caffeine							√
Duration of labour							√
Education		√	√	√			
Ethnic group			√				
Gestational age							√
Other neurotoxic exposure				√		√	
Head injury		√		√			
PNS pathology			√				
CNS pathology (not Mn induced)		√	√			√	
Gender			√				√
Smoking	√		√	√		√	√
Sociodemographic	√						
Substance abuse		√					

√ *confounding variables reported* *Blank - confounding variable not reported*

**No confounding variables reported by Banta and Markesbery (1977) and Finley* et al. *(2003)*

5.2.4 Sample Characteristics

Both sample size and participant characteristics may impact on the outcomes of the neuropsychological assessments reviewed here. They also provide an indication of the

current nature of neuropsychological toxicology investigation of manganese. Sample sizes used impact on the validity of findings. The sample size range is as follows:

- **Exposed group:** n=1 (Banta & Markesbery, 1977) to n=480 (Myers et al., 2003)
- **Control group:** n=20 (Brown et al., 1991) to n=137 (Deschamps et al., 2001)

The outcomes of the studies by Brown et al. (1991), Finley et al. (2003) and Sjögren et al. (1996) may have been influenced by the small samples used.

Like the studies on carbon disulphide, studies on manganese exposure have been conducted around the world, from South Africa (Brown et al., 1991) to Mexico (Santos-Burgoa et al., 2001). Participants comprise occupationally exposed workers (enamel and refinery workers) to community members living in mining areas. As in the studies conducted on carbon disulphide, the majority of neuropsychological toxicology investigations of manganese exposure were conducted on middle-aged men, with a mean age range of 35.7 years (Finley et al. 2003) to 55 years (Banta & Markesbery, 1977), with a standard deviation less than 17.43 years (Santos-Burgoa et al., 2001).

Old age is associated with a natural decline in neuropsychological performance (Lindeboom & Weinstein, 2004). In addition, participants in their later decades may develop neurodegenerative disorders such as Parkinson's disease, which is also associated with manganese exposure (Aschner, 2000). Therefore, a disadvantage of including geriatric participants is that it may be difficult to determine if the changes in participant outcomes are due to the natural ageing process, the development of true Parkinson's disease, manganese neurotoxicity or the development of unrelated neurodegenerative diseases. In addition, the inclusion of geriatric participants may skew the outcomes of this study due to a natural decrease in performance. Santos-Burgoa et al. (2001) correlated neuropsychological outcomes with quantitative measurements of exposure. Age may act as a third variable in these correlations if manganese accumulation occurs. This is because increased age may be associated with increased duration of exposure, which may correlate significantly with increased deficits. In this case it is not possible to determine if this correlation is due to the natural decline in outcomes of healthy geriatric participants or due to manganese-induced pathology. However, Santos-Burgoa et al.'s (2001) sample had a mean of 43.3 years and a standard deviation of 17.43 years; therefore, participants as old as 93 years may represent outliers in this group.

Takser et al. (2003) conducted the only study on prenatal exposure. They assessed for prenatal manganese exposure and then followed the babies to the age of six years. This longitudinal study is extremely valuable, as it not only sheds light on the effects of prenatal exposure (which is different from exposure later on in life due to the hypersensitivity of the developing unborn brain to neurotoxic damage), but also traces the impact of this damage on the children's development. This study highlights the importance of the assessment of

prenatal exposure, and is discussed in greater detail in the following section. No other study assessing prenatal exposure could be sourced for this review, indicating that, despite the great need for this type of research, this area of neuropsychological toxicology is greatly under-researched.

Contrary to the studies conducted on carbon disulphide, which only assessed male workers, 44% of the studies reviewed here include women. Gender differences may occur with both sensitivity to manganese as well as normal outcomes on neuropsychological tests; therefore, it is important to use control groups matched to gender (Anger et al., 1997). Although the inclusion of women in a sample may complicate the analysis of these studies, information regarding the sensitivity of women to neurotoxic chemicals is essential as they may respond differently. This is especially relevant as anaemia, which is common in children and adult females (Meyer et al., 1997), has also been associated with manganese hypersensitivity. People with anaemia may absorb almost twice as much manganese as those who do not have anaemia (Röllin et al., 2005). It is therefore likely that these subgroups of the population are more sensitive to manganese exposure. Previous NOAEL determined by studies conducted on men may therefore not be appropriate for women in the workforce.

Further factors that may increase sensitivity to manganese exposure include genetic influences, familial sensitivity, co-exposure, nutritive deficiency, pathology of respiration, the hepatic biliary excretion system and alcoholism (Bouchard et al., 2003). Deschamps et al. (2001) notes that the job turnover at the site of their investigation was significant. This may have lead to the super-selection of hyposensitized individuals for this study, as the more sensitive workers may have resigned due to the symptoms they incurred through neurotoxic exposure. Brown et al. (1991) also noted the inability of a cross-sectional study to control for the "healthy worker effect" discussed above. The other authors failed to consider individual sensitivity.

5.2.5 Trends in the Assessment of Manganese Neurotoxic Brain Injury

This section considers the medical, neuropsychological and psychological assessments employed by the studies reviewed here. As in the previous chapter, medical measures are only reported to the extent to which these are correlated with neuropsychological or psychological measures, which are the main focus of this review.

5.2.5.1 Medical Assessment

Twenty-four medical measures were employed by the various studies reviewed here. Like the assessments used for the evaluation of carbon disulphide exposure, these include a number of neurological assessments. The most popular neurological assessments used were

observations of features of Parkinson's disease (gait, posture, and balance) (44%), and a neurological examination (33%). The case study methodology employed by Banta and Markesbery (1977) enabled the use of additional neurological measures including a brain scan and cerebral angiogram. Electroencephalography was conducted by both Sjögren et al. (1996) and Banta and Markesbery (1977).

A number of measures were used to determine the participants' level of manganese exposure. This most frequently entailed the measurement of blood manganese levels and air sampling. Other measurements included the following.

- hair sample (Takser et al., 2003)
- auxiliary sample (Banta & Markesbery, 1977)
- faeces sample (Banta & Markesbery, 1977)
- frontal lobe biopsy (Banta & Markesbery, 1977)
- pubic sample (Banta & Markesbery, 1977)
- scalp sample (Banta & Markesbery, 1977)
- urinary sample (Banta & Markesbery, 1977; Brown et al., 1991)
- placenta sample (Takser et al., 2003)
- brain stem manganese levels (Sjögren et al., 1996)

In the following sections these measures are discussed with respect to their correlation with neuropsychological findings.

5.2.5.2 Neuropsychological and Psychological Assessment

Thirty-one tests and subtests were used to evaluate manganese exposure. These are shown in TABLE 5-3.

Table 5-3: Review of neuropsychological and psychological tests used to assess damage due to manganese exposure

Authors	Neuropsychological Assessment
Banta and Markesbery (1977)	• Not specified
Bouchard et al. (2003)	• Profile of Mood States (POMS) • Brief symptoms inventory
Brown et al. (1991)	• Adaptation from World Health Organisation-Neurobehavioural Health Core Test Batteries (WHO-NCTB) • Profile of Mood States (POMS) • Digit Span

Authors	Neuropsychological Assessment
	• Grooved Pegboard • Geometric Design Reproduction • Digit Symbol • Paragraph Memory
Deschamps et al. (2001)	• Similarities (WAIS-R/III) • Vocabulary (WAIS-R/III) • Visual Gestalts • Digit Span (WAIS-R/III) • Profile of Mood States (POMS)
Finley et al. (2003)	• Durkee Hostility Inventory • Interpersonal Behaviour Survey • State-Trait Anger Expression Inventory
Myers et al. (2003)	• Luria-Nebraska Test Battery • Swedish Performance Evaluation System (SPES) • Swedish Q16 • World Health Organisation- Neurobehavioural Health Core Test Batteries (WHO-NCTB)
Santos-Burgoa et al. (2001)	• Ardila-Ostroski • Hooper Visual Organization Test • Mini-Mental Screening test • WAIS subtests
Sjögren et al. (1996)	• Luria-Nebraska motor scale • Questionnaire on Mood • Swedish Performance Evaluation System (SPES) • Wechsler Adult Intelligence Scales subtests • Questionnaire 16 of symptoms
Takser et al. (2003)	• Brunet-Lezine scale (9 months) • MacCarthy Scale of Children's Abilities (3 and 6 years) • Unspecified (psychomotor abilities, attention, executive functioning, language, nonverbal memory, verbal memory, visuospatial)

Like the studies reviewed on carbon disulphide, standard neuropsychological toxicology batteries influenced authors' selection of neuropsychological tests. The table above shows that complementary batteries are often used in addition to standard batteries such as the WHO-NCBT and SPES. WAIS subtests are often used, probably due to the familiarity of authors with these measures. Nowhere did authors refer to an underpinning theory (including dynamic brain localisation theory), or evaluation of the chemical mechanisms of manganese

damage as a rationale for test selection. However, Myers et al. (2003) did report selecting tests based on test sensitivity reports in the literature. Deschamps et al. (2001) selected tests that were reported as valid and reproducible. Takser et al. (2003) selected measures of psychomotor deficits based on the literature, which revealed an association with manganese exposure. Finally, Santos-Burgoa et al. (2001) selected a battery that had been adapted for the Mexican environment. Interestingly, despite their acclaimed popularity in this field, computer batteries were not widely used in the studies reviewed here. Additional information regarding exposure history, confounding variables and subjective symptoms were collected in much the same way as carbon disulphide studies.

5.3 Discussion

The remainder of this chapter applies the information put forth in the preceding sections. This information is used to disentangle the various aspects of these studies so that meaning can be derived from their findings. The quantitative measurement of manganese exposure further enables the comparison of neuropsychological outcomes relative to exposure level. As previously stated, one of the primary objectives of this study is to investigate the sensitivity of various neuropsychological tests to damage sustained thought manganese exposure. More specifically, the sensitivity of psychomotor assessments is investigated, as these are conjectured to be sensitive to basal ganglia damage incurred through manganese exposure (Kaplan & Sadock, 1998; Lucchini et al., 2000).

For the purposes of these discussions, the definition of test sensitivity, which was noted in the previous chapter, is repeated here for the convenience of the reader. The sensitivity of the neuropsychological test can be defined as the ability of the test to discriminate between individuals who have been exposed to a neurotoxin and those who have not. Therefore, a sensitive test is one that is likely to measure the deficits resulting from damage sustained from neurotoxic exposure. The following information, obtained from the publications reviewed here, is used as an indication of test sensitivity.

- Cross-sectional studies: The assessment instrument measures significant changes in outcomes between experimental and control groups.
- Longitudinal study: The assessment instrument measures significant changes in outcomes between baseline and follow-up measurements.
- Correlation study: Deficits measured by the assessment instrument correlate significantly with increased manganese exposure.
- Case study: Deficits measured by the assessment instrument differ significantly from standardised norms, or performance is judged by a skilled test administrator to be significantly impaired.

5.3.1 Neuropsychological Outcomes at Regulatory Manganese Exposure Levels

This section looks at studies that evaluated participants exposed to manganese levels not exceeding the *American Conference of Governmental Industrial Hygienist Threshold Limit Value*. These include the studies conducted by Deschamps et al. (2001), Myers et al. (2003) and Bouchard et al. (2003). The outcomes of these studies, relative to their exposure level, are shown in FIGURE 5-1.

Deschamps et al. *(*2001) did not find significant differences between experimental and control groups on neuropsychological measures (WAIS subtests), psychological measures (POMS depression and dejection) or the neurological examination (probable Parkinson's diagnosis, tremors, cutaneous sensory deprivation, muscle power, reflexes and psychomotor functioning). This may be attributed to the fact that there was no significant difference in blood manganese concentrations between the experimental (170nmol/L) and the control group (166nmol/L). The blood manganese levels of both these groups are within the normal range. Despite this, the experimental group reported an increase in subjective complaints including asthenia, sleep disturbances and headache. The increase in these symptoms reported may be attributed to malingering as a double-blind method was not used and participants were informed about the aim of the research.

Myers et al. (2003) conducted a correlation design, using a variety of standard neuropsychological toxicology batteries (Luria-Nebraska Test Battery, SPES and WHO-NCTB). Myers et al. (2003) found no outcome correlations with blood manganese levels at this level of exposure, despite the fact that participants had been exposed for an extended period. The correlation of neuropsychological outcomes with quantitative measures of manganese exposure is an effective means of determining deficits. The findings of this study therefore lend support to the effectiveness of the current exposure regulatory limit. The studies conducted by Myers et al. (2003) and Deschamps et al. (2001) support the notion that no adverse effects are incurred in workers exposed to the current *American Conference of Governmental Industrial Hygienists Threshold Limit Value* over a number of years.

Bouchard et al. (2003) conducted a quasi-experimental design in which participant outcomes were compared with respect to both manganese and alcohol consumption through the use of ANOVA and students t-test. The authors report that high levels of alcohol consumption, in combination with manganese exposure, impact on mood state (POMS: tension, anger, fatigue, depression and confusion). This tendency was not observed among high alcohol consumers in low blood manganese categories. The POMS measurement was also employed by Deschamps et al. (2001); however, it did not measure any changes in these participants' mood. The outcomes of the Bouchard study may have been influenced by the lack of a double-blind methodology. In addition, Bouchard et al. (2003) did not control for all the

confounding variables recommended by Anger et al. (1997). Nonetheless, this study does highlight the importance of individual sensitivity to manganese. It also raises concerns that neurotoxic effects may occur in people who are exposed to regulatory levels of manganese but who are more susceptible to its toxicity, either through their lifestyle (i.e. high levels of alcohol use) or other factors (such as anaemia – see discussion above).

The study conducted by Sjögren et al. (1996) measured outcomes of participants exposed to manganese levels below recommended maximum levels, while Brown et al. (1991) evaluated participants exposed to higher levels. The outcomes of these two studies will now be discussed. (Takser's study investigated prenatal exposure, and will therefore be discussed separately. The study conducted by Finley et al. (2003) assessed participants exposed to dietary manganese, and it is therefore not possible to compare the relative exposure of this study with the others.) The outcomes of these studies, relative to their exposure levels, are shown in FIGURE 5-1.

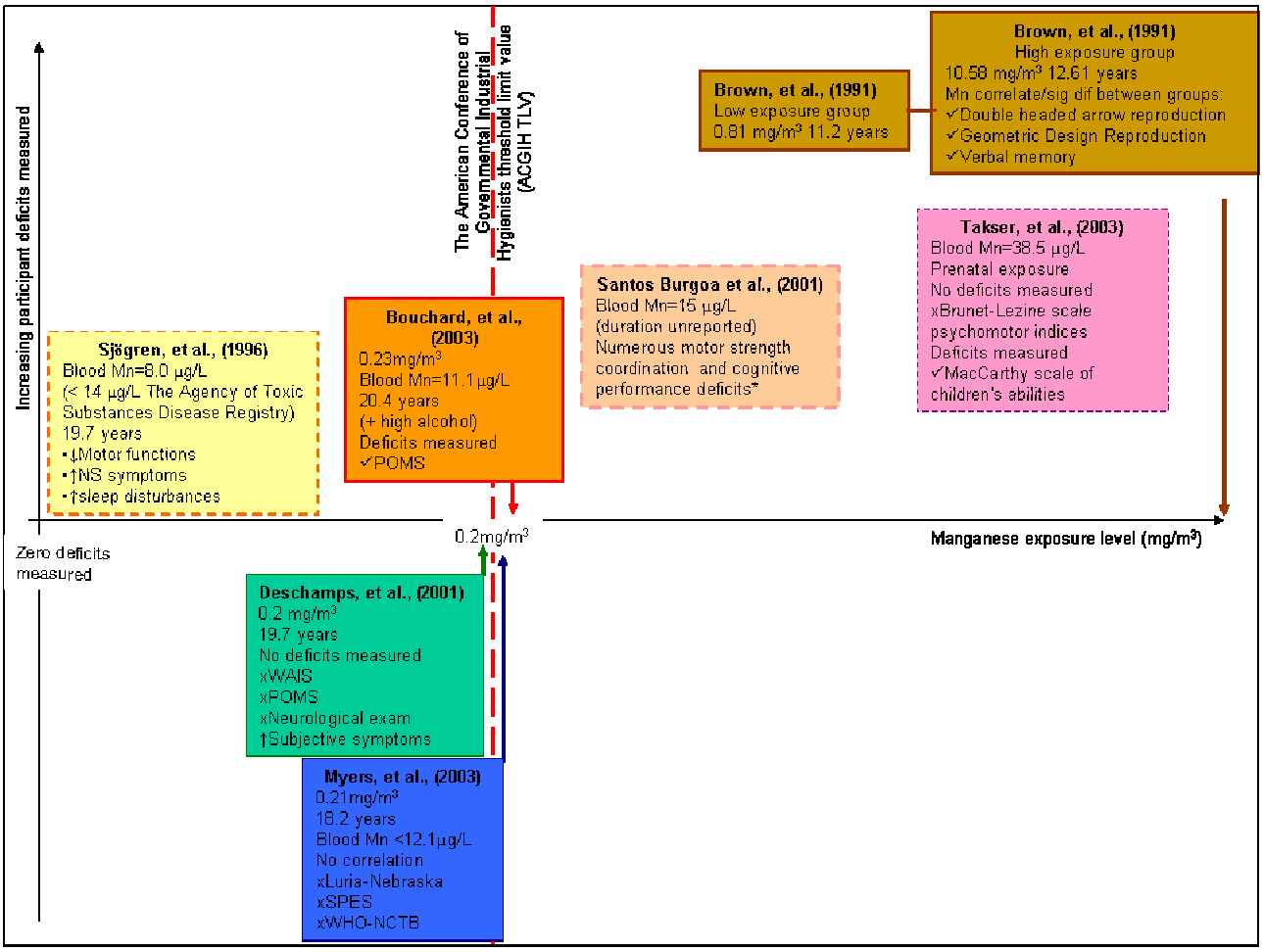

Figure 5-1: A schematic representation of a review dose-response curve of manganese neurotoxicity

Blood Mn and air sampling measures of manganese exposure are indicated in studies where these have been reported.

--- Indicates studies which provided blood manganese levels only and are therefore placed on the figure relative to the exposure levels of other studies

**Santos-Burgoa* et al. *(2001): used numerous motor strength, coordination and cognitive tests, including the following:*

- *motor strength coordination (motor strength continuous, motor strength categorical, finger-tip touching, asymmetric rhythm, election reaction, symbolic reaction)*
- *cognitive performance (mini-mental concentration, memory, following instructions, writing)*

In the study by Sjögren et al. (1996), participants' blood manganese levels were below the recommended maximum level. Nonetheless, the authors did measure changes in the experimental group even though no significant differences were observed between experimental and control group blood manganese levels. It is interesting to note that Sjögren et al. (1996) included a wide array of psychomotor assessments for this evaluation - this will be discussed shortly. Deficits measured include decreased motor functioning, increased latency of event-related auditory evoked potential, increased peripheral nervous system (PNS) and central nervous system (CNS) symptoms, increased sleep disturbances. Possible confounding variables, which may have biased the findings, include the lack of a double-blind method, age, gender, culture and education, as well as the simultaneous exposure of participants to aluminium. Despite these drawbacks, this study does emphasise the need for further research into the effectiveness of current NOAEL. It also raises questions about the impact of using multiple psychomotor tests on outcomes.

The study conducted by Santos Burgoa et al. (2001) evaluated participants exposed to only slightly higher levels of manganese than those stipulated by *American Conference of Governmental Industrial Hygienists Threshold Limit Value*. The authors correlated blood manganese levels with various neuropsychological measurements and concluded that motor strength coordination (motor strength continuous, motor strength categorical, finger-tip touching, asymmetric rhythm, election reaction, symbolic reaction) and cognitive performance (Mini-Mental States Exam Subtests; concentration, memory, following instructions, writing) contributed largely to the explanation of the effect in their statistical models. However, the highest R^2 for any assessment was 0.44 for motor strength. Cases of tremors and numbness were also identified. No quantitative measure was taken of the number of years these participants were exposed; therefore it is not possible to determine whether the changes in these outcomes, in comparison with the previous authors reviewed, were due to length of exposure.

Brown et al. (1991) studied participants exposed to considerably higher levels of manganese. Outcomes of the Double Headed Arrow Reproduction Test and the Geometric Design Reproduction Test correlated significantly with increased manganese exposure, and measured significant differences between the high and low exposure groups. Verbal memory (four-word sequence) and visuoconstructional (geometric design) tests also revealed significant differences between high and low exposure groups. Soft neurological signs were also reported in 31.4% of participants. Brown et al. (1991) conclude that exposure to these levels may be associated with visuconstructional dyspraxia. The small number of assessments that detected differences in the two research groups may be attributed to high exposure level of both research groups, as no normal unexposed control was used. It is likely that both groups incurred neurotoxic brain injury at these high exposure levels, therefore both groups may have performed poorly on neuropsychological assessments accounting for the lack of significant difference between groups.

5.3.1.1 Summary

Of the studies reviewed here, the Deschamps and Myers studies lend support to the effectiveness of the current *American Conference of Governmental Industrial Hygienist Threshold Limit Value*. However, the Sjögren and Bouchard studies report deficits in participants exposed to manganese at these levels. The lack of correspondence in these findings may be attributed to methodological differences, participant variation, methodological errors and differences in assessment methods.

Deschamps et al. (2001) and Myers et al. (2003), who both failed to detect any significant deficits in their participants, used subtests that largely measure cognitive constructs. However, Sjögren et al. (1996) was able to distinguish between exposed and control groups at lower exposure levels using psychomotor tests such as the Luria-Nebraska Motor Scale, Grooved Pegboard and Tapping Speed subtests (the impact of aluminium exposure of these participants and other methodological issues discussed earlier should be kept in consideration). Santos-Burgoa et al. (2001) tested participants exposed to slightly higher levels of manganese and concluded that motor strength coordination and cognitive performance which had a high explanation effect for their models.

The findings are not surprising as motor deficits are associated with manganese exposure (Zatta et al., 2003). From the preceding discussion, a pattern appears to be emerging that lends support to the analysis of manganese exposure using psychological measures, mood assessments and psychomotor evaluations. This is congruent with the expected behavioural deficits emerging from basal ganglia damage incurred through manganese exposure (Kaplan & Sadock, 1998; Lucchini et al., 2000). In the following section, the sensitivity of the various subtests to deficits incurred through manganese-induced damage is discussed in detail.

5.3.2 Psychomotor Outcomes

TABLE 5-4 shows a selection of tests taken from the original thirty-one tests and subtests employed by the authors reviewed here to assess manganese neurotoxicity. These tests have been reported by Lezak et al. (2004) and other authors to be effective in the evaluation of psychomotor deficits.

Table 5-4: Psychomotor tests employed for the assessment of manganese neurotoxicity

Authors	Myers et al. (2003)	Brown et al. (1991)	Sjögren et al. (1996)	Santos-Burgoa et al. (2001)	Takser et al. (2003)
Asymmetric Rhythm				√	
Brunet-Lezine Scale Psychomotor Indices					x
Digit Symbol	x				
Finger-tip Touching				√	
Luria Nebraska Motor Scale	x		√		
Motor Strength Continuous				√	
Motor Strength Categorical				√	
Pegboard		x	√		
Tapping Endurance			x		
Tapping Speed			√		
Symbolic Actions				√	

√ Test measured deficits in participants

X Test did not measure deficits in participants

Blank - test not employed in study

Of the assessments reviewed here, the probability of measuring deficit resulting from manganese-induced brain damage with a cognitive assessment is P=0.22, whereas the probability when using a psychomotor test is P=0.62. The probability when using a psychological test such as POMS is P=0.29.

Unfortunately, with the exception of the Digit Symbol subtest, these psychomotor tests were not used in a sufficient number of studies to facilitate the comparison of outcomes.

5.3.2.1 Digit Symbol subtest

The Digit Symbol subtest is primarily a test of psychomotor functioning. Lezak et al. (2004) describes it as a highly sensitive test, which can measure even slight differences in the functioning of participants, and performance is affected regardless of the location of the lesion. This test is therefore also recommended for screening purposes.

Table 5-5: Inter-study comparison of the Digit Symbol subtest

	Carbon disulphide			Manganese		Organophosphate								
	Aaserud et al. (1990)	Hanninen*	Cho et al. (2002)	Brown et al. (1991)	Myers et al. (2003)	Ames et al.* (1995)	Farahat et al.(2003)	London et al. (1997)	Maizlish et al. (1987)*	Reidy et al. (1992)	Richter et al. (1992)	Rosenstock et al. (1991)	Savage et al. (1988)	Steenland et al. (1994)*	Stephens et al. (1995)
digit symbol	√	√	x	x	x	x	√	x	√	x	√	√	√	√	√

√Test measured deficits in participants

X Test did not measure deficits in participants

** Hanninen, cited in Feldman et al. (1980)*

**Ames, Steenland, Jenkins, Chrislip & Russo (1995)*

**Maizlish, Schenker, Weisskopf, Seiber &. Samuels (1987)*

**Steenland, Jenkins, Ames, O'Malley, Chrislip & Russo (1994)*

Inter-neurotoxin comparison

The Digit Symbol subtest measured deficits in 67% of carbon disulphide studies and 70% of organophosphate studies. This attests to the efficiency of this test as a screening tool.

Intra-neurotoxin comparison

Myers et al. (2003) and Brown et al. (1991) employed the Digit Symbol for their assessments. Brown et al. (1991) found that this test did not measure any significant differences between the high and low exposure groups. However, as both these groups were exposed to very high levels of manganese and may have already incurred extensive damage, it is possible that this is a false negative finding. The findings from this study may further have been influenced by the use of a very small sample size (high exposure group n=19; low exposure group n=20). The possible confounding effect of sociodemographic issues was not considered. Myers et al. (2003) found that the measurements of this test did not correlate significantly with manganese

exposure measurements. The findings from this robust measurement do not provide support for the use of the Digit Symbol for the evaluation of manganese-induced deficits. However, further research is required to investigate this further.

5.3.2.2 Psychomotor Assessment in Children

Takser et al. (2003) aimed specifically to measure psychomotor changes in participants; however, the psychomotor indices on Brunet-Lezine Scale did not measure changes in these participants. A number of cognitive measures employed by Takser et al. (2003) did measure significant changes, however. As adult manganese-induced damage is associated with damage to the basal ganglia and motor deficits (Kaplan & Sadock, 1998; Lucchini et al., 2000), and Takser et al. (2003) measured predominantly cognitive and not motor deficits, this supports claims that the mechanism of damage sustained through prenatal manganese exposure is different from that of postnatal and adult exposure. This may be due to a number of factors, including the absence of a fully developed blood-brain barrier. There is possibly a cumulative effect of damage, as the number of cells that would have replicated from the precursor cells is significantly reduced. This then disrupts the natural process of brain formation (Harris & Blain, 2004; Hartman, 1995).

5.3.3 Psychological and Emotional Assessments

Psychological and emotional changes may precede motor outcomes in manganese-induced damage (Kaplan & Sadock, 1998; Lucchini et al., 2000). The sensitivity of psychological and emotional tests will now be investigated. Of the publications reviewed here, Bouchard et al. (2003), Brown et al. (1991), Deschamps et al. (2001) and Finley et al. (2003) made use of psychological and emotional assessments.

5.3.3.1 Profile of Mood States (POMS)

As previously mentioned, Bouchard et al. (2003) found that high levels of alcohol consumption combined with manganese exposure resulted in increased levels of tension, anger, fatigue, depression and confusion, based on the POMS measurement. However, Deschamps et al. (2001) used the same measurement at approximately the same exposure levels and did not measure any change. The deficits measured in Bouchard et al.'s (2003) participants may have been due to the compounding effect of alcohol or due to the different compounds of manganese to which they were exposed. Brown et al. (1991) did not measure any differences between high and low exposure groups with this measurement. The discrepancies in these outcomes may be due to the confounding variables and methodological issues already discussed.

5.3.3.2 Other Psychological and Emotional Assessments

The psychological and emotional changes associated with manganese exposure found in the Bouchard study are supported by the findings of Finley et al. (2003). These authors evaluated the effect of dietary manganese supplements and concluded that a high intake of manganese significantly decreased self-confidence and requesting help behaviour; however, on the Durkee Hostility Inventory, hostility, anger and aggression were not affected. This study was conducted exclusively on women.

The reports of depression in the case study participant assessed by Banta and Markesbery (1977) further support for the suitability of psychological and emotional measurements for manganese-induced deficits. Banta and Markesbery (1977) did not specify which neuropsychological assessment instruments were used. As in the case of carbon disulphide neurotoxicity, the depression noted in patients exposed to manganese may be due to the neurotoxic mechanism, similar to Parkinson's disease, and not merely due to the impact of having a severe disability (Lezak et al., 2004). Banta and Markesbery's (1977) use of a case study enabled the collection of in-depth psychological and emotional information from the patient's family. The family reported the following symptoms in the patient: hypomanic symptoms such as compulsive walking, increased working hours, poor attention and concentration insomnia, weight loss, irritability followed by aggression, confusion, moderate dysphasia and motor preservation, impaired attention and concentration, and markedly diminished recent memory. This patient later went on to develop many clinical signs associated with progressive Parkinson's disease.

The psychological signs and other symptoms reported by the authors reviewed here are consolidated in TABLE 5-6.

Table 5-6: Psychological symptoms measured in manganese-exposure participants

Psychological symptoms	Banta & Markesbery (1977)	Bouchard et al. (2003)	Brown et al. (1991)	Deschamps et al. (2001)	Finley et al. (2003)	Sjögren et al. (1996)
Aggression	√				X	
Apathy				X		
Anger		√			X	
Anorexia				X		
Anxiety		√				X
Arousal			√			

Psychological symptoms	Banta & Markesbery (1977)	Bouchard et al. (2003)	Brown et al. (1991)	Deschamps et al. (2001)	Finley et al. (2003)	Sjögren et al. (1996)
Assertiveness					√	
Asthenia				√		
CNS pathology (unspecified)						X
Confusion		√				
Dejection				X		
Diminished recent memory	√					
Depression		√		X		
Dizziness						X
Dysphasia	√					
Fatigue		√				X
Guilt					X	
Headache				√		
Hostility					X	
Hypomanic symptoms	√					
Impaired abstract thinking	√					
Impaired judgment	√					
Insomnias	√					
Irritability	√			X		X
Libedo				X		
Memory deficits						X
Negativisim					X	
PNS pathology						√
Personality			√			
Poor attention	√					
Positive attitude					X	
Psychological (unspecified)						X
Rebellion					X	
Requesting help					√	
Resentment					X	
Self-confidence					√	
Sleep disturbance				√	X	√

Psychological symptoms	Banta & Markesbery (1977)	Bouchard et al. (2003)	Brown et al. (1991)	Deschamps et al. (2001)	Finley et al. (2003)	Sjögren et al. (1996)
Suspicion					X	
Temporal orientation			√			
Tremor						X
Willingness to say no					X	

√ Symptom measured in or reported by participants

X Symptom measured but not significant

Blank - symptom not measured or reported

Santos-Burgoa et al. (2001) did not report on psychological symptoms

The studies discussed above allude to the possibility that in-depth psychological and emotional evaluations of manganese exposure may in effect be more effective than the evaluation of cognitive functions. This is because psychological and emotional changes appear to precede cognitive deficits in these participants. These findings are supported by the findings of Lucchini et al. (2000), who established a link between the affinity of manganese to the nigrostriatal tract, resulting in the auto-oxidation of dopamine and subsequent aggressive behaviour.

5.3.4 Investigation of Parkinson's Disease and Huntington's Disease as Models for the Assessment of Basal Ganglia Damage

As both Parkinson's disease and Huntington's disease are characterised by basal ganglia pathology (Lezak et al., 2004) similar to that of manganese neurotoxicity, the possibility of using the assessment used with these diseases as a model for the assessment of manganese exposure warrant further attention. The assessment of the former diseases has attracted significantly more research than manganese neurotoxicity.

Huntington's disease is characterised by both psychological and motor deficits. Measurements that tend to decrease during the progression of this disease include the Trail Making Test, Symbol Substitution, and Digit Recall. Similarities, Information, Comprehension and Vocabulary WAIS-R/III scores are preserved. Calculations, Digit symbol, Comprehension, Arithmetic scores generally deteriorate (Lezak et al., 2004). Of these measurements the Similarities, Vocabulary and Digit Symbol WAIS-R/III subtests were employed in the studies reviewed here. None of these measured any significant deficits in the participants.

As discussed in the literature chapter, Parkinson's disease is almost indistinguishable from the progressive stages of manganese poisoning (Aschner, 2000). Parkinson's disease is characterised by psychomotor deficits, the assessment of which has already been discussed, as was the high incidence of depression associated with Parkinson's disease and the measurement of depression in the studies reviewed here. Additional deficits found in this disease include attention span, memory, learning and visuospatial impairments, while vocabulary, grammar, Digit Span scores, thinking, reasoning and syntax may be normal (Lezak et al., 2004). As mentioned previously, the sensitivity of tests to psychomotor deficits exceeds that of cognitive assessments.

5.4 Conclusion

The majority of manganese neuropsychological toxicology studies reviewed in this chapter were published in the last five years. When compaird to the mostly older carbon disulphide studies, reviewed in the previous chapter, the contemporary nature of these studies demonstrates the progressive trend in the field of neuropsychological toxicology. The review of study aims illustrates a move towards asking more specific questions, rather than merely investigating the general effects of neurotoxic exposure, as was done in the majority of older carbon disulphide studies. Most notable was the specific investigation of psychomotor deficits, indicating an increased understanding of the neurotoxic mechanism of this neurotoxin, and a shift away from regarding neurotoxic brain damage as a homogenous phenomenon.

These trends are demonstrated by the three most recent studies conducted in 2003. Bouchard et al. (2003), Finley et al. (2003) and Takser et al. (2003) aimed specifically to assess psychomotor and mood changes in participants, as these are associated specifically with manganese neurotoxicity. Neuropsychological assessments were selected specifically to assess these constructs. These authors demonstrated the development of instrument selection from older studies such as those conducted by Deschamps et al. (2001) Myers et al. (2003) Brown et al. (1991) Santos-Burgoa et al. (2001), in which the specific effects of manganese are not considered. These studies aim only to assess the general effects of its neurotoxicity and none specific standardised batteries assessing global functions are used in much the same way as in carbon disulphide studies.

In comparison with the studies conducted on carbon disulphide exposure, the assessment of participants exposed to manganese levels below regulatory levels in a number of studies highlights the trend of moving away from evaluating high-level exposure to the evaluation of possible subclinical signs incurred through low-level exposure. In addition the inclusion of women as research participants provided much-needed information on this potentially hypersensitive group. Like the research conducted on carbon disulphide exposure, the majority of research participants were middle-aged. An exception to this was Takser et al.'s

(2003) investigation of prenatal exposure, which highlighted the potential severity of this type of exposure, the potentially different cerebral consequences (as opposed to adult damage), and most of all, the need for more research in this area amid concerns of increasing environmental exposure from MMT.

Although the issue of individual hypersensitivity is seldom considered in current neuropsychological toxicology investigations, the review in this chapter highlights the need for research in this area. Women, foetuses, children and geriatrics are more sensitive to neurotoxic exposure, yet are greatly under-represented in the research on neurotoxins. In addition, the study conducted by Bouchard et al. (2003) highlights the role of lifestyle in increasing sensitivity by demonstrating that high alcohol consumption may result in psychological deficits at exposure levels approximate to regulatory levels.

A further trend observed in the studies reviewed here is an increased tendency to use medical and occupational hygiene methods to quantitatively measure manganese exposure levels. This enabled the comparison of studies and the evaluation of current regulatory exposure levels. It is disconcerting that studies such as Sjögren et al. (1996) and Bouchard et al. (2003) measured deficits in participants exposed to manganese levels below regulatory limits. It is possible that the use of more psychological and psychomotor measures by these authors resulted in more sensitive measurements. However, the different methodologies and participant characteristics hinder any definite conclusions in this regard.

In addition to some authors' selection of psychomotor assessments, the use of standard neuropsychological toxicology batteries greatly influences assessment selection. The findings of this review provide support for the sensitivity of psychomotor and psychological assessments, such as those assessing depression. This is in line with the expected deficits associated with damage to the basal ganglia following manganese exposure. However, not all psychomotor and psychological assessments from all studies were sensitive to this damage. Further research to this regard is required. In addition, diseases characterised by basal ganglia pathology such as Parkinson's disease and Huntington's disease may provide a model for the further development of instruments to assess damange to this deep-lying structure.

CHAPTER 6: ORGANOPHOSPHATE

6.1 Introduction

Organophosphates were originally developed as nerve gas during World War II, and were only later introduced as pesticides. Four organophosphates are still used for military purposes as weapons of mass destruction. For example, Sarin was recently used in terrorist attacks (Lessenger & Reese, 1995). It is not surprising that organophosphates are more acutely toxic than many other pesticides (Hartman, 1995). It is estimated that worldwide there are three million severe cases of acute poisoning and 220 000 deaths caused by organophosphate exposure per year. Ninety-nine percent of these deaths occur in developing countries where up to 25 million cases of poisoning occur among agricultural workers alone (Rosenstock et al., 1991). The *Human No Observed Effects Level* (NOEL) for organophosphate exposure determined by WHO is 8.4mg/day (Maizlish et al., 1987).

Organophosphates consist of a large group of pesticides such as phosphonates, phosphoramidates or phosphororthioate. Although these pesticides have different chemical structures, all organophosphate neurotoxin action is the result of the same neurotoxic mechanism. Organophosphates inhibit the enzyme acetylcholinesterase, which plays an important role in acetylcholine metabolism. Acetylcholine is an omnipresent neurotransmitter. Acetylcholine-releasing neurons project to the entire cortex and are thought to play a role in learning, memory, motoric learning and the sleep-awake cycle (Schatz & Chute, 2000; Thiel, 2003). Acetylcholine is inactivated by the enzymatic action of acetylcholinesterase. Organophosphate inhibits the action of acetylcholinesterase, resulting in an acetylcholine overload (Daniell et al., 1992; Eyer, 1995). Central nervous system lesions such as lesions or changes to acetylcholine receptors may also occur (Hartman, 1995).

Depending on the extent of organophosphate exposure, either subclinical or clinical signs may develop in exposed individuals (Hartman, 1995). In the case of acute poisoning, acetylcholinesterase inhibition in the peripheral nervous system results in a number of signs ranging from hyper-salivation, lacrimation, ptosis, conjunctivitis, visual impairment, nausea, vomiting, abdominal pains, diarrhoea, tachycardia, hypertension, muscle weakness and pallor (Eyer, 1995; London, Nell, Thompson, & Myers, 1998; Rosenstock et al., 1991). Salivation, lacrimation, urination and diarrhoea are classically associated with organophosphate poisoning, so that the manifestation of this group of symptoms has been termed the so-called “SLUD” syndrome (Lessenger & Reese, 1995).

After the acute symptoms have subsided and before the onset of persistent symptoms, a stage known as “intermediate syndrome” occurs. This stage is characterised by potentially fatal muscle weakening. The intermediate syndrome is followed by delayed neuropathy.

Extrapyramidal signs such as spasticity, hyperreflexia and abnormal reflexes are associated with delayed neuropathy due to organophosphate exposure (Daniell et al., 1992; Eyer, 1995; Rosenstock et al., 1991).

In the central nervous system, organophosphate poisoning results in respiratory depression, tremors, tonic-clonic convulsions, headache, vertigo, general weakness, drowsiness, decreased concentration, slurred speech, confusion, emotional lability, hypothermia, coma and death (Eyer, 1995). Neuropsychological signs that may develop include impaired vigilance and concentration, reduced information processing and psychomotor speed, memory deficits, linguistic disturbances, depression, anxiety and irritability, nightmares aggression, hallucinations and schizophrenic reactions (Eyer, 1995; Hartman, 1995).

Long-term, low-level organophosphate exposure is associated with chronic organophosphate induced neuropsychiatry disorder (COPIND). COPIND is less well characterised than the symptoms associated with acute organophosphate poisoning, but is associated with decreased memory and concentration, chronic fatigue, difficulties in learning, increased anxiety, depression, psychosis, as well as a number of extrapyramidal signs including dystonia, resting tremors, bradidynesia, postural instability and rigidity of facial muscles (Salvi, Lara, Ghisolfi, Portela, Dias & Souza, 2003). There is little concurrence between the findings of low-level long-term organophosphate exposure studies, even though a large number of these studies have been conducted that report deficits (Jamal, Hansen & Julu, 2002).

This chapter reviews sixteen neuropsychological toxicology studies on organophosphate exposure, following the structure of the two preceding chapters. These articles represent all the articles that could be obtained on this topic during a systematic search of available databases. In the first section of this chapter, current trends in the neuropsychological evaluation of organophosphate are elucidated. This information will assist in our understanding of the extent to which these factors impact on the outcomes on these studies, discussed in the second section of this chapter. However, unlike the investigations in the previous chapters, these studies report insufficient quantitative measures of organophosphate exposure to allow a comparison of the outcomes relative to the participants' level of exposure. The second section of this chapter therefore investigates the sensitivity of neuropsychological and psychological assessments to organophosphate-induced brain damage. Further, particular attention is given to the sensitivity of memory tests to this type of damage. Organophosphate exposure disrupts the acetylcholine system, and so it is possible that memory tests are more sensitive to detecting the presence of this kind of neurotoxicity.

Table 6-1 Summary of organophosphate studies reviewed

Authors	Country	Design	Double Blind	Sample size	Description of participants	Gender	Age (as in publication)
Ames et al. (1995)	California USA	Cross sectional design	Not reported	Experimental group n=45 Control group n=90	Experimental group=California workers with a history of cholinesterase inhibited Control group= California workers with no history of pesticide exposure or cholinesterase inhibition	Male	Experimental group= 38.2(11.7) mean (SD) Control group=29.5(10.9) mean (SD)
Daniell et al. (1992)	Seattle USA	Cross sectional and longitudinal design	Not reported	Experimental group n=49 Control group n=40	Experimental group= Apple orchard pesticide applicators Control group= Beef slaughter house workers	Male	Pre-exposure Experimental group=36.1 mean Control group=32.1 mean Post exposure Experimental group=32.1 mean Control group=30.3 mean
Farahat et al. (2003)	Egypt	Cross sectional design	Not reported	Experimental group n=52 Control group n=50	Experimental group= Egyptian cotton pesticide application Control group= Clerks and administrators recruited form the ministry of agriculture	Male	Experimental group=43.63 (5.51) mean (SD) Control group=42.48 (5.54) mean (SD)
Fiedler et al. (1997)	New Jersey USA	Cross sectional design (experimental and control group)	Double blind	Experimental group n=57 Control group n=42	Experimental group= fruit tree farmers Control group= blue berry, cranberry growers and hard wear store owners	Male	Experimental group= = 47.6 (1.6) mean (SEM) Control group= 47.7 (1.7) mean (SEM)
Jamal, Hansen, Pilkington et al. (2002)	United Kingdom	Quasi experimental	Double blind	No neuropathy n=15 Possible neuropathy n=34 Probable or define neuropathy n=23	Experimental group= United Kingdom sheep farmers with neuropathy Experimental group= United Kingdom sheep farmers with possible neuropathy Control group= United Kingdom sheep farmers with out neuropathy	Male 87% Female 13%	Neuropathy experimental group=46.1 (11.0) mean (SD) Possible neuropathy experimental group=46.2 (10.6) mean (SD) Control group=38.8(13.3) mean (SD) Range for all groups (20-66)

Authors	Country	Design	Double Blind	Sample size	Description of participants	Gender	Age (as in publication)
London et al. (1997	Rural South African Western Cape	Cross sectional design	Double blind	Experimental group n=163 Control group n=84	Experimental group= deciduous fruit farm workers, spray operators Control group= non spray operators	Male	Mean age for both groups 36.9 years
Maizlish et al. (1987)	California USA	Cross sectional and longitudinal design	Not Double Blind	Experimental group n=50 Control group n=56	Experimental group= pest control workers lawn sprayers employed in Japanese beetle eradication programme Control group= non applicators supervisory personal	Experimental group= Male 70%/Female=30% Control group= Male 62%/ Female=38%	Experimental group= 29 (9) mean (SD) Control group= 32 (9) mean (SD)
Reidy et al. (1992)	California USA	Cross sectional design	Not reported	Experimental group n=21 Control group n=11	Experimental group= Hispanic migrant farm workers referred for neuropsychological evaluation by attorney who was representing them as they had been exposed to 2 acute poisonings Control group= voluntary cannery workers from same community.	Male	Not reported
Richter et al. (1992)	Israel	Cross sectional and longitudinal design	Not reported	Experimental group A n=51 Experimental group B n=39 Control group n=35	Experimental group A= Kibbutz workers Israel Experimental group B= Kibbutz residence living near spay fields Israel Control group=Kibbutz residence living far from spraying fields Israel	Male 76.4% Female 23.6%	All groups=27.7Mean Range 17-45
Rosenstock, et al., (1991)	Nicaragua Leon	Cross sectional design	Double bind	Experimental group n=36 Control group n=36	Experimental group= Agricultural workers in Nicaragua patients poisoned with OP discharged form university teaching hospital in Leon Control group=relative or friend of exposure participant	Male	Experimental group=27.6(9.5) mean (SD) Control group=27.8(9.3) mean (SD) Range both groups15-44
Salvi et al. (2003)	Brazil	Longitudinal study	Not double blind	Preseason n=37 Postseason n=25	Experimental group= Brazilian workers involved in family tobacco agricultural	Male 48% Female 52%	Experimental group= 37 (13.5) mean SD

Authors	Country	Design	Double Blind	Sample size	Description of participants	Gender	Age (as in publication)
Savage et al. (1988)	Colorado Texas USA	Cross sectional design	Double blind	Experimental group n=100 Control group n=100	Experimental group= selected from the Colorado and Texas pesticides poisonings roster (96% occupational poisoning/ 4%non occupational 2children/mechinist/ college student) Control group= matched to experimental group (not specified)	99 /100 pairs male	Both groups Mean 35 years Range 16-66 years
Steenland et al. (1994)	California USA	Cross sectional design	Double blind	Experimental group n=128 Control group n=90	Experimental group= Selected from Californian pesticide surveillance data Definite exposure group= OP exposure symptoms and inhibited cholinesterase Probable exposure group=not have cholinesterase data burt have exposure symptoms Control group= Friends of exposure not working with pesticides	Male	Experimental group=33.8 (9.5) mean SD Control group=29.5 (10.9) mean SD
Stephens et al., (1995)	United Kingdom	Cross sectional design	Not reported	Experimental group n=146 Control group n=143	Experimental group= United Kingdome sheep farmers Control group= Quarry workers	Male	Not reported
Stephens et al. (1996)	United Kingdom	Cross sectional and longitudinal design	Not reported	Experimental group n=77	Experimental group= United Kingdome sheep farmers Welsh and English Control group= Quarry workers	Male	Experimental group=45 Control group=not reported Both groups= Range16-65

Authors	Country	Design	Double Blind	Sample size	Description of participants	Gender	Age (as in publication)
Zeitz, Kakolewski, Imtiaz & Kaye (2002)	Mississippi Ohio USA	Cross sectional and longitudinal design	Double blind	First measurement Mississippi Experimental group n=147 Control group n=218 Ohio Experimental group n=104 Control group n=224 Second measurement Mississippi Experimental group n=85 Control group n=96 Ohio Experimental group n =49 Control group n=97	Experimental group= Selected from Mississippi and Ohio ASTDR database of homes illegally sprayed with MP. (Mississippi MP sample ≥151µg/100m^2 /PNP≥ 100ppb) (Ohio MP sample ≥132.9µg/100m^2 /PNP≥ 100ppb) Control group=unexposed children from the same communities	Male and Female	Experimental and control group= aged 6 years and younger at the time of exposure

6.2 Current Trends in Neuropsychological Toxicology Investigations of Organophosphate Exposure

The first section of this chapter focuses on current trends in the neuropsychological toxicology assessment of organophosphate. This includes a review of study aims, the assessment of organophosphate exposure levels and duration, methodology, sample characteristics and assessment tools (including medical, neuropsychological and psychological tests used). This information forms the basis of discussions in the second section of this chapter, and contributes to the development of recommendations for assessment methodology.

6.2.1 Neuropsychological Toxicology Study Aims as an Indication of the Direction of the Field

Studies conducted on organophosphate exposure can be divided into those that aim to characterise neuropsychological and medical outcomes resulting from various types of organophosphate exposure, and studies that have more in-depth aims. Of the studies reviewed here, 12/16 (75%) aimed merely to characterise or evaluate the effect of

organophosphate exposure. These are discussed in relation to either long-term exposure or acute poisoning, resulting in enduring deficits. Only 4/16 (25%) of the studies reviewed here conducted studies to better understand the nature and relationship of these deficits or investigate different means of assessing deficits. These will now be discussed.

Ames et al. (1995) aimed to investigate the effects of pesticide exposure, but used cholinesterase inhibition as a prerequisite to indicate that pesticide exposure had occurred.
Richter et al. (1992) conducted a review of previous organophosphate studies. This was done to provide recommendations for control measures. The studies reviewed by Richter et al. (1992) had objectives similar to the majority of studies reviewed here, namely, to determine if people who were exposed to organophosphate experienced changes in their neuropsychological and medical outcomes, which may indicate damage sustained by this exposure. Of the various studies reviewed by Richter et al., one study, conducted on Kibbutzim residences, utilised neuropsychological and psychological assessments as part of the assessment methods. The outcomes of this study are included in the following review.

Stephens et al. (1996) aimed to determine whether any relationship exists between acute and chronic organophosphate exposure effects. The purpose of this study was to determine whether the warning signs of toxic effects of acute exposure may be used as a kind of early warning system for chronically exposed workers. Jamal, Hansen, Pilkington, Buchanan, Gillham, Abel-Azis, Julu, Al-Rawas, Hurley and Ballantyne, (2002) also conducted a study in which the focus was slightly different to the majority of studies reviewed here. Jamal, Hansen, Pilkington et al. (2002) study differed in that the authors selected participants who had already incurred abnormal peripheral neuropathy due to organophosphate exposure. The aim of this study was to further classify the disease and to explore a neuropsychological profile of the neurophysiological damage sustained by these individuals.

A South African study by London et al. (1997) was the only study reviewed that aimed specifically to investigate the relative performance of neuropsychological assessments in a neuropsychological toxicology investigation. This study did not only investigate the effect of long-term organophosphate exposure on neuropsychological outcomes, but also examined the relative performance of an assessment battery developed according to the cognitive information processing theory, in comparison to the established WHO-NCTB. This was done in an attempt to evaluate the cultural validity of these assessments. Meta-level studies such as this one are critical to the field of neuropsychological toxicology if it is to continue to grow and develop new assessment methods that are sensitive to subtle subclinical signs.

Like the studies reviewed on manganese exposure, the organophosphate studies were published more recently and had more specific study aims. This attests to the development of neuropsychological toxicology investigations into organophosphates as our understanding of

this neurotoxin develops. It is interesting that the aim of the study conducted by Maizlish et al. (1987) was to investigate the effect of short-term, low-level exposure to organophosphates. This indicates that the possible harmful effects of low level exposure were queried as early as the 1980s.

6.2.2 Assessments Conducted at Various Exposure Levels of Organophosphate

The concentration (level) and duration of neurotoxic exposure has a direct impact on the nature and extent of damage sustained by the exposed individual (Rosenberg, 1995). This in turn impacts on the evaluation of the sensitivity of neuropsychological assessments to this damage. The nature of neurotoxin exposure assessed by the studies reviewed here is briefly investigated.

The publications reviewed here used a number of medical methods to assess the level of organophosphate to which participants were exposed. The most popular way of determining the extent of this exposure was through the evaluation of cholinesterase levels. Cholinesterase is an enzyme that is inhibited by organophosphate (Ames et al., 1995). Organophosphate exposure may be measured using red blood cell, plasma or serum cholinesterase levels. Forty-four percent of the publications reviewed used either red blood cell, plasma or serum cholinesterase level assessments, or did not specify how the cholinesterase levels were measured. Maizlish et al. (1987) and Stephens et al. (1996) assessed organophosphate exposure levels by measuring urinary metabolites of organophosphate such as diethylthiophosphate (DEPT) and dimethylthiophosphate (DMTP). Zeitz, et al. (2002) evaluated urinary P-nitrophenol (PNP). In addition, Maizlish et al. (1987) also made use of passive dermal badges, hand rinses and personal full shift breathing zone air samples. Jamal, Hansen, Pilkington et al. (2002) and London et al. (1997) reported on exposure level and duration simultaneously by calculating a cumulative exposure index and a job exposure matrix respectively.

This wide range of different and non-comparable assessment methods hinders the comparison of studies relative to the exact level of neurotoxic exposure. This process is further complicated by individual and seasonal variations in cholinesterase measurements (Lessenger & Reese, 1995). Furthermore, 31% of the studies reviewed here did not report quantitative measures of exposure level. Another factor to consider is that organophosphates represent a wide range of chemicals compounds. All these compounds have the same basic chemical mechanism, namely, the inhibition of the cholinesterase (enzyme in blood) and the inhibition of its equivalent, acetylcholinesterase (enzyme in synapsis). However, the different structures of these compounds render some organophosphates more acutely toxic than others. For example, chlorpyriphos has been associated with anxiety, depression and transient Parkinson's disease, whereas glyphosate, clomazone, flumentraline, iprodione and

imidacloprid have not been associated with neurotoxicity (Salvi et al., 2003). Only 50% of the authors report on which type of organophosphate or mixtures of organophosphates their participants were exposed to. These vary between one and nine different compounds per study, further preventing comparison.

As it is therefore not possible to compare the studies on quantitative measurements of organophosphate exposure, and any further comparison is reliant on the authors' subjective report of exposure level. Nervous system damage resulting from organophosphate exposure can be categorised into four groups: short-term low-level exposure, long-term low-level exposure, short-term high-level exposure, long-term high-level exposure. The studies reviewed here are placed in these categories in TABLE 6-2, in accordance with the exposure level reported by authors. It should be remembered that these categorisations are dependent on the judgement of the authors and may have been different if comparisons were made on quantitative exposure measurements. However, the duration of exposure was reported by a number of authors, and this is briefly summarised below.

Table 6-2: Summary of organophosphate exposure concentration and duration assessed

<table>
<tr><th colspan="2">Exposure duration
Long term (chronic exposure)</th><th colspan="2">Exposure duration
Short term (acute exposure)</th></tr>
<tr><th colspan="2">Exposure concentration</th><th colspan="2">Exposure concentration</th></tr>
<tr><td>Low level</td><td>High level</td><td>Low level</td><td>High Level</td></tr>
<tr><td>Ames et al. (1995)
Salvi et al. (2003)</td><td></td><td rowspan="3">Maizlish et al. (1987)</td><td rowspan="3">Reidy et al. (1992)
Rosenstock et al. (1991)
Savage et al. (1988)
Steenland et al. (1994)
Zeitz et al. (2002)</td></tr>
<tr><td colspan="2">Long term exposure (exposure concentration not specified)</td></tr>
<tr><td colspan="2">Daniell et al. (1992)
Farahat et al. (2003)
Fiedler et al. (1997)
London et al. (1997)
Richter et al. (1992)
Stephens et al. (1995)</td></tr>
</table>

- The short-term low-level exposure assessed by Maizlish et al. (1987) had a duration of 39 days.
- Three of the studies conducting assessments on long-term low-level and long-term unspecified exposure reported exposure durations ranging from 17.8 years (Salvi et al., 2003) and 19.4 years (London et al., 1997).

- The short-term high-level (acute poisoning) studies investigated between one and four incidences of acute poisoning in subjects, and tracked the long-term effects of these incidence for up to four years post-poisoning.

The studies conducted by Jamal, Hansen, Pilkington et al. (2002) and Stephens et al. (1996) are not included in the table. Jamal, Hansen, Pilkington et al. (2002) investigated varied occupational exposure, not specified, resulting in neuropathy. Stephens et al. (1996) investigated both long-term and short-term exposure, of which the long-term exposure lasted 15.1 years. Acute exposure in this study does not refer to an incidence of high-level acute poisoning, but merely refers to the assessment of participants 24 hours after normal sheep-dipping procedures.

6.2.3 Current Trends in Organophosphate Assessment Methodology

As in the studies reviewed on carbon disulphide and manganese exposure, the majority (56%) of neuropsychological toxicology studies investigating the effects of organophosphate exposure used cross-sectional designs. Thirty-one percent of the studies reviewed made use of both simulation cross-sectional and longitudinal designs. Daniell et al. (1992), Maizlish et al. (1987) and Richter et al. (1992) employed simultaneous cross-sectional and longitudinal designs. The outcomes of the exposed group were compared with those of a control group in the cross-sectional part of the study. The longitudinal assessments of sheep dippers made comparisons according to pre-season/post-season, peak season/post-season and pre-shift/post-shift outcomes respectively. Stephens et al. (1996) conducted a similar study in an attempt to determine if a relationship exists between the pathology observed with acute and chronic exposure. In this study, acute effects were studied pre- and post-shift, and chronic effects were determined by comparing the outcomes of exposed sheep dippers with non-exposed quarry workers. Zeitz et al. (2002) also conducted a simulation cross-sectional and longitudinal study on acutely poisoned children. Experimental group outcomes were compared to those of non-exposed children, and the children were tracked longitudinally for two years to determine the impact of the poisoning on their development. Jamal, Hansen, Pilkington et al. (2002) employed a quasi-experimental study in their attempts to construct a neuropsychological profile that may be associated with the neurophysiological damage sustained after organophosphate exposure. For this study, Jamal, Hansen, Pilkington et al. (2002) selected participants from a previously conducted cross-sectional study who exhibited definite or probable neuropathy. The control group consisted of farmers were exposed to organophosphate but did not exhibit any of these symptoms.

The various methodologies employed for the investigation of organophosphate exposure are vulnerable to various confounding variables. One such confounding variable is the observer effect. To minimise this, Jamal, Hansen and Julu (2002) recommends the use of the double-

blind method. This was only employed by 44% of the publications reviewed here. Additional confounding variables controlled for are indicated in TABLE 6-3.

Table 6-3: Confounding variables considered during neuropsychological toxicology investigation of organophosphate exposure

Confounding variables	Ames et al. (1995)	Daniell et al (1992)	Farahat et al. (2003)	Fiedler et al. (1997)	Jamal, Hansen, Pilkington et al. (2002)	London et al. (1997)	Maizlish et al. (1987)	Reidy et al. (1992)	Richter et al (1992)	Rosenstock et al. (1991)	Salvi et al. (2003)	Savage et al., (1988)	Steenland et al. (1994)	Stephens et al. (1995)	Stephens et al.(1996)	Zeitz et al. (2002)
Age	√	√	√	√		√	√	√	√	√		√	√	√	√	
Alcohol consumption	√	√	√	√	√	√	√	√		√	√		√	√	√	
Caffeine	√		√										√	√		√
CNS pathology			√	√		√	√					√	√			
Computer familiarity														√		
Demographics											√					
Diabetes mellitus			√										√			
Disease			√	√			√							√		
Drugs			√	√		√	√					√	√	√		
Education	√	√	√	√		√	√	√	√			√	√	√	√	
Sociocultural aspects	√	√		√				√		√		√	√	√	√	
Eye problems				√		√										
Lack of sleep													√			
Language	√	√												√	√	
Medical history																√
Nutrition	√		√			√										
Occupation					√											√
Other neurotoxic			√	√									√	√	√	√
PNS pathology			√													
Pregnancy																√

Confounding variables	Ames et al. (1995)	Daniell et al (1992)	Farahat et al. (2003)	Fiedler et al. (1997)	Jamal, Hansen, Pilkington et al. (2002)	London et al. (1997)	Maizlish et al. (1987)	Reidy et al. (1992)	Richter et al (1992)	Rosenstock et al. (1991)	Salvi et al. (2003)	Savage et al., (1988)	Steenland et al. (1994)	Stephens et al. (1995)	Stephens et al.(1996)	Zeitz et al. (2002)
health																
Residential history of child																√
Sex	√	√	√		√	√	√		√	√		√	√	√	√	
Sleep	√															
Smoking			√								√			√	√	
Socioeconomic status			√					√				√		√		

√ *confounding variables reported* *Blank - confounding variable not reported*

The large number of confounding variables considered by these authors again emphasises the vulnerability of neuropsychological toxicology investigations, especially those investigating chronic exposure, to possible bias. It also points to the need to re-evaluate the methodologies used in these studies. It is also difficult to determine the extent to which all these possible confounding variables will influence the findings discussed in the second section of this chapter.

6.2.4 Sample Characteristics

Two important sample characteristics may influence the findings of the studies discussed here. These include sample size and participant characteristics. Sample size has a direct impact on the validity of study findings. Participant characteristics may impact on the outcomes of neuropsychological assessments, the nature and extent of damage sustained by participants and, indirectly, the representativeness and validity of NOAEL determined from these findings. As these are pertinent to our further discussions, they will now be briefly reviewed.

The range of sample sizes in the various organophosphate studies is as follows:

- Experimental group n=21 (Reidy et al., 1992) to n=163 (London et al., 1997)
- Control group n=11 (Reidy et al., 1992) to n=224 (Zeitz et al., 2002)

The small sample groups used by Reidy et al. (1992) and Salvi et al. (2003) are a threat to the validity of the study findings.

The following participant characteristics are briefly reviewed: sociodemographic factors, age and sex. As with the studies conducted on carbon disulphide and manganese, organophosphate neuropsychological toxicology assessment has been conducted globally, ranging from the assessment of United Kingdom sheep dippers (Stephens et al., 1995), South African deciduous fruit farm workers (London et al., 1997) and Egyptian cotton pesticide sprayers (Farahat et al., 2003). This does, however, raise concerns about the cultural validity and comparability of assessments and may explain some of the variability in outcomes of findings discussed in the next section.

The majority of participants of the studies reviewed here were agricultural workers, male and middle-aged. Of the studies reviewed, 56% were conducted exclusively on men, whereas the other studies included women into their samples but did not use exclusively female samples.

The youngest participants were assessed by Rosenstock et al. (1991), and the oldest by Fiedler et al. (1997). The mean age of all participants was as follows:

- Experimental group**: 27.6 years** to **47.6 years**
- Control group**: 27.8 years** to **47.7 years**

As standard deviations for both the experimental and control groups were less than or equal to 11 years, it can be concluded that the majority of research participants were middle-aged. The exception is the study conducted by Zeitz et al. (2002), which was conducted on children aged six years and younger. Like the research on manganese and carbon disulphide, it appears that even though children and geriatrics have increased sensitivity to neurotoxins, these groups are under-researched. A possible explanation for this may be that the majority of organophosphate neurotoxicity research is done on agricultural workers where exposure is most likely, and these workers are predominantly middle-aged (Hartman, 1995). This highlights the need for research on children and older people as these groups may easily sustain brain damage through to neurotoxic exposure.

6.2.5 Assessment Tools Employed for the Evaluation of Organophosphate Toxicity

As in previous chapters, the focus of this review is the neuropsychological and psychological assessment of neurotoxic damage. A brief discussion on the use of medical evaluations in the assessment of organophosphate exposure is presented to facilitate the discussion later in this chapter. Medical measures are discussed to the extent that they provide an indication of the extent of damage sustained by participants, and to which neuropsychological outcomes can be compared. In addition, the correlation of medical measures, such as exposure levels in cholinesterase measurements, provides a good indication of the sensitivity of these

neuropsychological assessment methods as they are less vulnerable to possible confounding variables.

6.2.5.1 Medical Assessment Instruments

The studies used a total of 36 different medical measures to evaluate damage sustained through organophosphate exposure. However, the majority of these were not correlated with neuropsychological measures and are therefore reviewed only briefly. The most popular medical assessments included tests of nervous system functioning such as neurological examination (31%), nerve conduction tests (19%), motor system functioning (25%), sensory system functioning (18%) and vibration tests (25%). Some authors employed assessments not directly related to nervous system functioning such as liver and kidney functioning tests.

A number of authors used medical measures that provide an indication of the level of organophosphate exposure. These include cholinesterase measurements and the analysis of urinary organophosphate metabolites. (These measurements were discussed at length in the section of this chapter pertaining to exposure level.) Assessments of organophosphate exposure level are correlated with neuropsychological outcomes, in the studies conducted by Ames et al. (1995), Daniell et al. (1992), Maizlish et al. (1987) and Farahat et al. (2003). These studies calculated dose response relationships between cholinesterase activity and neuropsychological outcomes. On the whole, the majority of assessment outcomes did not correlate with cholinesterase activity. The only neuropsychological assessment measure that was significantly correlated with cholinesterase activity was Serial Digits in the study conducted by Ames et al. (1995). No other neuropsychological assessments correlated significantly with cholinesterase activity. The absence of a significant relationship between these variables may be attributed to the unreliability of cholinesterase activity as a constant. This is due to factors such as individual and season fluctuations in acetylcholinesterase/cholinesterase activity discussed earlier in this chapter. The comparison of cholinesterase activity relative to baseline measurements may provide more accurate findings (Lessenger & Reeser, 1995).

6.2.5.2 Neuropsychological and Psychological Assessments

Thirty-seven neuropsychological and psychological tests and subtests were employed by the authors reviewed here to assess the impact of organophosphate exposure. The batteries these assessments comprise are indicated in TABLE 6-4.

Table 6-4: Review of neuropsychological and psychological tests used to assess damage due to organophosphate exposure

Authors	Neuropsychological Assessment
Ames et al. (1995)	• Neurobehavioural Evaluation System (NES) • World Health Organisation (WHO) Test Battery • Santa Ana Dexterity Test and Pursuit Aiming Test
Daniell et al. (1992)	• Neurobehavioral Evaluation System (NES)
Farahat et al. (2003)	• Neuropsychological battery not specified (verbal abstraction/problem solving attention, memory, visuomotor speed, personality assessment) • Eysenck Personality Questionnaire
Fiedler et al. (1997)	• The Wide Range Achievement Test - Reading (WRAT-R) • Wechsler Adult Intelligence Scales (WAIS-R) • Neurobehavioral Evaluation System (NES) • Minnesota Multiphasic Personality Inventory (MMPI)
Jamal, Hansen, Pilkington et al. (2002)	• National Adult Reading Test • The Cambridge Neuropsychological Test Automated Battery (CANTAB) • Rey Auditory Verbal Learning Test • Hospital Anxiety And Depression Scales • General Health Questionnaire
London et al. (1997)	• World Health Organisation - Neurobehavioural Health Core Test Batteries (WHO-NCTB) • Cognitive Information Processing Tests
Maizlish et al. (1987)	• Computerised Neurobehavioural Test Battery • Symptoms questionnaire
Reidy et al. (1992)	• The Neuropsychological Screening Battery (CNS/B-I) • Minnesota Multiphasic Personality Inventory (MMPI)
Richter et al. (1992)	• World Health Organisation (WHO) Core Test Battery • Profile of Mood State (POMS) • Benton Visual Retention Test
Rosenstock, et al., (1991)	• World Health Organisation (WHO) Neuropsychological Test Battery • three additional tests (verbal attention/ visual memory/ visumotor speed/ sequencing/ problem solving/ motor steadiness/ dexterity) • Profile of Mood State (POMS) • Scandanavian Questionannaire 16 (Q16)

Authors	Neuropsychological Assessment
Salvi et al. (2003)	• Mini International Neuropsychiatric Interview • Extrapyramidal Symptoms Rating Scale • Mini Mental And Word Span Test
Savage et al. (1988)	• Wechsler Adult Intelligence Scale (WAIS) • Halstead-Reitan Battery • Minnesota Multiphasic Personality Inventory (MMPI) • Patient's and Relative's Assessment of Patient Functioning Inventories • Peabody Individual Achievement Test
Steenland et al. (1994)	• Neurobehavioral Evaluation System (NES) • WHO Core Battery • Santa Ana Dexterity Test and Pursuit Aiming Test
Stephens et al., (1995)	• Subjective memory questionnaire
Stephens et al. (1996)	• Neurobehavioural Evaluation System (NES) • Automated Cognitive Testing system • General Health Questionnaire • Subjective Memory Questionnaire
Zeitz et al. (2002)	• SPES (Swedish Performance Evaluation System) • PENTB (cognitive/motor/ sensory and affect)

As is indicated in the table above, the majority of authors utilised a standard neuropsychological toxicology battery and supplemented these tests with cognitive, mood, motor or personality assessments. An additional rationale for test selection was reported by Zeitz et al. (2002), who selected the PENTB as it is used by ASTDR in large-scale studies to evaluate neuropsychological effects of neurotoxic exposure in children. London et al. (1997) used an assessment developed from cognitive information processing theory in an attempt to minimise cultural and educational influences. Fiedler et al. (1997) selected tests according to the symptoms associated with exposure in the literature. This is congruent with the test selection trend for carbon disulphide and manganese exposure assessments. The dynamic brain localisation theory was not mentioned as a rationale for test selection.

In contrast to the assessments of carbon disulphide and manganese, a number of authors who assessed organophosphate exposure made use of computerised batteries. These include Ames et al. (1995), Daniell et al. (1992), Fiedler et al. (1997), Jamal, Hansen, Pilkington et al. (2002), Steenland et al. (1994) and Stephens et al. (1996). The implications of administering measures through computerised batteries instead of skilled administrators has been discussed at length in previous chapters.

6.2.5.3 Additional Assessment Instruments

Additional assessments instruments used in the studies include the Mini International Neuropsychiatry Interview, General Health Questionnaire (which assesses mood and affect for anxiety and depression), Subjective Symptoms Questionnaires and Brief Symptoms Inventory/Questionnaire 16 (Scandinavian questionnaire). Information regarding medical and exposure history as well as socioeconomic background was collected in these studies in much the same way as all the other studies.

6.3 Discussion

The remainder of this chapter deals with the information discovered in the preceding sections. Here we investigate the sensitivity of various neuropsychological tests to the damage sustained thought organophosphate exposure, and more specifically, the sensitivity of memory assessments to organophosphate damage. Acetylcholine projections are reported to play an important role in memory functioning (Schatz & Chute, 2000; Thiel, 2003).This system is disrupted by organophosphate exposure (Daniell et al., 1992; Eyer, 1995). It is therefore hypothesised that memory assessments may be sensitive to organophosphate damage.

The definition of test sensitivity for the purposes of these discussions, noted in the previous chapters, is repeated here for the convenience of the reader. The sensitivity of the neuropsychological test can be defined as the ability of the test to discriminate between individuals who have been exposed to a neurotoxin and those who have not. Therefore, a sensitive test is a one that is likely to measure deficits resulting from the damage participants sustained from neurotoxic exposure. The following information obtained from the publications reviewed here will be used as an indication of test sensitivity.

- Cross-sectional studies: the assessment instrument measures significant changes in outcomes between experimental and control groups.
- Longitudinal study: the assessment instrument measures significant changes in outcomes between baseline and follow-up measurements.
- Correlation study: deficits measured by the assessment instrument correlate significantly with increased organophosphate exposure.
- Case study: deficits measured by the assessment instrument differ significantly from standardised norms, or performance is judged by a skilled test administrator to be significantly impaired.

In addition, the possible impact of methodological issues on the outcomes of these studies is considered.

6.3.1 Outcomes of Memory Assessments

The use of different organophosphate compounds, different methods of assessing organophosphate exposure, inconsistencies in measurements, as well as the large number of studies which do not offer any quantitative measurements of the exposure levels, make it unfeasible to compare these studies on the basis of relative exposure. Rather, the outcomes of specific tests are evaluated with respect to their assessment of constructs that are associated with pathophysiology induced by organophosphate exposure, with a special focus on memory.

The comparison of tests across studies on both organophosphate as well as different neurotoxins is facilitated by the widespread use of the Benton Visual Retention Test and the Digit Span subtest of the Wechsler scales. The Benton is primarily an assessment of memory, while the Digit Span also entails a strong memory component (Lezak et al., 2004). This comparison enables an evaluation of test sensitivity to neuropsychological constructs, which are predicted to be compromised by specific neurotoxic mechanisms of organophosphate.

6.3.1.1 The Benton Visual Retention Test

The Benton Visual Retention Test was employed in a number of studies assessing carbon disulphide and organophosphate, but not manganese exposure. TABLE 6-5 indicates that, despite different methodologies, participant characteristics and exposure levels, the Benton Visual Retention Test did not measure neuropsychological change in any of the studies conducted on carbon disulphide exposure, although this instrument detected neuropsychological changes in nearly all the studies conducted on organophosphate exposure.

Table 6-5: Inter-study comparison of the Benton Visual Retention Test

Neurotoxin	Carbon disulphide				Organophosphate				
Study	Hanninen*	Reinhardt et al. (1997)	Takebayashi et al. (1998)	Aaserud et al. (1990)	London et al. (1997)	Rosenstock et al. (1991)	Richter et al. (1992)	Farahat et al. (2003)	Reidy et al. (1992)
Benton Visual Retention Test	x	x	x	x	x	√	√	√	√

√ Test measured deficits in participants

X Test did not measure deficits in participants

** Hanninen, cited in Feldman et al. (1980)*

Inter-neurotoxin outcomes

The Benton Visual Retention Test is primarily a measure of memory (Rosenstock et al., 1991). Lezak et al. (2004) states that this assessment measures visuomotor abilities, visuospatial perception, visual abilities, verbal conceptualisation, and immediate memory span. This may explain its sensitivity to organophosphate exposure, which is implicated in memory functioning. Carbon disulphide exposure is not primarily associated with memory deficits and is more strongly associated with frontal lobe pathology (Rosenberg, 1995). This clearly supports the finding that neurotoxic brain damage is not a unitary phenomenon and that neurotoxic damage may therefore be more effectively assessed using specialised assessment instruments.

Intra-neurotoxin outcomes

London et al.'s (1997) study is the only organophosphate study in which the Benton Visual Retention Test did not measure neuropsychological deficits in exposed participants. This discrepancy in outcomes does not seem to be due to variations in exposure level of participants as Richter et al. (1992), Farahat et al. (2003) and London et al. (1997) all assessed long-term exposure (even though, due to lack of quantitative measurements, it is not possible to determine the exact level of exposure). A possible explanatory factor is that London and colleagues used a cross-sectional study design. Neuropsychological toxicology cross-sectional studies may be particularly vulnerable to the effect of confounding variables. However, London et al. (1997) did control for all the confounding variables recommended by Anger et al. (1997), they used a double-blind method, a large sample size and did not use

control subjects that were exposed to organophosphate. Therefore, the discrepancy in these findings may be attributed to confounding variables that were not considered, such as possible methodological errors made by the other studies. Other possible factors are lower levels of damage in London et al.'s participants, so that impairment is below detectable levels of assessment. This emphasises the impact of methodology on these findings and the resultant inability to derive robust findings from these studies.

6.3.1.2 Digit Span

The outcomes of the Digit Span assessment were discussed in depth in the chapter on carbon disulphide exposure. A brief summary of the outcomes of this assessment are included here.

Table 6-6: Inter-study comparison of Digit Span

	Carbon Disulphide			Manganese				Organophosphate							
Study	Takebayashi et al. (1998)	Aaserud et al. (1990)	Cho et al. (2002)	Brown et al. (1991)*	Deschamps et al. (2001)*	Myers et al. (2003)*	Sjögren et al. (1996)*	London et al. (1997)	Rosenstock, et al. (1991)	Richter et al. (1992)	Savage et al. (1988)	Stephens et al. (1995)	Farahat et al. (2003)	Fiedler et al. (1997)*	Reidy et al. (1992)
Digit span	√	x	x	x	x	x	x	x	√	√	√	x	√	x	x

√ Test measured deficits in participants

X Test did not measure deficits in participants

Inter-neurotoxic outcomes

While the Digit Span subtest requires short-term memory (Lezak et al., 2004). It seems more sensitive to the damaged incurred through exposure to organophosphate than to carbon disulphide and manganese. This measurement detected deficits in 50% of the organophosphate studies in which it was used. This may be due to the role of organophosphate in disruption of acetylcholine cells, which play a role in normal memory functioning (Schatz & Chute, 2000; Thiel, 2003). The disruption of memory is not strongly associated with the neurotoxic mechanisms of carbon disulphide and manganese, although

these deficits are occasionally reported. However, Digit Span is reported as an effective measurement of frontal lobe damage if special attention is given to the characteristic errors patients make in this test (Lezak et al., 2004). The extent to which authors note these details is not reported in the majority of publications. Together with numerous other methodological reasons, this may account for the inability of this assessment to measure deficits in carbon disulphide patients.

Inter-neurotoxin outcomes

The Digit Span appears to be more sensitive to the damage incurred through acute high-level exposure than chronic exposure. All the authors discussed above used cross-sectional designs and controlled for all the confounding variables recommended by Anger et al. (1997). However, the findings may have been influenced by lack of a double-blind methodology in the studies conducted by Farahat et al. (2003), Richter et al. (1992) and Reidy et al. (1992), as well as by the small sample size used by Reidy et al. (1992). The organophosphate exposure of the control group in the Rosenstock study may also impact on findings. The discrepancies in the outcomes of these studies may be attributed to unknown exposure levels and the fact that Digit Span is not primarily a memory assessment. It is therefore not possible to draw any conclusions regarding the test sensitivity of this assessment with confidence, although we may speculate about the role of memory functioning in the pattern test. Further research is therefore recommended to clarify the role of this test.

6.3.1.3 Pattern Memory Test

The Pattern Memory Test was employed by a number of authors to assess organophosphate exposure, but not carbon disulphide or manganese exposure. This assessment is not widely published in the literature and further information regarding the constructs it assesses, or the type of damage to which it is sensitive, could not be obtained. These findings are presented in TABLE 6-7.

Table 6-7: Inter-study comparison of the Pattern Memory Test

	Organophosphate			
Study	Ames et al. (1995)	Daniell, et al. (1992)	Maizlish et al. (1987)	Steenland et al. (1994)
Pattern Memory Test	x	x	√	X

√ Test measured deficits in participants

X Test did not measure deficits in participants

Maizlish et al. (1987) conducted an assessment on short-term low-level exposure, whereas the other authors presented here conducted assessments on participants who had been exposed to either higher levels of organophosphate (Steenland et al., 1994) or longer periods of exposure (Ames et al., 1995; Daniell et al., 1992). Therefore, the discrepancy in these outcomes do not appear to be due to exposure level, although this interpretation is dependent on the subjective evaluation of authors as quantitative comparisons is not possible. The variation in outcomes on this assessment may therefore be attributed to methodological differences. For example, Maizlish et al.'s (1987) measurements were conducted pre- and post-shift, while Daniell et al. (1992) conducted measurements pre- and post-season. Ames et al.'s (1995) findings may have been influenced by the lack of a double-blind methodology. To conclude, this assessment does not appear to be effective in the assessment of organophosphate-induced damage; however, more research is required.

6.3.1.4 Additional Neuropsychological Memory Assessments Employed for the Evaluation of Organophosphate

The following tests were not employed by a sufficient number of authors to permit the comparison of their outcomes across studies, a comparison of the assessment of different neurotoxins, or comparisons with other studies conducted on organophosphate. Nonetheless, the results of these studies are reviewed here to investigate any trends in memory test sensitivity. The following memory tests measured deficits in participants who were exposed to organophosphate:

- Semantic Access (animal postures 1 and 11) (London et al., 1997)
- Serial Digit Learning (Ames et al., 1995)
- Story Recall Part A (Farahat et al., 2003)
- Short Term Memory Test - Learning (Savage et al., 1988)
- Short Term Memory Test - Memory (Savage et al., 1988)

The following memory test did not measure deficits in exposed participants:

- Continuous Visual Memory Test (Fiedler et al., 1997)
- Echo Praxis (London et al., 1997)
- Manipulating Numbers I II III (London et al., 1997)
- Memory Passages (Reidy et al., 1992)
- Mini Mental Word Scale (Salvi et al., 2003)
- Pointing Arrows (London et al., 1997)
- Rey Auditory Verbal Learning Task (Rosenstock et al., 1991)
- Serial Digit Learning (Steenland et al., 1994)
- Serial Word Learning Test (Stephens et al., 1995)
- Short-term Memory Scanning (London et al., 1997)

- Speaking Arrows (London et al., 1997)
- Stimulus Resistance (London et al., 1997)
- Story Recall Parts A and B (Farahat et al., 2003)
- Subjective Memory Questionnaire (Stephens et al., 1995)
- Tactical Performance Time (Savage et al., 1988)
- Visual Reproduction (Fiedler et al., 1997)
- Visual spatial memory test (Stephens et al., 1995)
- Wechsler memory scale (Reidy et al. 1992)
- WMS memory- learning (Jamal, Hansen, Pilkington et al., 2002)

The above list demonstrates that there is no clear pattern of test sensitivity of memory tests in the assessment of organophosphate. Overall, the probability of measuring a deficit with a memory test in the studies reviewed here is p=0.34, whereas the probability when non-motor memory cognitive tests are used is p=0.51. This is similar to the probability (p=0.5) when using a motor test. Methodological issues were not considered in this calculation; therefore, the numerous confounding variables discussed may have influenced this probability. In addition, the choice of tests may also impact dramatically on this probability. If studies conducted on participants who experienced extensive damage were more inclined to use a particular type of neuropsychological assessment, these assessments would appear to be more sensitive.

6.3.2 Special Investigations

Unlike the studies on carbon disulphide and manganese, a number of studies reviewed here conducted special investigations to evaluate specific neuropsychological aspects of organophosphate exposure. These were discussed in the aims section of this chapter. The findings of these studies warrant special attention, and are therefore discussed in this section.

Jamal, Hansen, Pilkington et al. (2002) aimed to identify neuropsychological profiles for participants with organophosphate-induced deficits. Although Jamal, Hansen, Pilkington et al. (2002) did not report on the outcomes on individual neuropsychological tests, they did state that “there was no evidence that whatever effect was responsible for the neurophysiological and psychological disturbances also produced memory impairment” (Jamal, Hansen, Pilkington et al., 2002 p.439). These findings may have been influenced by the small sample size used in this study. This is congruent with the findings from this review in that no clear pattern of memory test sensitivity to organophosphate exposure could be identified.

Stephens et al. (1996) investigated the relationship between acute and chronic exposure. These authors measured deficits on the Symbol Digit Substitution and the Syntactic Reasoning Tests following chronic exposure. No significant correlation was found between

acute and chronic deficits. This may indicate that the accumulative damage resulting from chronic exposure differs with respect to the nature of the damage incurred through short-term exposure.

London et al. (1997) aimed to investigate the validity of tests based on cognitive information processing theory, in comparison with the WHO-NCTB. This investigation was undertaken as part of a neuropsychological toxicology investigation of a South African cohort. The cognitive information processing theory was selected as a possible culturally fair instrument. Exposure effects were noted on two of the seven NCTB tests and one of the twenty-one information processing assessments. The Santa Ana Pursuit Aiming Test of the NCTB measured deficits in participants whereas the Semantic Memory - Animal Postures 1 and 2 tests, which are part of the information processing assessments, were sensitive to participant deficits. These results may have been influenced by multiple comparison. London et al. (1997) conclude that "although information processing performance probes are factorially simpler, empirical evidence in this and other studies suggest that the more complex NCTB tests are more useful neurobehavioral assessment tools for occupational exposure" (p.142). The findings of this study provide support for the continued use of standard batteries such as the WHO-NCTB.

6.3.3 Psychological Outcomes

In addition to motor and cognitive assessments, a number of psychological tests and self-reporting psychological symptoms questionnaires were used for the assessment of organophosphate damage. These will now be discussed.

There are a limited number of publications on the role of the acetylcholine system in psychological constructs such as personality and emotion. For this reason, outcomes regarding these deficits could be compared against the expected deficits associated with damage to the brain areas under investigation. Findings regarding psychological deficits resulting from organophosphate exposure may help to shed some light on the role of the acetylcholine system in normal functioning. The psychological aberrations measured in organophosphate-exposed participants are indicated in TABLE 6-8.

Table 6-8: Psychological symptoms measured in organophosphate-exposed participants

Psychological Symptoms	Ames et al. (1995)	Farahat et al. (2003)	Fiedler et al. (1997)	Jamal, Hansen, Pilkington et al. (2002)	Maizlish et al. (1987)	Reidy et al. (1992)	Richter et al. (1992)	Rosenstock et al. (1991)	Salvi et al. (2003)	Savage et al. (1988)	Steenland et al. (1994)	Stephens et al. (1995)
Anger	X						√					
Anxiety				√		√	√		√	√		
Blurred vision					X	√						
Communication										√		
Consciousness level						X				x		
Confusion	X					X				√		
Concentration					X			X				
Criminality		X										
Defensiveness			X							√		
Depression	X			√	X	√	√	X	√	√		
Dizziness		√			X							
Extraversion		X										
Fatigue	X	X			X	√	√		√			
Follow directions										√		
Headache		X			X	√		X	√			
Hostility							√					
Hypochondriasis			X									
Hypomania			X									
Hysteria			X									
Increased vulnerability to psychiatric illness								X	√			√
Irritability					X	√		x		√		
Light-headedness						√						
Masculinity and			√									

Psychological Symptoms	Ames et al. (1995)	Farahat et al. (2003)	Fiedler et al. (1997)	Jamal, Hansen, Pilkington et al. (2002)	Maizlish et al. (1987)	Reidy et al. (1992)	Richter et al. (1992)	Rosenstock et al. (1991)	Salvi et al. (2003)	Savage et al. (1988)	Steenland et al. (1994)	Stephens et al. (1995)
femininity												
Memory						√				√		
Mood											√	
Neuroticism		√										
Orientation										X		
Paranoia			X							√		
Personality						X				√		
Problem solving										√		
Psychasthenia			X									
Psychosis		X										
Psychopathic deviation			X									
Schizophrenia			X									
Sleep disturbances						√						
Social introversion			X							√		
Tension	X						√					
Understanding speech										√		
Written word										√		

√ Symptom measured in or reported by participants

X Symptom measured but not significant

Blank - symptom not measured or reported

Zeitz et al. *(2002): results will be published in future articles, which could unfortunately not be accessed for this review.*

London et al. (1997), Daniell et al. (1992) and Stephens et al. (1996) did not measure any self-reported psychological symptoms.

The table above demonstrates the wide variation in symptoms experienced by participants exposed to organophosphate. It should be noted that the studies reviewed here assessed

different psychological symptoms, which plays a major role in determining which symptoms are found to be associated with organophosphate exposure. A number of authors did not indicate what symptoms were measured, but only reported on those that were significant. With this in mind, a high incidence of anxiety and depression was confirmed by a number of studies. This is discussed in the following sections with reference to the assessment methods employed.

With the exception of Maizlish et al. (1987) and Ames et al. (1995), all the studies reviewed here found significant increases in psychological and somatic symptoms in exposed participants, regardless of the length or level of exposure or the methodology employed. This indicates that this is an effective means of measuring the impact of organophosphate exposure in participants.

A number of authors reported a high incidence of anxiety and depression. Further support for a pattern of anxiety and depression among organophosphate-exposed individuals is offered by the study conducted by Jamal, Hansen, Pilkington et al. (2002), in which higher rates of anxiety and depression were found in participants with neuropathy due to organophosphate exposure than in other groups evaluated in the study. Significant increases in anxiety and depression were also reported by Richter et al. (1992) and Salvi et al. (2003). Richter and colleagues employed the Profile of Mood State (POMS) and found a significant increase in fatigue, anger hostility, tension, anxiety and depression, among participants with occupational exposure. Salvi et al.'s (2003) findings on the Mini International Neuropsychiatric Interview provide support for the efficiency of anxiety and depression measurements in assessing organophosphate deficits. Further research is required to further investigate these findings.

6.3.3.1 Minnesota Multiphasic Personality Inventory

Further indications of depression amongst organophosphate-exposed participants were reported on MMPI measurements. Fiedler et al. (1997), Reidy et al. (1992) and Savage et al. (1988) employed the Minnesota Multiphasic Personality Inventory (MMPI). Fiedler et al. (1997) reported significant changes on the masculinity and femininity scale of the MMPI of these participants following long-term exposure. These authors conducted a cross-sectional double-blind study, and found no difference between groups in terms of age, gender, ethnicity, and education. Control subjects were not exposed to organophosphate. For these reasons it is unlikely that the results were biased; and this provides support for the use of the MMPI in organophosphate assessment.

The criteria for the study by Savage et al. (1988) were the same as those for the Fiedler study. However, these authors investigated the effects of acute exposure whereas Fiedler et al. measured long-term exposure. This may explain the difference in their findings. Savage et

al. (1988) found significantly higher rates of social introversion, defensiveness and paranoia among their participants, although mean scores were within normal limits. In addition, the Savage study participants reported a host of other somatic and cognitive complaints, based on self-report questionnaires as well as relatives' independent reports.

Reidy et al. (1992) also used the MMPI to assess the impact of acute organophosphate poisoning. They found significant increases in rates of anxiety and depression, although their findings may have been influenced by the small sample size and the lack of a double-blind method. Despite the different methods and different types of exposure assessed, the MMPI results of these studies all concur that personality changes occur after organophosphate exposure. This assessment therefore appears to be effective in measuring organophosphate-induced deficits.

6.3.3.2 The NES Mood Scales

Ames et al. (1995) and Steenland et al. (1994) used the NES Mood Scales to assess changes in psychological variables due to organophosphate exposure. Ames et al. (1995) did not measure any significant changes in the psychological profile of participants, while Steenland et al. (1994) found significant changes. The different results may be explained by the fact that Steenland's study assessed acute poisoning, while Ames measured damage resulting from low-level, long-term exposure. The same methodology was used in both studies, as both controlled for the same confounding variables. With the exception of the use of double blind method not reported by Ames et al. (1995)

Other psychological assessments used in these neuropsychological toxicology investigations include the Eysenck Personality Questionnaire used by Farahat et al. (2003). This assessment revealed an increase in neurotism in exposed participants.

To conclude: a wide range of psychological and emotional symptoms are reported by participants exposed to organophosphate. Increased incidence of anxiety and depression is confirmed by numerous studies. In addition the NES mood scales and MMPI appears to be highly effective in evaluating changes in participants resulting from organophosphate exposure. Further research is required to test the sensitivity of these assessments for organophosphate exposure assessment. As well as to further investigate the characteristic psychological and mood deficits associated with this exposure. This may shed light on the role of the Acetylcholine system, disrupted by organophosphate, in the normal functioning of emotions and other psychological constructs.

6.4 Conclusion

More neuropsychological toxicology studies on organophosphate exposure could be sourced for this review than studies conducted on manganese and carbon disulphide. Comparison of these studies is impeded by the absence of information regarding the nature of exposure of participants, the reliability of such comparisons, different methodologies and samples. These sentiments are shared by Colosio, Tiramani & Maroni (2003), Reidy et al. (1992) and Jamal, Hansen, Pilkington et al. (2002). As with other neurotoxins reviewed, the majority of these studies were conducted on men, and the impact of neurotoxic exposure on women, children, geriatrics and hypersensitive individuals remain under-researched. Most of the authors reviewed used standard neuropsychological toxicology batteries, supplemented with additional motor, cognitive, emotional or personality assessments. The studies reviewed here did not seem to consider toxicodynamics (dynamic brain localisation theory) as a tool for the selection of assessment batteries. This may be attributed to a general tendency of these publications to omit this information in the test selection process, and the limited number of publications on the neuropsychological functioning of this system. However, the lack of studies investigating this brain-behaviour relationship, and related pathology, perpetuates this situation. Furthermore, memory tests were not found to have increased sensitivity to organophosphate exposure in comparison with other cognitive tests or motor tests. The wide range of subjective symptoms reported by participants, as well as various reported cognitive and psychological symptoms, reveal no clear pattern of deficit. This may be due to a lack of clear understanding of the normal functioning of the acetylcholine system. The wide dispersal of acetylcholine neurons in the brain raises the possibility that many brain functions may be affected by organophosphate exposure. Lucchini et al. (2000) states that neuropsychological findings such as these can make an important contribution to the better understanding of neurotoxic mechanisms. Therefore, a thorough study of the effects of organophosphate exposure may shed light on the psychological role that this neurotransmitter plays in the brain. This represents a bridge for neuropsychologists from the study of the localisation of damage to the study of functionality based on dispersed cellular pathology.

CHAPTER 7: CONCLUSION AND RECOMMENDATIONS

7.1 Introduction

In this dissertation the need for effective assessment instruments and methodologies for the assessment of subclinical neurotoxic exposure was addressed. Key findings regarding both neuropsychological tests and assessment methods will now be discussed.

7.2 Key Findings: Neuropsychological Toxicology Tests

The trends noted in this review indicate the following:

- Standard neuropsychological toxicology batteries have a large influence on the selection of instruments.
- Dynamic brain localisation theory is not widely used as a rationale for instrument selection.

7.2.1 Standard Neuropsychological Toxicology Batteries have a Large Influence on the Selection of Instruments

Spurgeon (1996) observes a current stage of transition in neuropsychological toxicology assessment. In the last 20 years neuropsychological toxicology has undergone rapid formation and proliferation to meet the urgent need for the assessment of neurotoxic brain damage. During this time original standard neuropsychological toxicology batteries were developed to meet this pressing demand. Although these tests were able to provide some answers, Spurgeon (1996) notes that the current process of transition is marked by the need for refined theoretically based techniques for the assessment of particular chemicals. These specialised flexibile battieres for specific toxins, may be more sensitive to sub clinical deficits associated with specific damage. The findings of this review indicate that only a few of the most recent publications, such as those conducted for the assessment of manganese, consider the uniqueness of different neurotoxic damage. The tendency to treat all neutoxic damage as a homogenous phenomenon is demonstrated by the pervasive influence of standard neuropsychological toxicology batteries on instrument selection in this field. These standard batteries have similar conceptual schemas and are not specially designed for the assessment of a particular neurotoxin, but are rather intended to assess brain damage caused by any neurotoxic exposure. In addition no clear theoretical base is evident for the inclusion of the subsets of these standard batteries (Lezak et al., 2004).

The wide spread use of standard neuropsychological toxicology batteries and their subtests, do however, provide some advantages. Firstly, they facilitate the comparison between studies (such as those conducted by this review). Secondly, these assessments test a large number of neuropsychological abilities. This is beneficial because our understanding of the neurotoxicodynamics of most chemicals is not complete and by testing global functions we may gain insight into additional brain areas or physiological processes affected. In addition although dynamic brain localisation theory was used in this dissertation to identify specific neuropsychological functions associated with a specific system, it should be remembered that psychological functioning is not attributed to isolated brain structures but emerges through the dynamic interaction between different areas and systems. Cellular or anatomical pathology to one system may present in neuropsychological deficits in addition to those deficits which are traditionally associated with a particular pathological system. Therefore, no psychological test is process pure. This is demonstrated by memory deficits of frontal lobe patients, which may in fact represent a lack of the ability to plan the process of remembering rather than pathology to the memory system (Spreen & Strauss, 1998). Testing a wider range of psychological functions may facilitate the measurement of these additional deficits. The utility of standard neuropsychological batteries in the assessment of neurotoxic insult was also demonstrated in the study conducted by London, et al. (1997) discussed previously.

The use of standard neuropsychological batteries, or their subtests and the lack of consideration for the different toxicodynamics of different neurotoxins (treating all neurotoxins as if they result in the same type of damage) typifies the historical approach to neuropsychological toxicology assessments. This is further demonstrated by the recommendations put forward by Anger and Cassitto (cited in Hartman, 1995) who recommend the use of the same subtests for the subclinical evaluation of any neurotoxic exposure. However, this approach is contradictory to the recommendations proposed by White et al. (1990) who recommend the use of tests which are sensitive to a particular toxin. In the studies reviewed here a few authors did attempt to select tests which are sensitive to the damage caused by a specific neurotoxin. These studies were most likely to select sensitive tests from publications of previous studies, rather than look at the brain areas and systems affected by the neurotoxic exposure under investigation. Stephens and Barker (1998) state that the lack of clearly defined function in standard batteries has discouraged the development of new improved methods and that the lack of understanding of underlying psychological constructs of these tests has lead to the replication of these assessments.

During this transition phase a debate is emerging in neuropsychological toxicology, regarding advantages of the use of flexible batteries, which are sensitive to the specific deficits, associated with specific neurotoxic damage, and the use of standard fixed batteries, which test global functions regardless of the neurotoxicodynamics of the neurotoxin under

investigation. This debate mirrors the long-standing debate of the advantages of flexible vs. fixed batteries in mainstream neuropsychology.

7.2.2 Dynamic Brain Localisation Theory is Not Widely Used as a Rational for Instrument Selection

In addition to Spurgeon (1996) who raised the need for theoretically based techniques for the assessment of particular chemicals, Tilson (2000) emphasises the need for mechanistic data for the validation of biologically based dose-response models for risk assessment. Landrigan et al (2004) also notes that the understanding of these neurotoxic mechanisms will assist in these calculations and in the development of new improved NOAEL. These recommendations are an indication of a shift in neurotoxic assessment, where second generation assessments may be directed towards the assessment of specific neurotoxins on the basis of a thorough understanding of their toxicodynamics. In this dissertation dynamic brain localisation theory is proposed as a theoretical guide for the interpretation of cellular and anatomical pathology, caused by the toxicodynamics of a specific neurotoxin, into neuropsychological constructs which may be measured as a means of increasing test sensitivity and specificity. The use of this theory may aid the development of this field away from the assessment of neurotoxic injury as a unitary phenomenon and towards a theoretically based specialised investigation of specific neurotoxins. In spite of the use of dynamic brain localisation theory as a theoretical tool in the assessment of traumatic brain injury, the findings from this review indicate that the use of this theory was not employed by the majority of studies reviewed here. In fact dynamic brain localisation theory was only employed by one other author who investigated the role of neurotransmitters in the mechanisms of behavioural alterations resulting from neurotoxic exposure (Lucchini et al., 2000).

The disadvantage of treating neurotoxic brain damage as a unitary phenomenon was demonstrated in the review of carbon disulphide studies. The toxicodynamics of this neurotoxin results in maximum damage to the frontal lobes (Rosenberg, 1995). Dynamic brain localisation theory has shown that deficits to these areas are associated with social dysinhibition and dysexecutive syndrome (Funahashi, 2001; Spreen & Strauss, 1998). However this exposure was mostly assessed with cognitive assessments which are reported as ineffective for the assessment of frontal lobe damage (Funahashi, 2001). With regards to the assessment of manganese, no authors reported the consideration of the basal ganglia damage caused by this neurotoxin as influencing their selection of tests. However the widely known association of this neurotoxin with psychomotor deficits resulted in a large number of these assessments used for manganese evaluation. The review indicates that the use of psychomotor tests for the assessment of this neurotoxin may have increased sensitivity of these measurements. However, methodological factors and confounding variables prevent

the drawing of robust conclusions to this regard. In addition, the review of effective instruments for the assessment of manganese demonstrated the possible efficacy of psychological assessments as screening instruments for this neurotoxin. Psychological deficits (such as changes in mood and personality) are also associated with basal ganglia damage in diseases such as Huntington's disease (Lezak et al., 2004). This demonstrates an additional advantage of dynamic brain localisation theory in the neuropsychological toxicology context. When the neurotoxicodynamics of a particular neurotoxin are understood, it is possible to draw from information regarding the assessments there of from other research contexts, such as in the case of Huntington's disease. Therefore a theoretical foundation facilitates the linking to previously generated information. Literature regarding Alzheimer's disease provides some clues to the effective assessment of organophosphate as both affect the cholinergic system, although they appear to have opposite effects on this system. However, the lack of neuropsychological literature regarding damage to the cholinergic system hinders the identification of neuropsychological tests which may effectively assess organophosphate exposure. Further research into the effect of this exposure may provide insight into the brain behaviour relationship of this system as well as the impact of organophosphate on this system. This is supported by the proposal of Lucchini et al. (2000) who states that neuropsychological findings can make an important contribution to the better understanding of neurotoxic mechanisms.

The use of specific neuropsychological tests to assess the deficits incurred by damage to specific cells or brain areas is supported by the outcomes of the review process. Although methodological issues, confounding variables and different exposure levels must be kept in mind, the outcomes of tests such as the Benton Visual Retention tests emphasis the importance of test specificity. This test was highly effective in assessing deficits incurred through organophosphate exposure and ineffective as a tool for carbon disulphide assessment. The Digit Span subtest also measured more deficits in organophosphate-exposed participants than in those exposed to carbon disulphide. Although Digit Span is recommended as a test for frontal lobe dysfunction, this measure is only effective if attention is paid to the qualitative mistakes made by participants (Lezak et al., 2004). Digit Span is also essentially a test of memory (Lezak et al., 2004). The qualitative assessment of participant behaviour was not reported in the majority of studies reviewed here, and may not have been possible for large cohorts. This may explain the increased sensitivity of this assessment to the memory deficits incurred by organophosphate exposure than carbon disulphide exposure.

However, not all assessments that were predicted to be effective in assessing the damage incurred by a specific neurotoxin and sensitive to types and location of damage incurred were so. Tests such as the Block Design and Digit Symbol were not effective in discriminating between participants exposed to different neurotoxins. In addition to methodological issues, this outcome may be attributed to the fact that these tests function more effectively as

screening tools, which test large areas of the cortex and measure deficits regardless of the location of the lesion (Lezak et al., 2004).

Another finding from this review is that although a particular test is predicted to be sensitive to the area damaged by a specific neurotoxin, not all the studies, in which the test was employed to assess that neurotoxin, measured deficits with the particular test. This is true for all the tests that were employed in a sufficient number of studies to permit comparison. Firstly, this may be attributed to the methodological issues discussed above. Secondly, this may also be explained by the complexity of the human brain and the variety of functions associated with a single structure. Thirdly, the level of exposure and therefore the extent of damage sustained by participants differed between studies.

The use of specific tests selected in accordance with dynamic brain localisation theory may provide advantages for both screening and diagnostic assessments. Tests which measure deficits incurred through a specific toxic mechanism may be more sensitive as a screening tool and less likely to result in false negative findings, as incurred deficits are more likely to be measured. In addition tests which measure deficits associated with the toxic mechanism can be more easily linked to toxin-deficit causality. This is an important criterion for the Bradford hill method (Stephens & Barker, 1998) and may even contribute to ruling out malingering.

7.3 Key findings: Current Trends in Neuropsychological Toxicology Methodology

In addition to the investigation of neuropsychological tests which may be effective in assessing subclinical deficits this review aimed to identify a best practise methodology for these assessments. Key findings of current trends in neuropsychological toxicology methodology identified during the review can be summarised as follows.

- Advances in medical measures not only enable the revealing of the neurotoxicodynamics, but also facilitate the comparison of outcomes in a dose response relationship contributing to the understanding of the nature of specific neurotoxins.

- Subclinical deficits resulting from chronic exposure are difficult to assess, differences in methodology and confounding variables hinder comparison of results and often result in inconclusive findings.

- Lack of research regarding effective assessment instruments and assessment methods, as well as research on participants with different neurotoxic sensitivity

(woman, foetuses, children, geriatrics and hypersensitive individuals) is hindering the development of neuropsychological toxicology.

7.3.1 Advances in Medical Measures not only Enable the Revealing of the Neurotoxicodynamics of Chemicals Assess but also facilitate the Comparison of Outcomes in a Dose-Response Relationship Greatly Contributing to the Understanding of the Nature of Specific Neurotoxins.

Developments in medical measures, such as neuroimaging techniques, have changed the type of information that is available to neuropsychologists working in interdisciplinary teams on neurotoxic assessments. This is demonstrated in the assessment of carbon disulphide in which MRI findings could be compared to neuropsychological outcomes of the same patients. This facilitates the use of dynamic brain localisation theory as a theoretical guide for the selection of instruments which are sensitive and specific to these deficits, as discussed in the previous section. However, this review has found that the majority of medical measures are not correlated with neuropsychological outcomes in the studies reviewed here. The outcomes of which may greatly increase our understanding of the relationship between observed cellular and anatomical pathology and neuropsychological deficits (Weiss & Elsner, 1996).

In addition to the identification of areas and systems affected by a specific neurotoxin developments in medical methods have enabled the measurement of quantitative exposure levels. This has provided a number of advantages. Firstly in correlation design studies neuropsychological deficits may be correlated against exposure levels, controlling for a number of confounding variables. Secondly, these exposure measurements enabled the comparison of neuropsychological test outcomes relative to the amount of damage sustained at different exposure levels providing a more accurate way of analysing test sensitivity. This method was employed in this dissertation. Thirdly, outcomes of different studies may be compiled into a dose-repose curve providing a means of determining improved NOAEL (Landrigan et al., 1994). Fourthly, medical monitoring may be used to exclude control group exposure (Takebayashi et al., 1998). Control groups which have been exposed to the neurotoxin in question may result in false negative findings. Findings may also be biased by neurotoxins such as lead and manganese which have become ubiquitous to the environment. Researchers drilling into glaciers determined that the atmosphere was free of lead prior to its introduction in petrol in 1920s (Bryson, 2005). It is likely that all participants, both experimental and control, assessed around the world have been exposed to this neurotoxin. The implication for neuropsychological toxicology research is, firstly, that our “normal” unexposed controls may be elusive; and secondly, that they may perform at lower levels than their grandparents would have. In addition, finding participants that have been exposed to a single neurotoxin only may prove impossible. This review uncovered that the analysis of neuropsychological outcomes relative to exposure level is hindered by a number of factors

including participant exposure to multiple toxins, authors omission of the specific compound to which participants are exposed and the absence of these measurements in some studies.

7.3.2 Subclinical Deficits Resulting from Chronic Exposure are Difficult to Assess, Differences in Methodology between Studies and Confounding Variables Hinder Comparison of Results and Often Result in Inconclusive Findings.

The choice of methodology employed may impact on the type of findings made by a study as well as the impact of confounding variables on these findings. The majority of publications reviewed here conducted cross-sectional studies in which experimental group outcomes were compared to those of a control group. This methodology is particularly susceptible to the effect of confounding variables. A large number of confounding variables were reported by the studies reviewed here and as can be expected, none were able to control for all variables. This may contribute to the inconclusiveness of findings. These sentiments are shared by authors such as Colosio, et al. (2003); Jamal, Hansen, Pilkington et al. (2002) and Reidy et al. (1992). These confounders are more easily controlled for by using longitudinal or correlation designs. However, longitudinal designs are vulnerable to the impact of natural decline in neuropsychological outcomes as a result of ageing, while correlation designs remain vulnerable to the impact of third variables (Babbie & Mouton, 2001). Specifically in the case of neuropsychological toxicology research, a variable such as age is relevant, as duration of exposure increases with age, and age is also associated with a natural decline in outcomes (Anger et al., 1997; Spurgeon, 1996).

7.3.3 Lack of Research Regarding Effective Assessment Instruments and Assessment Methods, as well as Research on Participants with Different Neurotoxic Sensitivity (Woman, Foetuses, Children, Geriatrics and Hypersensitive Individuals) is hindering the Development of Neuropsychological Toxicology.

The large number of confounding variables and methodological factors which may impact on neuropsychological toxicology assessments and the resultant inconclusiveness of findings of these studies, is a definite indication for research into better methods of assessment. This is especially relevant in the assessment of subclinical deficits as Stephens and Barker (1998) notes that subclinical deficits may easily be mimicked or hidden by confounding variables. However, this review indicates that few authors conducted investigations to improve on current assessment methods or assessment instruments, which are greatly needed during the transition to the assessment of subclinical deficits. The majority of studies merely aimed to investigate whether neurotoxic exposure results in detrimental effects, with the general answer being a fairly simplistic ‘yes’. Although these findings may be effective in creating awareness about this problem, they do not go a long way in contributing towards the development of effective regulatory levels or clinical interventions.

In addition, the majority of neurotoxic research is conducted on middle aged men, and as was demonstrated in the discussions regarding manganese, findings from these studies may not be generalisable to woman due to physiological differences between these groups. Physiological differences in children, foetuses and geriatrics result in increased susceptibility of these individuals to neurotoxic effects (Dietert et al., 2000; Hartman 1995). This review indicates that despite their increased vulnerability these groups remain under researched. In addition the consideration of individualistic differences in neurotoxic sensitivity is almost absent in the studies reviewed here. Highly sensitive individuals may drop out of jobs where neurotoxic exposure occurs, and may therefore be excluded from cross-sectional studies (Brown et al., 1991). In addition, the majority of studies reviewed here reported on mean outcomes of groups. This does not consider the deficits incurred by the bottom outliners, who may be more sensitive and have incurred more deficits than average participants.

The findings of this review have identified an increased need for the assessment of subclinical neurotoxic deficits and the difficulty with which these are assessed. Two steps are recommended for the effective evaluation of these deficits. Firstly, it is recommended that testers use neuropsychological tests with the highest possible sensitivity (ability to discriminate between exposed and non-exposed participants). Secondly, a methodology should be employed to control for as many confounding variables as possible.

7.4 Recommendations

7.4.1 Neuropsychological Toxicology Tests

During the review process advantages were identified for the use of both standard neuropsychological toxicology batteries and the use of dynamic brain localisation theory as a theoretical guide for the selection of neuropsychological tests which measure deficits associated the damage of specific brain areas and systems by the neurotoxicodynamics of the neurotoxin under investigation. It is therefore recommended that in research and clinical settings, both standard neuropsychological batteries and tests which test neuropsychological deficits associated with the cellular and anatomical pathology caused by the toxicodynamics of the neurotoxin under investigation be used. The use of standard neuropsychological batteries provides a means of testing global functions and facilitating comparability between studies and the use of tests which are sensitive to the specific neurotoxic mechanism under investigation will increase the sensitivity and specificity of the measurement. This method of test selection may aid the field of neuropsychological toxicology to participant in the transition from the assessment of neurotoxin damage as unitary phenomenon towards the assessment of neurotoxins as distinct entities with different neurotoxin mechanisms, resulting in different damage and consequences of exposure.

Example of neuropsychological toxicology test selection for specific neurotoxins
Carbon disulphide= standard battery (example WHO NCTB) + frontal lobe tests (such as dysexecutive syndrome and social inhibition assessments)
Manganese= standard battery (example WHO NCTB) + basal ganglion tests (such as psychomotor and personality assessments)
Organophosphate = standard battery (example WHO NCTB) + cholinergic tests (memory and sleep awake cycle)*

*The neuropsychological evaluation of the cholinergic system has mostly been developed for the assessment of Alzheimer's disease, as previously stated although this disease affects the same system as organophosphate these pathologies have opposite effects (Kamel & Hoppin, 2004). Therefore the assessment of organophosphate exposure may further increase our understanding of the brain behaviour relationship or this system.

In addition it may be necessary to include more than one of these assessments as this review has indicated that not all tests which are traditionally associated with sensitivity to a specific area measured deficits in all patients.

It is recommended that these assessments should not be limited to cognitive assessments but should include psychological and psychomotor assessments. The evaluation of subjective symptoms and the qualitative investigation of patient symptoms may provide further insights into the measurement of these deficits.

7.4.2 Neuropsychological Toxicology Best Practice Methodology

The following recommendations for a methodological best practice of the assessment of subclinical neurotoxic deficits can be summarised as follows.

- Increased use of medical measurement of neurotoxic exposure and neurotoxicodynamics may facilitate the development of neuropsychological toxicology assessments.

- Simultaneous use of cross sectional and longitudinal designs may control for a large number of confounding variables encountered during the assessment of subclinical signs, thus facilitating the comparison of outcomes between studies.

- Research regarding effective assessments instruments and methods for subclinical neuropsychological deficits of specific neurotoxins will advance the development of the field of neuropsychological toxicology. Research on woman, foetus, children, geriatric and hypersensitive individuals is also urgently required.

7.4.2.1 Increased use of Medical Measurement of Neurtoxic Exposure and Neurotoxicodynamics may facilitate the Development of Neuropsychological Toxicology Assessments.

The findings of this review has identified a number of advantages of the use of medical measurements of neurotoxic exposure for neuropsychological assessments these are discussed in the previous section. The recommendations for the use of these measurements by Neuropsychologists are summarised below

- Dynamic brain localisation theory may be used a theoretical guide for the selection of neuropsychological instruments when the toxicodynamics of a neurotoxin are known.
- Comparison of medical measures (such as MRI and EEG) with neuropsychological outcomes is effective in increasing our understanding of the brain behaviour relationship.
- Conducting quantitative medical measures of participant exposure levels and duration facilitates the comparison between studies and determining improved NOAEL.
- Correlation of neuropsychological outcomes with quantitative measures of exposure level and duration is effective in determining dose-response relationship and identifying sensitive tests.
- Conducting quantitative exposure measurement to rule out exposure to control group may prevent false negative findings.
- Conducting quantitative measurement of experimental and control group to exclude exposure to other neurotoxins may ensure that findings can be related to the neurotoxin under investigation.
- Reporting on the exact compound of neurotoxin investigated may facilitate the comparison of studies as different compounds may have different neurological consequences such as demonstrated by the different organophosphate compounds.
- Cognisance of and controlling for incidence of high-level exposure may prevent the confusion of permanent damage from a single episode of high-level exposure to chronic low-level exposure.

7.4.2.2 Simultaneous use of Cross Sectional and Longitudinal Measurements may Control for a Large Number of Confounding Variables Encountered During the Assessment of Subclinical Signs, thus facilitating the Comparison of Outcomes Between Studies.

There are a vast number of confounding variables that may obscure the subtle effects of subclinical deficits associated with low-level exposure. Resources permitting, it is recommended that more longitudinal and correlation assessments be employed. In a longitudinal study each participant represents his or her own control group. This would account for the majority of the abovementioned confounders. Colosio et al. (2003) recommend this method as it also allows the monitoring of exposure levels over time. Using follow-up assessments with this method may provide insight into the prognostic significance of the compounding effects of subclinical deficits incurred through long-term exposure (Colosio et al., 2003). Longitudinal assessments are also recommended for the measurement of subclinical deficit assessments in forensic and clinical contexts, although this may require baseline measurements prior to exposure.

However, one confounding variable, which is not controlled for and may mimic neurotoxic effects in longitudinal designs, is the impact of ageing (Anger et al., 1997; Spurgeon, 1996). This is further complicated by the association of neurodegenerative diseases with neurotoxic exposure, as well as with ageing (Rosenberg, 1995). It is therefore necessary to discern, as far as possible, the aetiology of these disorders and the impact they have on neuropsychological assessment. It may therefore be beneficial to simultaneously employ both a cross-sectional and a longitudinal design for neuropsychological toxicology studies. This will enable before and after measurements of the experimental group to assess the extent of neurotoxic damage, while controlling for confounding variables such as age and the practice effect. Comparisons of the matched control and experimental groups may give an indication of the impact of the normal ageing process on these results, and provide an indication of the aetiology of the neurodegenerative disorders. This methodology may also contribute to the understanding of differences in individual sensitivity to neurotoxic exposure as well as the diversity in human brain functioning. This illustrated in FIGURE 7-1.

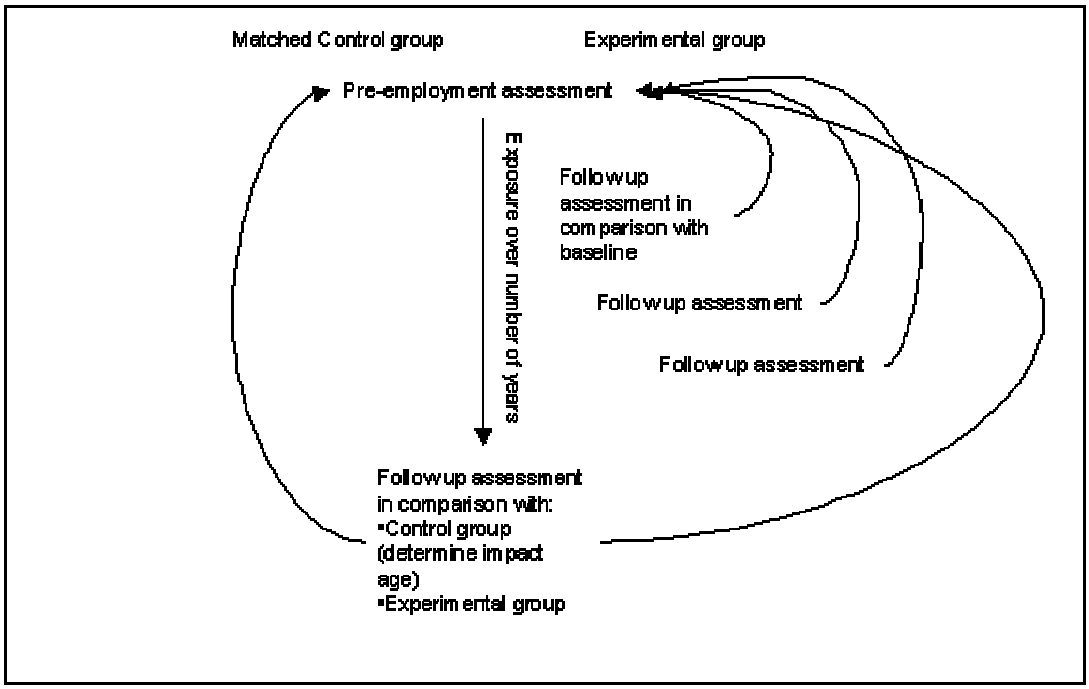

Figure 7-1: Recommended methodology for neuropsychological toxicology assessments

7.4.2.3 Urgent Research is required into the Assessment Instruments and Methods for Measurement of Subclinical Deficits of Specific Neurotoxins, and under Research Groups.

As the field of neuropsychological toxicology is currently in a transition stage, research regarding improved assessment methods is essential for the development of this field. This review has identified key areas where future research may be beneficial. These include the identification and evaluation of neuropsychological tests that are effective in assessing sublcinical deficits for specific neurotoxic damage. The possible advantages of the use of correlation designs in this process has already been discussed. Further more it is recommended that research is conducted to investigate effective methodologies for the evaluation of subclinical deficits as this has proven to be rather tricky often resulting in inconclusive findings. In addition it is recommended that future research focuses on previously under research groups such as women, foetuses, children, geriatrics and hypersensitive individuals. The measurement of deficits incurred by hypersensitive individuals may be facilitated by the continuous measurement of participants that may resign from jobs involving neurotoxic exposure. The full impact of neurotoxic effects may be demonstrated further by reporting on the outcomes of bottom outliners (hypersensitive individuals) and not only sample means.

Therefore future research in the field of neuropsychological toxicology will assist it in overcoming its current transitional phase and continue to deliver valuable contributions to the scientific community in the future. This is required because neurotoxic chemicals results in nervous system damage to those who are exposed to them, however as we are globally dependent on neurotoxins such as pesticides for the maintenance of food supplies, among other things (Zakrzewski, 1991). This dependence indicates that neurotoxins appear to be here to stay, at least for the time being. The challenge to neuropsychologists is to effectively assess these deficits so as to more effectively help patients who have already incurred damage, and to assist in developing effective NOAEL to ensure that neurotoxic exposure does not do harm. With the unique contribution that neuropsychological toxicology can make in the assessment of neurotoxic exposure it is likely that this field will continue well into the future. It is also important for this field to continue to develop and adapt to meet the increasing challenges that it faces.

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APPENDIX 1: STANDARD NEUROPSYCHOLOGICAL TOXICOLOGY BATTERIES

- **1983 World Health Organisation – Neurobehavioural Health Core Test Batteries (WHO-NCTB).** This battery of tests was sponsored by the WHO and the United States National Institute for Occupational Safety and Health. Subtests of this battery were selected from tests which had proved to be sensitive to neurotoxic damage (Anger et al. 1996). These include motor steadiness (Aiming (Pursuit Aiming II), response speed (Simple Reaction Time), fine motor coordination (Santa Ana Dexterity Test), perceptual speed (Digit Symbol Test), visual perception/ memory (Benton Visual Retention Test), Auditory attention/memory (Digit Span), and current experience of affect (Profile of Mood States) (Hartman, 1995).
- **1983 Neurobehavioural Test Battery.** This battery includes nine cognitive tests as well as a profile of mood state (Lezak et al., 2004).
- **1984 TUFF Battery.** This battery was developed in Sweden and is a collection of Swedish as well as American tests (Lezak et al., 2004). These include a Solvent Screening Questionnaire, Vocabulary Synonyms and Antonyms, Figure Classification, Block Construction, an Unfolding test, Visual Gestalt Test, Digit Symbol Test, Dot Cancellation Test, Number Underlining test, Bolt Test and Pin Test, Cylinders, Benton Visual Retention Test, Auditory Perception and Retention as well as neurobehavioral tests from NIOSH worksite studies (Hartman, 1995).
- **1984 The London School of Hygiene Test Battery.** This battery consists of nine tests including Trail Making Tests, WAIS-R subtests including Digit Symbol and Block Design as well as the Grooved Pegboard Test, Dotting Test, Visual Search Test, Buschke Selective Reminding Memory Test, Simple Reaction Time and the Nelson Adult Reading Test (Hartman, 1995; Lezak et al., 2004).
- **1985 NES Neurobehavioural Evaluation System.** This system includes 22 behavioural tests of which seven are adapted from the WHO-NCTB. This test is computer-administered (Anger et al., 1996). Please refer to the WHO-NCTB tests for further information.
- **1986 California Neuropsychological Screening Battery** This battery includes 14 cognitive tests as well as anxiety and emotional distress subtests from the MMPI (Lezak et al., 2004). Cognitive tests include verbal (WAIS-R vocabulary), attention and concentration (WAIS-R Digit Span, WMS-R Visual Memory Span, WMS-R Mental Control and the Cancel H). Visuospatial and visuomotor speed included WAIS-R Digit Symbol, test A of the Trail Making Test and the Cancellation H Test. Cognitive flexibility included Digit Span Backwards, Stroop Color/ Word Test, Trailmaking Test B. Memory tests included WMS-R Verbal Memory Index, Visual

Memory Index, General Memory Index, Attention/Concentration Index, Delayed Recall Index, Information and Orientation, Figure Memory as well as the Digit Symbol recall of the WAIS-R. Learning included tests taken from the WMS-R, Verbal Paired Associates I, and II, Logical Memory II and Visual Reproduction II (Hartman, 1995).

- **1987 Pittsburgh Occupational Exposure Test**. This test consists of 16 tests that measure cognitive functioning (Lezak et al., 2004). These include the WAIS-R intelligence subsets: Information, Similarities, Digit Span, Digit Symbol, Picture Completion and Block Design, Visual Reproduction and Visual Memory, including delayed recall of Wechsler Memory Scale Form 1 design cards as well as immediate reproduction. Other tests include Verbal Association Learning, Symbol Digit Learning, Incidental Memory from the WAIS-R Digit Symbol Substitution Test, Recurring Words, Boston Embedded Figures, Mental Rotation Test, Trail Making Test and the Grooved Pegboard Test (Hartman, 1995).
- **1990 Individual Neuropsychological Tests for Neurotoxicity**. This battery is a combination of the WAIS-R and eight cognitive tests. Items are also included for measuring malingering and emotional status (Lezak et al., 2004).
- **1992 AENBT Adult Neurobehavioural Test Battery**. This was developed by the Agency For Toxic Substances And Disease Registry (ATSD) and includes tests from the NCTB and a computerised battery such as the NES (Lezak et al., 2004).
- **SPES (Swedish Performance Evaluation System) Battery.** This is a computerised battery designed from the following tests: Simple Reaction Time, Choice Reaction Time, Color Word Vigilance, Colour Word Stress, Search and Memory, Symbol Digit, Digit Span, Additions, Digit Classification, Digit Addition, Verbal Reasoning, Vocabulary (WAIS-R/III), Finger Tapping Speed, Finger Tapping Endurance. Mood, performance, acute symptoms and long-term symptoms are also assessed through self-rating scales (Hartman, 1995).

Other less well-known batteries include the Institute of Occupational Health Battery, Tuttle Wood and Grether Battery, Valcuikas and Lilis Battery, Putz-Anderson et al. Battery, Smith and Langolf Battery, Williamson, Teo and Sanderson Battery, Instituto de Medicina del Trabajo, MANS Milan Automated Neurobehavioral System, Psychometric Assessment, System/Dementia Screening Battery, MTS Microcomputer-Based Testing System Battery, Naval Biodynamics Laboratory Battery, Walter Reed Performance Assessment Battery, Cognitive Functioning Scanner, and Automated Performance Test System (Hartman, 1995).

APPENDIX 2: LIST OF ABBREVIATIONS

ACGIH TLV	American Conference Of Governmental Industrial Hygienists Threshold Limit Value
ANBT	Adult Neurobehavioural Test Battery
TTCA	2-thio-1,3-thiazolid-4-carboxylic
CANTAB	The Cambridge Neuropsychological Test Automated Battery
CNS	Central nervous system
COPIND	Chronic Organophosphate Induced Neuropsychiatry Disorder
CT	Computer tomography
DDT	Dichlorodiphenyltrichloroethane
DEPT	Diethylthiophosphate
DMTP	Dimethylthiophosphate
EEC	Electroencephalography
EMG	Electromyography
EVP	Evoked potentials
IQ	Intelligence quotient
MCS	Multiple chemical sensitivity
MMPI	Minnesota Multiphasic Personality Inventory
MMT	Methylcyclopentadienyl manganese tricarbonyl
MRI	Magnetic resonance imaging
NCS	Nerve conduction studies
NES	Neurobehavioural Evaluation System
NOAEL	No adverse effect level
NOEL	No observed effect level
PET	Emission tomography
PNP	P-nitrophenol
PNS	Peripheral nervous system
POMS	Profile of Mood State
Q16	Swedish Questionnaire 16
SPECT	Single photon emissions
SPES	Swedish Performance Evaluation System
WAIS	Wechsler Adult Intelligence Scale
WHO	World Health Organisation
WHONCTB	World Health Organisation - Neurobehavioural Health Core Test Batteries
WRAT-R	The Wide Range Achievement Test - Reading

APPENDIX 3: GLOSSARY

Anaemia: Low red blood cell count

Anorexia: Loss of appetite

Ataxia: Incoordinated movements

Bradidynesia: Slow movements

Conjunctivitis: Inflammation of eyes

Dysphagia: Unpleasant eating

Dyspnea: Painful breathing

Dystonia: Involuntary spasm of muscles

Hyperreflexia: Hyperactive reflexes

Hypertention: High blood pressure

Hypokineasia: Decreased movements

Hypothermia: Decreased temperature

Insomnia: Inability to sleep

Lacrimation: Tearing

Neurotoxicodynamics: Neurotoxic mechanism

Ptosis: Drooping of the eyelid

Vertigo: Dizziness with an illusion of rotation