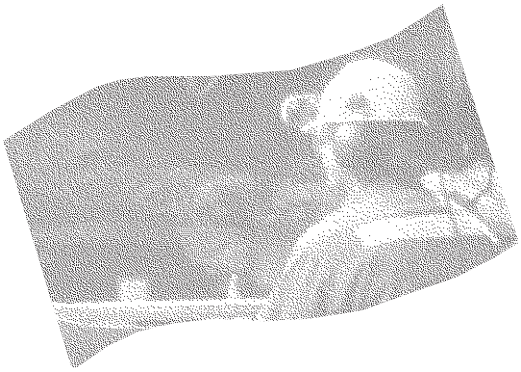
Management of Occupational Manganism

Consensus of an Experts' Panel



STUDIES AND RESEARCH PROJECTS

Claude Ostiguy
Paul Asselin
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Daniel Nadeau
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R-417

REPORT

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This study was financed by the IRSST. The conclusions and recommendations are those of the authors.

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SUMMARY

Background

In recent years, many workers exposed to manganese fumes have developed symptoms evoking occupational manganism. CSST (la Commission de la santé et de la sécurité du travail), the compensation body in the province of Québec was confronted with the fact that there were no standardized procedures for the primary, secondary and tertiary prevention of manganism, leading to possible medico-legal disputes and a possible lack of equity for workers or employers.

Objective

To establish the definition and classification of occupational manganism, provide medical specialists, and the compensation body with standardized procedures for the diagnosis, investigation, treatment and, monitoring of workers exposed to manganese (Mn), and with safe conditions for rehabilitation.

Methods

A medical committee was formed to provide answers on the clinical aspects of the problem; a synthesis of scientific knowledge was collected and a multidisciplinary panel of international experts was convened to reach, as much as possible, a consensual approach to the issue of diagnosis of manganism.

Results

Manganism is defined as a specific clinical central nervous system syndrome caused by manganese. Factors that might lead to manganism include excessive exposure, reduced clearance, increased absorption rate, and individual susceptibility to manganese. Then, occupational manganism could be defined as a specific clinical central nervous system syndrome caused by workplace exposure to manganese. Three risk factors were identified that have been shown to increase the accumulation of Mn in the central nervous system (CNS): liver diseases, iron deficiency and alcoholism, whose effects add to the neurotoxic action of Mn.

Based on the level of diagnostic certainty, manganism can be classified as clinically possible, clinically probable or clinically definite. Independent of the level of diagnostic certainty, and based on the clinical assessment of functional and social capacities, impairment can be rated as mild, moderate or severe.

Criteria have been proposed for classifying cases of occupational manganism. A worker is recognized as a **clinically possible** case of occupational manganism if the following three conditions are present: a documented identifiable source of occupational Mn exposure; at least one neurological element among tremor, bradykinesia, rigidity and postural instability and symptoms and clinical signs of neuropsychological disturbances, mainly motor ones. A diagnosis of a **clinically probable** case of manganism includes items from a possible case of manganism plus neuropsychological disturbances related to basal ganglia origin, absence or unsustained pharmacological response to levodopa (L-dopa) and exclusion of other neuropsychological diseases related to basal ganglia, such as Parkinson's disease, secondary parkinsonism or atypical parkinsonism syndromes. Finally, a case of occupational manganism can be recognized as **clinically definite** if a clinically probable case is reinforced by histopathological data. A normal Fluoro-Dopa positron emission tomography (F-Dopa PET) scan is another approach that would also confirm clinically definite manganism, but an abnormal F-Dopa PET scan would not exclude manganism.

In order to diagnose a case of occupational manganism, a three-step approach is proposed. In the first step, for a worker suspected of having occupational manganism, the occupational physician should perform a thorough evaluation of Mn occupational exposure along with an evaluation of the presenting clinical picture. A clinical case history should also be performed that includes the history of current clinical symptomatology, the history of past clinical problems and the family history. He then performs a complete physical examination with an emphasis on neurological examination to identify clinical signs of parkinsonism. The physician should detail occupational exposure to any neurotoxic contaminants. Starting with an occupational history, he will search work records indicating Mn exposure and specific work assignments known to be associated with Mn exposure. He will also gather data, past or present, from occupational hygiene investigations (whenever these exist). If the occupational physician deems it appropriate, he could gather basic neuropsychological data using a standardized questionnaire and/or a short battery of tests and complementary investigations such as liver testing and complete blood count, and iron stores. Depending on the temporal relationship between the time of the Mn exposure and the examination, blood and urine Mn levels and a magnetic resonance imaging (MRI) could be ordered as well as other pertinent tests depending on the clinical history. After this initial data collection, he could refer the worker to a neurologist specialized in movement disorders if further exploration is deemed to be appropriate.

In a second step, a neurologist knowledgeable in movement disorders should assess the patient to determine if the clinical picture is consistent with a diagnosis of manganism. Tests and procedures required to determine the correct diagnosis should be ordered as appropriate.

In the third and final step, complementary investigations could include formal neuropsychological evaluation, MRI (if not already done and appropriate time-wise), levodopa trial and Fluorodopa PET scan or other imaging study to assess the integrity of the nigrostriatal system. Based on these assessments, the neurologist will determine if in his opinion a given case suffers from clinically possible, probable or definite manganism. The diagnosis may be modified based on subsequent examinations and the acquisition of further information.

The experts agreed that there was no specific treatment plan for manganism. Antiparkinsonian drugs may have a positive effect on parkinsonian symptoms and signs, but this effect is temporary and of short duration, if present at all. Antioxidants have been recently studied but benefits have not been proven. Chelation is still considered investigational. Symptom relief and rehabilitation therapies are all that remain. The main intervention consists of stopping significant exposure to manganese as well as to other recognized neurotoxic agents as soon as possible, when the symptoms and signs may still be reversible. The experts also agreed on a medical monitoring plan in the first year and later as appropriate. If a change is seen in the worker's condition, then the diagnosis can be reviewed.

A worker considered as a definite, probable or possible case of occupational manganism and who has the physical capacity to work should be kept from any further significant exposure to manganese in the workplace. Furthermore, he should not be returned to a workplace significantly contaminated with any other recognized neurotoxic agent. The level of Mn exposure should be as low as possible but never exceed 0.03 mg Mn/m^3 (expressed as respirable dust).

A wide variety of psychoneurological tests have been used in studies of groups of asymptomatic individuals exposed to low doses of manganese. None of these functional tests is specific to the neuropsychological effects of manganese. However, a consistent pattern of abnormalities has been associated with manganese, including deterioration of the rapidity of neurosensorial response, motor function, mood, and memory tests. There is no data from longitudinal studies allowing an assessment of the value of any test or combination of tests for predicting the occurrence of clinical manganism. On an

individual basis, it is thus impossible to predict who will develop a syndrome of clinical manganism among asymptomatic workers exposed to low doses of manganese and having some abnormal functional tests.

Based on current scientific knowledge and the World Health Organization (WHO) criteria to be met in order to implement screening program and therefore good medical practice, no recommendation can be made for a screening program targeting asymptomatic workers exposed in the workplace. A prospective longitudinal controlled study could be useful to learn more about the progression from pre-manganism or some preclinical effects of Mn to clinical manganism.

The only preventive intervention that could be proposed to reduce or eliminate the risk of developing clinical manganism is the reduction of exposure.

Conclusion

Valuable information on the clinical aspects of occupational manganism will lead to standardized procedures for the diagnosis and management of workers exposed to manganese fumes and dusts. CSST compensation parameters and management procedures for cases should be reconsidered taking into account the information included in the present report.

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INTRODUCTION

In recent years, many workers in the province of Québec have developed symptoms evoking manganism. Most of these people are welders exposed to manganese (Mn) fumes during heavy equipment maintenance. These workers have received medical, neurological, neuropsychological and psychiatric evaluations and some of them have been diagnosed as having manganism at different stages. Non-standardized diagnostic procedures have been used and the conclusions could lead to medico-legal disputes.

To deal efficiently with this emerging situation, a medical committee has been formed by the CSST; IRSST and physicians from the Québec prevention network were invited to participate. The IRSST and the CSST produced a synthesis of the scientific knowledge and different specialists have been consulted in the province of Québec. It has been concluded that establishing a diagnosis for manganism is particularly challenging since standardized evaluation protocols do not exist and important parameters to consider are controversial.

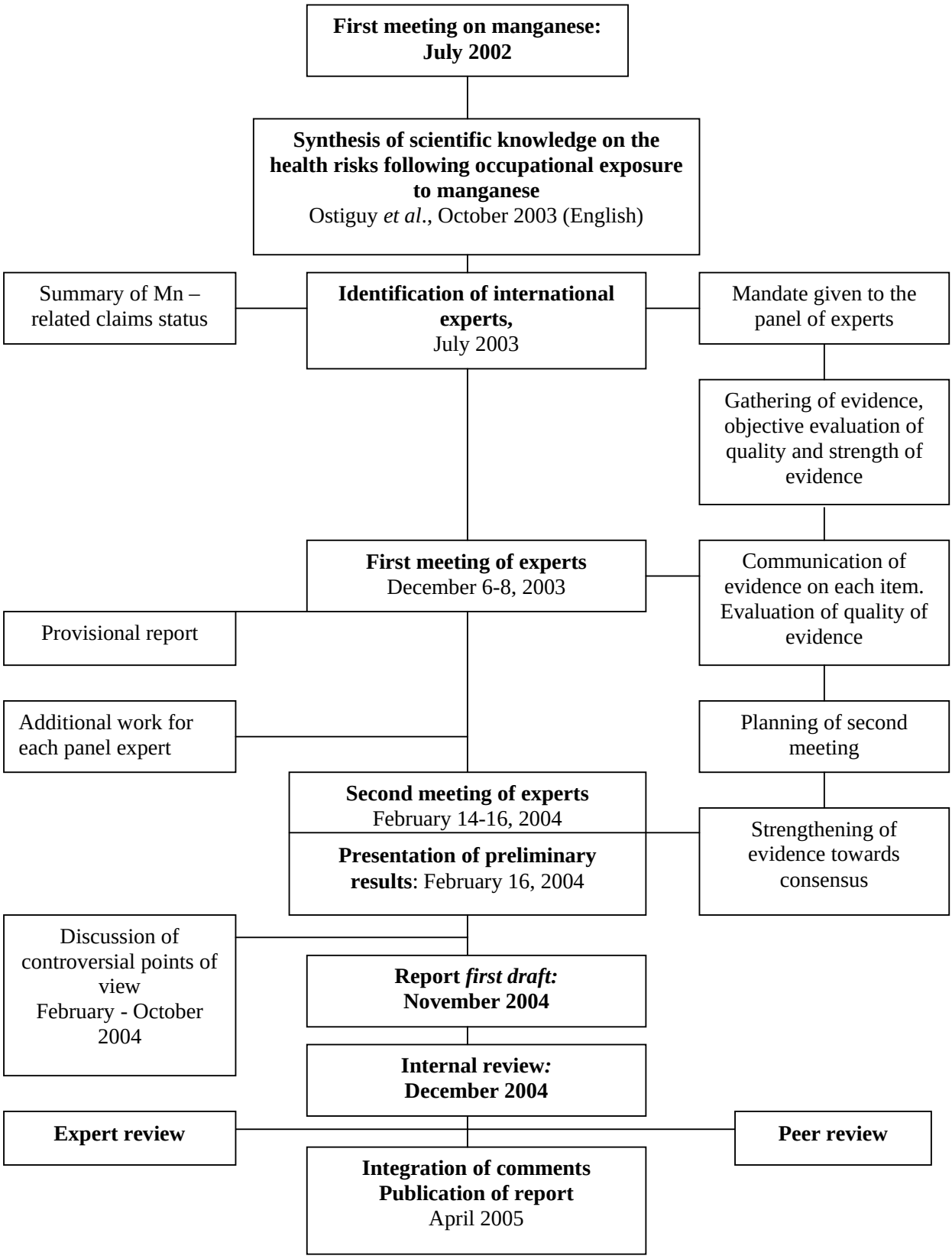
A standardized evaluation procedure, on which all the representatives of the different stakeholders (workers, employers, the medical profession, the prevention network, IRSST and the CSST) could agree, seems strongly desirable for an optimal management of this particular situation. In fact, neurologists and other specialists should be able to come to the same conclusions when they meet a worker who has been exposed to manganese. The procedure should be known and shared among the specialists so that employers and workers as well as the CSST, which has to manage the compensation claims, know exactly the criteria leading to the conclusion of the claims.

With the objective of proposing guidelines for the diagnosis of occupational manganism and the management of affected workers, the IRSST invited a group of five internationally renowned specialists to form an international panel that would guide the Québec medical committee on manganese. This panel included a neurologist (USA), a neuropsychologist (USA), an industrial physician (Italy), a toxicologist (Belgium) and a physician specialized in epidemiology and in community health (Québec). The first three are internationally renowned specialists on manganese, the fourth has extensive expertise in metal toxicology, and the fifth has worked on many international consensus panels and has acted as president of the panel.

A mandate document and support document were prepared for the experts who then met twice for three days each time, at a two-month interval. The experts did work not only during, but also before, between and after the meetings. An extensive correspondence was exchanged with and between the experts to come to a consensus on each of the seven questions that were addressed by the medical committee members who also participated in the meetings but did not take a position in the establishment of the consensus. The stages of the study of the medical committee are summarized in Figure 1.

This report, which has been peer-reviewed by other experts, give the final position of the five members of the experts' panel, expressing the points on which the scientific knowledge lead to a consensus as well as the point on which a consensus was impossible to reach.

Figure 1. Stages of the study by the medical committee



MANDATE 1

Propose a definition of manganism

Recommendations

Manganism is defined as *a specific clinical central nervous system syndrome caused by manganese.*

This report focuses on central nervous system (CNS) aspects of manganese-related health effects. The manifestations of manganism may vary with duration and level of exposure. The clinical features include parkinsonism with neuropsychological and/or psychiatric disturbances. Manganism is related to the accumulation of manganese in the brain and may be related to occupational or other sources of exposure. It can be influenced by susceptibility risk factors, which act as effect modifiers. Factors that might lead to manganism could include:

- Excessive exposure
- Reduced clearance
- Increased absorption rate
- Individual susceptibility to manganese

It should be noted that manganese can also affect other systems such as the respiratory and reproductive systems, but this is outside the scope of the present mandate.

Occupational manganism could be defined as *a specific clinical central nervous system syndrome caused by workplace exposure to manganese.*

Risk factors

Some factors have been shown to increase the accumulation and effect of Mn on the CNS. Three risk factors were identified:

- Liver diseases, which increase the body load of Mn;
- Iron deficiency, which favours the entry of Mn in the CNS;
- Alcoholism, whose effects add to the neurotoxic action of Mn.

Consensus status

These recommendations were agreed upon by consensus.

Rationale

Occupational exposure to manganese

Mn and some of its compounds are used in different industrial processes. The most common forms are metallic Mn, Mn^{+2}, Mn^{+3} and Mn^{+4} found mainly as $MnCl_2$, $MnSO_4$, $MnPO_4$, MnO_2 and Mn_3O_4. Alloyed with different metals, mainly iron, Mn makes these products extra hard. Manganese chloride is used as a catalyst but also as an animal food supplement. Manganese dioxide as well as chloride are both used in the manufacture of dry batteries. Manganese dioxide also has several other applications: fireworks, matches and porcelain. Manganese sulfate is used as fertilizer, in ceramics, glazes and varnishes, as a food supplement, as well as a fungicide (ACGIH 2001). Manganese's organic compounds have three main uses: manganese methyl cyclopentadienyl tricarbonyl (MMT) as an anti-knock additive in gasoline, two pesticides, (maneb and mancozeb), as well as mangafodipir used for diagnosing certain forms of hepatic cancers (ATSDR 2000; ACGIH 2001).

Occupational exposures to inorganic compounds of Mn occur almost solely from the inhalation of dusts and fumes containing Mn. They are mainly related to emissions from automobiles and trucks during maintenance in countries where MMT is used, as well as to the dusts from ores during extraction and processing, to steel preparation operations using Mn, in dry battery manufacturing plants, as well as in steel welding operations using manganese and electrodes with high Mn content (ATSDR 2000; ACGIH 2001; WHO 1986; HSDB 1993).

Concentrations from 1.5 to 450 mg Mn/m^3 have been reported in mines (US EPA 1984), 0.30 to 20 mg Mn/m^3 in ferroalloy production foundries (Saric *et al*. 1977), 3 to 18 mg Mn/m^3 in the dry battery manufacturing sector (Emara *et al*. 1971), from 1 to 4 mg Mn/m^3 in welding operations (Sjögren *et al*. 1990), and up to 14 mg Mn/m^3 in welding operations with welding wire (CICADS 1999). More recent studies, however, have reported much lower average concentrations of 1 mg Mn/m^3 or less in several of these workplaces (Roels *et al*. 1985, 1987a, 1987b and 1992; Mergler *et al*. 1994; Lucchini *et al*. 1995). For exposed workers, Mn absorption may become much more significant by inhalation than by ingestion through food (Ostiguy *et al*. 2003).

Manganese absorption and distribution

Manganese is an essential trace element that is thought to be primarily absorbed via the gastrointestinal tract and the lungs. Dietary manganese is largely excreted through the liver by way of biliary excretion and elimination in the feces. Manganese is a component of many proteins and can be found in almost every tissue in the body. It is an essential cofactor in several enzyme activities playing a role in bone mineralization, in protein and energy metabolism regulation, in cellular protection and in the formation of glycosaminoglycans (ATSDR 2000). However, long-term exposure to excessive levels can cause adverse health effects although there are many variables that are not completely understood such as particle size, formulation, solubility and bioaccumulation. The main target organ systems after chronic inhalation exposure to manganese are the lungs, and the reproductive and the central nervous systems.

The level of absorption of manganese by the gastrointestinal tract is maintained between 3-5% in healthy individuals (Andersen *et al.* 1999; Mena *et al*. 1969; Davidsson *et al*. 1988; Oberdoerster 1988; EPA 1995).

Absorption of manganese by inhalation is in relation to particle size, with the absorption level being close to 100% for small particles (diameter less than 1µm). Absorption by this route bypasses the control processes in the gastrointestinal tract. Manganese absorbed by inhalation is apparently oxidized to its trivalent form and binds to the iron-carrying protein, transferrin. Brain uptake of manganese occurs via transferrin receptors located in various brain regions (Andersen *et al.* 1999; Aschner *et al*. 1999).

Several researchers suggest that the olfactory neurons could serve as an entry pathway for manganese to the brain. Intranasal infusion of manganese in animals resulted in manganese uptake directly into the olfactory bulb. Studies showed that manganese absorbed via primary olfactory neurons could migrate to other regions of the brain via secondary and tertiary olfactory neurons (Tjälve *et al*. 1996; Brenneman *et al*. 2000; Dorman *et al*. 2001, 2002).

Absorption of manganese by the skin is negligible (ATSDR 2000).

Manganism

Chronic Mn exposure may lead to damage to the central nervous system, called manganism. Manganism is a progressive syndrome that typically begins with relatively mild, nonspecific symptoms, which can gradually evolve to a severely debilitating disease with some features that are similar to Parkinson's disease (PD) (Mena *et al*. 1967; Rodier 1955; Inoue and Makita 1996; Olanow 2004; Schuler *et al*. 1957; Tanaka and Lieben 1969; Smyth *et al*. 1973; Yamada *et al*. 1986; Huang *et al*. 1989, 1993, 1998; Wennberg *et al*. 1991; Ky *et al*. 1992; Calne *et al*. 1994; Chu *et al*. 1995; Hochberg *et al*. 1996; Mergler and Baldwin 1997; Pal *et al*. 1999).

The exact biochemical mechanism responsible for manganese neurotoxicity is not clearly established (Aschner and Aschner 1991). Neuropathological changes are detectable in the basal ganglia of people with manganism. There is substantial evidence that the primary sites of damage are the globus pallidus, the striatum and the substantia nigra pars reticulata, while the nigrostriatal system is relatively spared (Olanow 2004; Yamada *et al*. 1986).

Manganese toxicity shows great interindividual variability, and the exposure level for which no effect occurs is not well defined. The clinical effects of high-level inhalation exposure to manganese do not become apparent until several years, but some individuals may begin to show signs after as few as one to three months of exposure to very high concentrations (Rodier 1955). It appears that the occurrence of manganism cases increases with the duration of exposure, suggesting that the seriousness of the symptoms increases with cumulative exposure. (Roels 1987a, 1987b, 1992; Lucchini 1999; Rodier 1955; Schuler 1957; ATSDR 2000).

It is hypothesized by many authors that the health effects, particularly on the central nervous system, occur in a "continuum of dysfunction" which would be dose-related (Mergler *et al*. 1999; ATSDR 2000; ACGIH 2001). In other words, slight and imperceptible effects may be caused by low but physiologically excessive quantities of Mn and these effects increase in severity when the exposure level and the duration increase. Manganese effects begin as a slow deterioration in well-being, which can initially be detected as early neurofunctional changes detectable solely in exposed groups; later, as individual preclinical and then clinical signs; and finally, as a complete neurological disease whose development depends on the exposure dose, the exposure duration and individual susceptibility (Mergler *et al.* 1999). Overt manganism will then be a complex CNS syndrome involving damage to the regions of the brain most sensitive to Mn, and lead to a specific form of clinical parkinsonism. To our knowledge, no longitudinal epidemiological study exists that

has shown the progression from Mn overexposure to overt manganism. Because of the actually limited scientific knowledge on the progression of the disease and the challenges in establishing a diagnosis, Mandates 3 and 4 will discuss these aspects in detail.

Many factors may increase the concentration of Mn in the CNS.

Liver disease

Since manganese is mainly excreted through the biliary pathway, individuals with chronic liver failure are at risk of developing hepatic encephalopathy, which would probably be caused by an accumulation of manganese in the brain (Butterworth *et al.* 1995; Krieger *et al.* 1995; Pomier-Layrargues *et al.* 1995; Spahr *et al.* 1996; Layrargues *et al.* 1998). It has been shown that portosystemic shunting, biliary atresia and liver dysfunction give rise to the accumulation of manganese in the brain (Hauser *et al.* 1996; Layrargues *et al*. 1998; Rose *et al*. 1999; Ikeda *et al.* 2000). There is evidence that extrapyramidal signs related to manganese accumulation in the basal ganglia and minimal hepatic encephalopathy are linked in patients with cirrhosis (Jover *et al.* 2003).

Iron deficiency

Manganese and iron compete for the same carrier transport system. Plasma iron overload significantly decreases the uptake of manganese across the blood brain barrier, whereas iron deficiency (serum ferritin < 10-20 µg/L) is associated with an increased central nervous system burden of manganese (Mena *et al.* 1974; Aschner *et al.* 1990).

There is clear evidence from animal studies that gastrointestinal absorption of manganese is inversely related to the iron concentrations in the diet. Hence, high concentrations of iron lead to a lower absorption of manganese, while low levels of iron promote manganese absorption (Baldwin *et al*. 1999; Chandra and Tandon 1973; Davis *et al*. 1992a, 1992b; Diez-Ewald *et al*. 1968; Rehnberg *et al*. 1982).

Alcoholism

Chronic alcoholic patients may develop liver disease that can lead to hepatic encephalopathy (Butterworth 2003). Also, anaemia is a common problem associated with alcoholism. Alcohol may induce a variety of effects on hematopoiesis, notably in damaging erythroid precursors and leading to anaemia in chronic alcoholics (Eichner 1973; Guthrie *et al.* 1983; Savage *et al.* 1986; Michot *et al.* 1987; Heermans 1998). Furthermore, there is some evidence of interaction between alcohol and manganese on mood states and an increase in neuropsychiatric symptoms (Sassine *et al.* 2002; Bouchard *et al*. 2003).

Other factors

Aging was not retained as a specific factor because of the lack of scientific evidence. However, it seems that it diminishes the ability of the brain to compensate and, in so doing, increases the susceptibility to neurotoxic effects (Pal *et al*. 2002; Mergler *et al.* 1999; Apostoli *et al.* 2000; Levy *et al*. 2005).

Factors like gender and genetic factors may or may not increase the susceptibility of developing manganism. However, further studies are necessary in these fields of research.

MANDATE 2

Propose a classification system for cases of manganism in relation to the severity of the disease and the level of diagnostic certainty

Recommendations

Level of diagnostic certainty

Manganism can be classified as:

- Clinically possible
- Clinically probable
- Clinically definite

Criteria used to define this classification are discussed in the next chapter (Mandate 3).

Severity scale

Independent of the level of diagnostic certainty, and based on clinical assessment of functional and social capacities, impairment can be rated as:

- Mild
- Moderate
- Severe

Rating scales used to assess the severity and impact of Idiopathic Parkinson Disease (IPD) may be helpful. In Québec, the most widely used rating scale is the Unified Parkinson Disease Rating Scale (UPDRS).

Consensus status

These recommendations were agreed upon by consensus.

Rationale

Level of diagnostic certainty

Diagnosis of manganism is difficult. The experts on the panel all agreed that a simple scale reflecting levels of diagnostic confidence would be helpful. Criteria used to classify cases of manganism are based on different sources such as:

- Exposure data
- Clinical data
- Pharmacological data
- Neuro-imaging data
- Pathological data.

Using these different sources of data, one can classify cases of manganism according to the level of etiological certainty that a clinician can assert. They can be rated as:

- Clinically possible
- Clinically probable
- Clinically definite

The clinical criteria used for such classification are the subject of the next mandate and will not be discussed here.

Severity scale

Regarding the severity scale based on clinical assessment of functional and social capacities, the impairment can be rated as:

- Mild
- Moderate
- Severe

In fact, the endpoint is to recognize and quantify the reduction in the autonomy of the affected workers taking into account cognitive and emotive aspects.

Rating scales used to assess the severity and impact of Parkinson's disease (PD) already exist. Parkinson's disease is a progressive neurodegenerative disorder. Motor functions of patients with Parkinson's disease are determined by its cardinal symptoms: bradykinesia, tremor, rigidity and disturbed postural reflexes. To evaluate the degree of disability and the rate of progression, simple but reliable and reproducible rating scales are essential. These or some of these could be used to correctly assess the autonomy of a given individual affected by manganism. Emphasis should be put on functional and social capacities.

Some examples of widely used rating scales developed to assess Parkinson's disease are listed below. These can be used as well to assess the autonomy of patients affected by manganese exposure in evaluating their functional and social capacities.

Activities of Daily Living (ADL)

The ADL scale measures the impact of PD on 14 categories of routine daily life (Newton and Brody 1969).

Schwab and England Activities of Daily Living

The Schwab and England scale reflects the patient's ability to perform daily activities in terms of speed and independence (Schwab and England 1969).

Hoehn and Yahr Staging of Parkinson's Disease

This was the simplest and most popular severity scale for PD (Hoehn and Yahr). However, it lacks sensitivity to changes in the patient's functional condition. This system has been largely supplanted by the more complicated UPDRS.

Unified Parkinson Disease Rating Scale (UPDRS)

The UPDRS is a rating tool to follow the longitudinal course of Parkinson's disease. It is an overall assessment scale that quantifies all the motor and behavioural aspects of the disease as a single number. It is widely used in clinical research and drug trials (Fahn and Elton 1987).

The Movement Disorder Society Task Force on rating scales for Parkinson's disease prepared a critique of the UPDRS. The strengths of the UPDRS are its wide utilization, its wide clinical spectrum of PD, its coverage of motor symptoms and its clinimetric[1] properties, including reliability and validity. Its weaknesses: some ambiguities in the text, some metric flaws and the absence of screening questions on several important non-motor aspects of PD.

The Movement Disorder Society Task Force recommended that the Movement Disorder Society sponsor the development of a new version of the UPDRS and encourage efforts to establish its clinimetric properties as well as test its correlation with the current UPDRS (Movement Disorder Society Task Force on Rating Scales for Parkinson's Disease 2003). Indications are that it has been done and will shortly be published.

[1] Clinimetric properties are to be defined as "overall quality of a scale in regard to its internal validity and external validity. Internal validity includes concepts as construct validity, content validity, and predictive validity (sensitivity, specificity, predictive positive value, etc…). External validity relates more to reliability considerations i.e. reproducibility" (Feinstein 1984; Nunnaly 1978).

MANDATE 3

Propose criteria for classifying cases of occupational manganism and for differentiating them from other neurological pathologies, including idiopathic Parkinson's disease

Recommendations

Many tests exist that can contribute to the establishment of a diagnosis of manganism. However, many of these tests have important limitations and scientific knowledge on the development of the disease is rather limited. With this scientific gap, a standardized and recognized list of criteria leading to the diagnosis of manganism does not exist. Based on current knowledge, the following classification is proposed.

1) A clinically POSSIBLE case of occupational manganism would include:

a. A documented identifiable source of occupational Mn exposure

b. At least one neurological element among tremor, bradykinesia, rigidity and postural instability

c. Symptoms and clinical signs of neuropsychological disturbances, mainly motor

Such a picture would warrant public health interventions in order to implement preventive measures.

2) A clinically PROBABLE case of manganism would include:

- Items from a possible case of manganism plus:
- Neuropsychological disturbances related to basal ganglia origin
- Absence or unsustained pharmacological response to L-dopa
- Exclusion of other neuropsychological diseases related to basal ganglia, such as Parkinson's disease, secondary parkinsonism or atypical parkinsonism syndromes.

3) A clinically DEFINITE case of occupational manganism would include:

- Items from a probable case plus:
- Histopathological data

  OR

- A normal F-Dopa PET scan would confirm manganism but an abnormal F-Dopa PET scan would not exclude manganism.

Consensus status

These recommendations were agreed upon by consensus except for the use of the F-Dopa PET scan to confirm a definite case.

Rationale

Manganism is one of the clinical syndromes in the broad category of neurodegenerative disorders presenting with parkinsonism. Since manganese neuro-intoxication is classically associated with Mn accumulation in, and damage to, the globus pallidus, striatum and substantia nigra pars reticulata, with relative sparing of the nigrostriatal dopaminergic system[2] (Yamada *et al*. 1986; Calne *et al*. 1994; Olanow *et al*. 1996; Sziraki *et al*. 1998; Newland 1999; Normandin and Hazell 2002; Olanow 2004), its clinical presentation and pharmacological response to levodopa, as well as images stemming from different technologies and histopathological evidence, will reflect this particularity and help differentiate manganism from other types of parkinsonism (Calne *et al*. 1992; Pal *et al*. 1999). However, the reader must keep in mind that a limited number of cases are described in the scientific literature, which remains insufficiently documented, and many questions are still unanswered. Among these is the progression of symptoms as the disease evolves from early non-specific health effects to chronic manganism.

- *Early health effects of chronic Mn exposure*

Before the appearance of signs of overt manganism, workers exposed to low levels of Mn dusts and fumes can present non-specific subtle symptoms that are labelled in the literature as sub-clinical or pre-clinical. These subtle effects can constitute manganese-induced changes in the same areas of the brain as overt manganism, namely the basal ganglia and particularly the globus pallidus, striatum and substantia nigra pars reticulata. It is quite plausible, although it has not been proven, that these early effects could be of relevance to later clinical disease without being clearly predictive. It remains that the most sensitive end point of Mn toxicity is neurological/neuropsychological. In the last fifteen years, health research on Mn has been centred on the evaluation of these subclinical neurobehavioral / neurotoxicological early effects of chronic exposure to low-levels of Mn dusts and fumes. To our knowledge, no large scale epidemiologic study has been done that quantifies the risk of developing parkinsonism following the appearance of subtle early effects.

These early effects are mainly motor but they can also be cognitive. They should concern mainly:

- Deficit in attention allocation and filtering;
- Impaired implicit learning and memory leading usually to acquisition of behaviours and efficiency in working memory by motor learning, sequencing and movements (Ring *et al*. 2002).

A careful neuropsychological examination using a standardized battery of tests should help identify these deficits early in the diagnostic process. A short and a thorough versions of batteries of tests are presented in Appendices A, B and C. It is important to take into account the fact that, most of the time, the very early symptoms and signs are nonspecific as described earlier and are usually dependent on the degree of exposure.

Five sets of data can be used to evaluate a suspected case of occupational manganism. These are:

- Occupational exposure data
- Clinical data
- Pharmacological data
- Imaging data
- Histopathological data

[2] It is to be remembered that classical idiopathic Parkinson's disease (IPD) is characterized by degeneration of dopamine neurons in the substantia nigra compacta (Calne 1994; Olanow 2004).

Each has its utility and will intervene at different points in time during proper evaluation of a suspected case, but overall, the gathered information will be mainly relevant in two ways: first to evaluate the nature and extent of disability in an afflicted individual and second to establish a causal relationship between the observed clinical picture and manganese exposure. Using bits of information given alternatively by each set, a clinician will gain confidence in his assertion that a given case is indeed a case of occupational manganism and not any other parkinsonian disorder. As the overall picture of the case evolves, the clinician will progressively be able to label a case as accurately as possible as, clinically possible, clinically probable, or clinically definite (Jankovic *et al*. 2000; Hobson 2003). Some of the information given by each set of data will serve to establish a case while some other information will serve to exclude other diseases as alternative explanations for the presenting clinical extra-pyramidal syndrome (Litvan *et al*. 2003).

- *Occupational exposure documentation*

Basically and of utmost importance, one should consider that a case could be occupational manganism if there is a source of documented occupational exposure to excessive levels of Mn.

It is possible that some individuals with a reduced clearance for Mn, increased absorption or individual increased susceptibility, such as people with alcoholism, liver cirrhosis or iron reserve depletion, may develop a syndrome of manganism when exposed to levels of Mn that do not cause intoxication in healthy subjects (Devenyi *et al*. 1994; Hauser *et al*. 1994, 1996; Layrargues *et al*. 1995; Pomier-Layrargues *et al*. 1995; Spahr *et al*. 1996; Herrero Hernandez *et al*. 2002; Ellingsen *et al*. 2003; Fiedler 1996). Toxic exposure could be a function of exposure duration and exposure intensity. It is possible that a cumulative index will more likely be associated with the development of symptomatic manganism (Chandra *et al.* 1981; Roels *et al.* 1987a and b, 1992; Lauwerys *et al*. 1987; Iregren 1990, 1992,1996; Feldman 1992; Chia *et al.* 1993a and b; Mergler *et al.* 1994; Lucchini *et al.* 1995, 1997, 1999; Sjögren *et al.* 1996; Gibbs *et al.* 1999; ATSDR 2000; Ostiguy *et al*. 2003). It is important to note that symptoms and signs can persist or progress long after exposure to Mn has stopped (Huang *et al*. 1989; Pal *et al*. 1999; Roels *et al*. 1999).

Historical as well as current exposure data coming from different sources will be used, such as[3]:

- Work history records indicating Mn exposure or work assignments known to be associated with Mn exposure; reports, past or present, from occupational hygiene investigations (whenever these exist).
- Biological measurements (Huang *et al*. 1989), such as blood or urine Mn, only reflect recent exposure and, on an individual basis, are poorly correlated to current Mn exposure (Chandra *et al*. 1981; Roels *et al*. 1987; Jarvisalo *et al*. 1992; Bader *et al*. 1999; Apostoli *et al*. 2000; Ellingsen *et al.* 2003). They also poorly reflect the body burden of Mn, although blood Mn can be associated with cumulative exposure a few days after cessation of exposure (Lucchini *et al*. 1995). Adverse health effects due to previous higher exposure can be present in the absence of positive biological measurements when the patient is diagnosed (Roels *et al*. 1987; Huang *et al*. 1998). Biological measurements are not correlated to the ulterior development of clinical manganism (Jimenez-Jimenez *et al*. 1995).
- The $CaNa_2EDTA$ (ethylenediaminetetraacetic acid calcium and sodium salts) mobilization test could be used to document a high body burden of Mn (Feldman 1992; Discalzi *et al.* 2000);

[3] Evidence from one of these is usually sufficient to establish excessive exposure.

however, since reference values are not established, it is still considered an experimental procedure.

- MRI may also provide a measure of manganese exposure within no more than 4-6 months of exposure to Mn, with a high signal in the globus pallidus and striatum on the T1-weighted image. Note that MRI signal can be seen in patients who are clinically intact. This aspect will be discussed in detail on page 15.

Biomarkers of exposure should be assessed in a timeframe that reflects the half-life of Mn in the body: negative results when these tests are performed more than 4 to 6 months after cessation of exposure are not conclusive of non-exposure. The half-life of Mn is about 10-42 days in blood and more than 200 days in the brain (Mena *et al*. 1967; Newland *et al*. 1987).

- *Clinical data*

To illustrate the historical difficulty inherent in making the right diagnosis, it has been shown that, within a typical movement disorder clinic, only about 75 per cent of patients with a parkinsonian syndrome and who were diagnosed as having PD turn out to have pathological changes of PD at post mortem (Duffau *et al.* 2002). Other forms of parkinsonism that could be mistaken for PD include Multi-System Atrophy (MSA) and Progressive Supranuclear Palsy (PSP). The latter two syndromes are more similar, clinically, to manganism than is Parkinson's disease: the pathologies of PSP and MSA manifest in the basal ganglia, and are only minimally responsive to L-dopa. Very little is known about the etiology of PSA and MSA. An analysis indicated that the features that most accurately predict PD pathology with damage to the substantia nigra pars reticulata are: a) resting tremor, b) asymmetry of motor features, and c) poor or unsustained response to levodopa. Using these criteria, a correct diagnosis of PD with damage to the substantia nigra pars reticulata was established at post mortem in 98.6% of cases (Ward and Gibb 1990; Hughes *et al.* 1992, 2002). This illustrates that these features can help to differentiate Parkinson patients with PD from patients with parkinsonism due to other causes.

From the comparison they have made between IPD and manganism, Calne *et al.* (1994) and Olanow (2004) drew the following conclusions:

1. There are similarities between PD and manganism, notably the presence of (a) generalized bradykinesia and (b) widespread rigidity.
2. There are also dissimilarities between PD and manganism. In PD, patients are more likely to have parkinsonism with resting tremor, asymmetry, and a good response to levodopa. Patients with manganism are more likely to have: (a) less frequent and atypical tremor, (b) more frequent dystonia (especially grimacing and cock walk), (c) a particular propensity to fall backward early on, (d) failure to achieve a good or sustained therapeutic response to levodopa, and (e) absence of reduced striatal fluorodopa uptake as assessed by PET.

At an early stage, psychiatric symptoms could dominate the clinical picture of manganism (Calne *et al*. 1994; Olanow, 2004) but the precise symptoms and clinical signs of neuropsychological disturbances remain to be documented (Dietz *et al*. 2001).

These early disturbances reported for Mn overexposure are mainly motor, but other deficits related to basal ganglia alterations such as deficits in attention, memory and implicit learning can lead to reduced motor learning, coordination, and sequencing (Bowler *et al*. 1999; Bowler *et al*. 2003). Some functional neuropsychological tests, related more specifically to deterioration of the rapidity of neurosensorial response, motor function and memory, were reported to be more likely altered

early in Mn chronic exposure (Johnson *et al.* 2004). These tests are hand-eye coordination, hand steadiness and simple visual reaction time (Wennberg *et al.* 1991; Iregren 1992; Lucchini *et al.* 1995, 1999; Mergler and Baldwin 1997; Iregren 1999; Roels *et al.* 1999). Nonetheless, the scope and extent of the neuropsychological alterations will extend as the severity of the CNS alteration increases. However, careful neuropsychological examination using a standardized battery of tests will help identify these alterations more precisely (Mergler *et al.* 1994; Despres *et al.* 2000). Such batteries of tests are listed in Appendices A, B and C. These alterations, although very sensitive and usually dependent on the degree of exposure, are nonspecific to manganism (Beuter *et al.* 1994; Edwards and Beuter 1997; Pal, *et al.* 2001).

Neurological examination will identify parkinsonism and dystonia, and help to differentiate PD and manganism. Both can have parkinsonian features including bradykinesia, rigidity, masked facies, speech disturbance, micrographia and gait disturbance. The presence of resting tremor, asymmetry, and a good response to levodopa support a diagnosis of PD. In contrast, manganism is supported by early onset of gait dysfunction with a propensity to fall backward (Huang *et al.* 1989; Olanow 2004). Tremor, when present, tends to be postural or kinetic rather than resting, as seen in IPD[4] (Huang *et al.* 1989; Calne *et al.* 1994). Patients with manganese-induced parkinsonism also frequently experience characteristic forms of dystonia consisting of facial grimacing and/or plantar flexion of the foot, which interferes with gait and is known as "cock-walk" (Huang *et al.* 1989, 1993, 1997, 1998; Rodier, 1955; Schuler *et al.* 1957; Mena *et al.* 1967; Tanaka and Lieben 1969; Smyth *et al.* 1973, Yamada *et al.* 1986; Wennberg *et al.* 1991; Ky *et al.* 1992; Calne *et al.* 1994; Chu *et al.* 1995; Hochberg *et al.* 1996; Mergler and Baldwin 1997; Pal *et al.* 1999).

A compatible clinical picture must be present in the context of excessive exposure in order to have a possible case of manganism. The experts suggested that the most sensitive endpoint is neurological/ neuropsychological. The neuropsychological points of interest have already been described. A complete neurological examination by a neurologist specialized in movement disorders should confirm signs of parkinsonism (extrapyramidal manifestations) such as gait and speech disturbances, postural instability, bradykinesia, rigidity, micrographia and masked facies, which are consistent with classical manganism. Tremor, more rarely present than in IPD, tends to be postural rather than resting.

These examinations, coupled with a complete occupational history, should lead to a provisional diagnosis. Neuro-imaging should take the diagnosis to the next level.

Given the progressive nature of manganism, it is important to emphasize that, as stated in the introduction to this section, individuals should be followed and clinical data gathered dynamically and re-evaluated periodically. In doing so, the clinician will increase his confidence that a given case is indeed a case of manganism: from a single mild isolated neurological dysfunction accompanied by documented slight neuropsychological dysfunction that could be labeled as a possible case, towards a probable case where two or three of the neurological symptoms described earlier are better defined while neuropsychological tests showing abnormalities are starting to group, culminating in a typical neurological (extrapyramidal manifestations and dystonia) and neuropsychological picture from which a case can be labeled as clinically probable with confidence (Fiedler 1996; Mergler *et al.* 1999; Lucchini *et al.* 2000). As information is gathered, the physician may choose to reclassify the patient based on the new information.

[4] Note that the classical clinical picture of IPD, showing much more frequent asymmetric alterations and tremor, is of resting nature.

- *Pharmacological response*

A challenge or therapeutic trial with levodopa is very useful in distinguishing IPD from other forms of parkinsonism. IPD typically responds well to L-dopa therapy and patients have a sustained benefit. In addition, chronic treatment is frequently associated with the development of motor complications (dyskinesia, motor fluctuations). However, movement disorders from manganism will show poor or unsustained improvement with a therapeutic trial of L-dopa (Lu *et al*. 1994) and levodopa-induced motor complications have not been described. This is because chronic manganese intoxication spares the nigrostriatal system and is thought to cause parkinsonism by damaging output pathways that are downstream from the nigrostriatal dopaminergic pathway (Shinotoh *et al.* 1995). This absence of pharmacological response is one of the most widely cited key features in distinguishing manganism and other parkinsonism sharing the same physiologico-pathological mechanism as IPD (Huang *et al.* 1993; Calne *et al.* 1994) even if it is based on a limited number of reported cases in the literature. A similarly poor response to levodopa is seen in other parkinsonian disorders such as MSA and PSP.

- *Imaging data*

Positive MRI (bilateral, symmetrical, high signal T-1 weighted images in the globus pallidus and to some extent in the substantia nigra pars reticulata) in an asymptomatic individual is indicative of Mn accumulation at its target organ (Newland *et al*. 1989; Nelson *et al*. 1993; Dietz *et al*. 2001). According to Hulka and Wilcosky (1988, 1990), this finding constitutes a biological marker of the effective dose in the Hulka's classification. It does not, however, necessarily correlate with the development of manganism. Positive MRI in a symptomatic individual could be considered a manifestation of degeneration of the striatal / pallidal system (Hauser *et al*. 1994; Layrargues 1995). However, given the half-life of Mn in the brain, a negative result when the exam is performed more than 4-6 months after cessation of exposure is not conclusive (Kim *et al.* 1999).

This test may be helpful in differentiating manganism from IPD and possibly other forms of parkinsonism (Shinotoh and Calne 1995). In IPD patients, the striatum and pallidum appear normal on T-1 weighted images (Calne *et al*. 1994). However, with gray and white matter signal-suppression inversion recovery sequences, signals from the substantia nigra pars compacta are abnormal in the majority of IPD patients (Hu *et al*. 2001). The same author also concluded that this test was less reliable than fluorodopa positron emission tomography (F-dopa PET) scan in discriminating patients with moderately severe PD from normal subjects.

T1-weighted signal hyperintensities can be associated with lipid, hemoglobin breakdown products, melanoma, neurofibromatosis, and calcification (Kim 2004), but they can usually be differentiated from manganese by the pattern of involvement and imaging with CT Scan and T2-weighted MRI.

Striatal fluorodopa uptake on the fluorodopa positron emission tomography (F-dopa PET) scan, a measure of the functional integrity of the nigrostriatal system, is consistently reduced in IPD (Martin *et al.* 1989; Pal *et al.* 2001), especially in the posterior putamen (Caparros-Lefebvre *et al.* 1998). The same test was normal in one series (4 cases) of highly probable cases of occupational manganism and in animals with experimentally induced manganese toxicity (Wolters *et al*. 1989; Kim *et al.* 1998, 1999). These findings have been confirmed in other cases with pictures strongly suggesting manganism (Kim *et al.* 1999; Abe *et al.* 1999). The F-dopa PET scan is thus regarded as one of the most promising tools for excluding the diagnosis of IPD (Calne *et al.* 1997; Abe *et al.* 1999; Kim *et al.* 1999; Piccini and Whone 2004). The nigrostriatal system is affected in most other forms of primary degenerative parkinsonism (MSA, PSP) and hence F-dopa PET is abnormal, differentiating these conditions from manganism (in addition to differences in clinical features etc).

Thus, a clinical picture of parkinsonism with no response to levodopa and a normal F- dopa PET scan strongly supports a diagnosis of manganese induced parkinsonism. Nevertheless, its specificity has yet to be confirmed in discriminating manganism from other causes of parkinsonism. In fact, it cannot be excluded that in more severe cases of manganism, the damage extends from the pallidum to the nigrostriatal system, causing abnormal F-Dopa uptake (Racette *et al*. 2005). This means that an abnormal F-Dopa PET scan would not exclude manganism. However, if all other forms of parkinsonism have been excluded by other means, a normal F-Dopa PET scan can support a definite case of manganism. PET requires substantially more validation before it can be widely recognized as useful in the differential diagnosis of manganism. F-Dopa PET scan does not have a strong linkage to the clinical outcome of manganism and Ravina *et al*. (2005) do not support the use of radiotracer imaging in such conditions.

- *Histopathological data*

Degeneration of dopaminergic neurons in the nigrostriatal pathway coupled with intracytoplasmic Lewy bodies and a loss of striatal dopamine are the pathological hallmarks of IPD (Calne *et al*. 1994). IPD is also associated with degeneration and Lewy bodies in other regions, including the locus coeruleus, the nucleus basalis of Meynert, the hypothalamus, the dorsal motor nucleus of the glossopharyngeal and vagal nerves, as well as selected neurons of the cerebral cortex, spinal cord, and peripheral components of the autonomic nervous system (Olanow and Tatton 1999).

The extranigral pathology in IPD may also be quite extensive, involving the dorsal motor nucleus of the glossopharyngeal and vagal nerves, subnuclei of the reticular formation and the raphe system, the coeruleus and subcoeruleus complex, the magnocellular nuclei of the basal forebrain, and many subnuclei of the thalamus and amygdala (Braak *et al*. 2003).

In manganism, degenerative lesions were demonstrated in the globus pallidus and subthalamic nucleus, red nuclei thalami, caudate nucleus and the putamen, with less frequent and less severe injury to the substantia nigra pars reticulata. There are no Lewy bodies. Chronic exposure to excessive Mn leads to neuronal loss and gliosis in these basal ganglia structures together with characteristic astrocytic changes known as Alzheimer type II astrocytosis (McKinney *et al.* 2004; Normandin *et al.* 2002; Olanow 2004; Mergler *et al.* 1996).

Histopathological studies in manganese-intoxicated animals reveal damage primarily in the globus pallidus, mainly gliosis and Alzheimer type II astrocytosis, with sparing of the substantia nigra pars compacta and striatal dopamine levels (Olanow *et al.* 1996). Glial cells are known to sequester Mn^{2+} by a high affinity transport mechanism (Aschner *et al*. 1999) and are considered to be the likely initial targets of manganese neurotoxicity (Spanger *et al*. 1998; Henriksson *et al*. 2000).

These pathological findings form the basis for differentiating PD and manganism, for understanding the clinical, pharmacological and imaging findings, and are useful in confirming the diagnosis at post mortem.

- *Differential diagnosis*

Manganism must also be differentiated from other forms of parkinsonism as well as PD.

In a possible case of occupational manganism, the clinician should gather clinical and para-clinical information that can exclude all of the other disorders in the differential diagnosis of parkinsonism

before any conclusion of probable or definite manganism is made. Of particular interest will be other causes of occupational parkinsonism (Tanner 1992). While many classifications and lists of those diseases exist, a classification published recently by Hobson is presented in Appendix D (Hobson 2003). For example, impaired vertical eye movements suggest progressive supranuclear palsy (PSP), impaired autonomic function suggests multiple system atrophy (MSA), impaired cerebellar function suggests olivopontocerebellar atrophy (OPCA), focal hand dystonia and cortical myoclonus or apraxia suggesting cortical basal ganglionic degeneration (CBGD). It is beyond the scope of this report to give details on the different criteria for the clinical diagnosis of each of these diseases; the reader can refer to the original article for further information. Many articles were devoted to the differential diagnosis of parkinsonism (Feldman 1992; Tanner and Aston 2000; Facca and Koller 2003; Hobson, 2003; Litvan *et al.* 2003; Mitra *et al*. 2003).

MANDATE 4

Propose the ideal avenue for establishing or invalidating the diagnosis of occupational manganism, taking into account the human and technological resources available in Québec[5]

In this section, the objective is to specify which exam or test will be most useful for correctly diagnosing a case of manganism and to specify in which sequence intervene.

Recommendations

In order to diagnose a case of occupational manganism, the following avenue is proposed:

Step 1.

For a worker suspected of having occupational manganism, the occupational physician should perform a thorough evaluation of Mn occupational exposure along with an evaluation of the presenting clinical picture.

A) He should first perform a thorough clinical case history that includes:

- The history of current clinical symptomatology
- The history of past clinical problems
- The family history

B) He then performs a complete physical examination with an emphasis on the neurological examination to identify clinical signs of parkinsonism.

C) The physician should detail occupational exposure to any neurotoxic contaminants. Starting with an occupational history, he will search work records indicating Mn exposure and specific work assignments known to be associated with Mn exposure. He will also gather data, past or present, from occupational hygiene investigations (whenever these exist).

D) If the occupational physician deems it appropriate, he could gather basic neuropsychological data using a standardized questionnaire and/or a short battery of tests.

E) Complementary investigations: liver testing and complete blood count (CBC), iron stores[6]. Depending on the temporal relationship between the time of the Mn exposure and the examination, blood and urine Mn levels and an MRI could be ordered as well as other pertinent tests (e.g., blood copper, ceruloplasmin, neuroacanthocytes, etc.), depending on the clinical history.

After this initial data collection, the occupational physician could then refer the worker to a neurologist specialized in movement disorders if further exploration is deemed to be appropriate.

[5] The following recommendation also takes into account Québec's specific occupational medicine structure and accessibility to different resources

[6] Depending on the results of the CBC.

Step 2.

A neurologist knowledgeable in movement disorders should assess the patient to determine if the clinical picture is consistent with a diagnosis of manganism. Tests and procedures required to determine the correct diagnosis should be ordered as appropriate.

Step 3.

Complementary investigations could include:

- Formal neuropsychological evaluation
- MRI, if not already done and appropriate time-wise since cessation of exposure to Mn
- L-dopa trial
- Fluorodopa PET scan or other imaging study to assess the integrity of the nigrostriatal system.

Based on these assessments, the neurologist will determine if in his opinion a given case suffers from clinically possible, probable or definite manganism. The diagnosis may be modified based on subsequent examinations and the acquisition of further information.

Consensus status

These recommendations were agreed upon by consensus.

Rationale

Step 1

In Québec, an occupational physician is responsible for a given workplace. He is in charge of the development and execution of a specific health program for each given workplace. As such, his knowledge of the settings makes him ideally suited to do the initial investigation of workers suspected of manganese intoxication (Levy and Nassetta 2003).

Workers showing suspect symptoms of manganese intoxication should be investigated initially for both the magnitude of exposure and clinical status.

It is possible that cumulative lifetime exposure to Mn contributes to the likelihood that the patient will develop manganism. Two situations should be considered: a short-term high intensity exposure or long-term chronic overexposure to lower levels of Mn. It is thought by some that overexposure is more likely to occur after long-term chronic exposure; therefore, information on all aspects of exposure must be collected. An accurate job description is also important since exposure levels can be very different depending on the different tasks a worker performs. In the case of a welder, information on welding rods and the materials used is important, particularly regarding manganese content. Information on ventilation and personal protective devices must also be collected. Other possible neurotoxic exposures should be documented as they might also induce parkinsonism or chronic toxic encephalopathy (Wennberg 1994). A list of neurotoxic substances is presented in Mandate 6. Quantitative data on manganese exposure in the occupational environment determined by industrial hygiene investigation and surveillance is of utmost importance when available. If not, qualitative data may be helpful and yield significant information. Unfortunately, past exposure data are often unavailable.

Blood and urine Mn sampling has been used to reflect recent exposure. Although more usable as a group value than as an individual value, it can nonetheless prove informative if consistent with environmental data (Luse *et al*. 2000).

One way to assess the accumulation (via overexposure or decreased clearance) of manganese in the basal ganglia is by a brain T-1 weighted MRI. It would show bilateral, usually symmetrical hyperintensities in the globus pallidus if done during exposure or within 4-6 months after cessation of overexposure. This result is to be considered as a biological biomarker for Mn accumulation in the basal ganglia but not necessarily intoxication.

An additional way to try and assess manganese body burden is by the chelation test, which is a way of assessing the overall amount of manganese in the body. This test has to be considered investigational until clear normal values are established.

Regarding clinical aspects, neurological and psychiatric signs and symptoms of manganism should be evaluated, including extrapyramidal disturbances, dystonia, tremor and aggressive components of mood. Particular attention also has to be paid to the worker's personal and familial clinical history. A list of personal and family diseases likely to cause or be associated with parkinsonism is presented in the differential diagnosis section above. Other pertinent questioning and testing by the occupational physician can be based on including conditions in, or eliminating them from this list in the differential diagnosis of parkinsonism. If the physician finds a case with possible parkinsonism, he should consult the list of parkinsonian syndromes and ask pertinent supplementary questions and/or perform appropriate tests to try and determine whether the patient suffers from one of these

conditions rather than manganism. Some of these conditions can be screened out almost immediately by a good medical questionnaire for medication, drug use or abuse, age of the patient, history of occupational exposure and findings on examination. Others can be screened with blood tests or genetic testing. Most importantly, if a patient is thought to have parkinsonism, the patient should be referred to a neurologist with expertise in movement disorders.

Some functional neuropsychological tests (finger tapping, Luria-Nebraska motor tasks, symbol digit and digit span), related more specifically to impairment of neurosensorial response, motor function and memory, show abnormal results early in patients with Mn chronic exposure. These tests detect abnormal hand-eye coordination, hand steadiness and simple visual reaction time (Iregren 1992, 1999; Lucchini *et al.* 1995, 1999; Mergler *et al.* 1997; Roels *et al.* 1987, 1992, 1999). The occupational physician might decide to administer the neuropsychological tests proposed in Appendix A.

Steps 2 and 3

As noted by the experts, a diagnosis of manganism is mainly a diagnosis of exclusion in a patient with parkinsonism and a history of exposure. This means that this diagnosis is accepted when other diseases that would produce a similar clinical picture are excluded. The neurologist will have to take steps to exclude these other diseases from his differential diagnosis list.

Since IPD is present in about 3% of the population, diseases with parkinsonian symptoms and signs, including manganism, must first be differentiated from idiopathic PD (Shinotoh and Calne 1995). Manganism may be difficult to differentiate from IPD in the early stages, but with time it is usually possible to separate these conditions based on the clinical picture, response to levodopa, development of motor complications, and imaging studies (Olanow 2004; Poewe and Wenning 2002; Wolters *et al.* 2000; Pal *et al.* 2002). As PD is a relatively common disorder and many individuals have welded, it is possible that PD may develop in a person who has a history of manganese exposure. It is also possible that IPD and manganism may coexist in the same individual (Racette *et al.* 2001). Some criteria pertinent to other parkinsonian disorders such as impaired vertical eye movements, orthostatic hypotension, cerebellar signs, cortical apraxias and myoclonus may help to establish the correct diagnosis (Hobson 2003; Litvan *et al.* 2003).

Further data to help in establishing a diagnosis can be obtained by using a more formal neuropsychological battery of tests than the one suggested at the beginning of this section (See Appendices B and C).

As stated earlier, a therapeutic trial with levodopa is very useful in distinguishing IPD from manganism and other forms of parkinsonism. In manganism, a patient will show a poor or an unsustained response after levodopa treatment. It is important to note that, in order to correctly assess an improvement in clinical symptoms, these have to be easily assessed; consequently, this trial is of most value in the presence of clearly defined parkinsonian features. Also, it is important to ensure that an adequate trial of levodopa (time and dosage) has been employed.

Striatal fluorodopa uptake on PET, a measure of the functional integrity of the nigrostriatal system, is consistently reduced in PD, especially in the posterior putamen, but exams were normal in a series of 4 patients with highly probable occupational manganism (Wolters *et al.* 1989). Similar normal F-Dopa PET results have been reported in other patients with manganese induced parkinsonism (Abe *et al.* 1999; Kim.*et al.* 1999). In addition, F-Dopa PET studies were normal in primates rendered parkinsonian by manganese intoxication. Further, post mortem studies in patients and animals demonstrate preservation of the nigrostriatal system following manganese intoxication (Yamada *et*

al. 1986; Olanow *et al.* 1999). The F-dopa PET scan is thus regarded as one of the most promising tool for excluding IPD and other causes of parkinsonism but its specificity has yet to be confirmed in larger cohorts. It could thus become the "de-facto" gold standard for establishing definite manganism when all other causes of parkinsonism have been excluded by other available tests.

As already discussed (p. 15-16), the specificity of the PET scan imaging has yet to be confirmed in its capacity to discriminate manganism from other forms of parkinsonism. In fact, it cannot be excluded that in more severe cases of manganism, the damage extends from the pallidum to the nigrostriatal system, causing abnormal F-Dopa uptake (Racette *et al.* 2005). This means that an abnormal F-Dopa PET scan would not exclude manganism. However, if all other forms of parkinsonism have been excluded by other means, a normal F-Dopa PET scan would confirm a definite case of manganism. PET requires substantially more validation before it can be widely recognized as useful in the differential diagnosis of manganism. F-Dopa PET scan does not have a strong linkage to the clinical outcome of manganism and Ravina *et al.* (2005) do not support the use of radiotracer imaging in such conditions.

In fact, since manganese-induced high signals usually disappear within one year following cessation of exposure, the F-Dopa PET scan or dopamine transporter signal-photon emission computed tomography [^{123}I] β-CIT SPECT should be obtained in order to discriminate between IPD and manganism, especially if the worker presents signs of parkinsonism or neuropsychological disturbances more specific to basal ganglia origin, in the context of a normal T1-weighted MRI and more than six months after withdrawal from the source of Mn accumulation in the brain.

Toxic substances that affect the basal ganglia and spare the nigrostriatal system are known: they are carbon monoxide (CO) intoxication (mostly acute, affects the putamen); cyanide (CN) intoxication (mostly acute, mostly the putamen and globus pallidus and sparing the substantia nigra); long-term exposure to carbon disulfide (CS_2) may produce a form very similar to manganism or MSA but, most of the time, would cause pyramidal signs, cerebellar ataxia as well as axonal polyneuropathy; the brain MRI would show hyperintensity lesions in T1-weighted images in the subcortical white matter, basal ganglia and brain stem through microangiopathy (Ku *et al.* 2003). Finally, there is neuro-intoxication with MPTP. This drug specifically affects the dopamine neurons and has clinical pharmacologic and imaging features different from manganese intoxication. All of these causes of toxic parkinsonism are extremely rare.

MANDATE 5

Propose a medical follow-up and treatment plan for workers with occupational manganism

Recommendations

The experts agreed that there was no specific treatment plan for manganism. Antiparkinsonian drugs may have a positive effect on parkinsonian symptoms and signs, but this effect is temporary and of short duration if present at all. Antioxidants have been recently studied but benefits have not been proven. Chelation is still considered investigational. Symptom relief and rehabilitation therapies are all that remain.

The main intervention consists of stopping significant exposure to manganese as well as other recognized neurotoxic agents as soon as possible, when the symptoms and signs may still be reversible.

The experts also agreed on medical monitoring plan in the first year and later as appropriate. If a change is seen in the worker's condition, then the diagnosis can be reviewed as in Mandate 4.

Consensus status

These recommendations were agreed upon by consensus.

Rationale

- *Treatment*

As already mentioned, "Manganese neuro-intoxication is classically associated with Mn accumulation in, and damage to, the globus pallidus, striatum and substantia nigra pars reticularis with relative sparing of the nigrostriatal system" (Olanow 2004; Yamada *et al*. 1986).

Neuropsychological disturbances related to basal ganglia origin are mainly motor and characterized by deficits in attention allocation and filtering, implicit learning and memory, leading usually to acquisition of behaviours and efficiency in working memory by motor learning, sequencing and movements (Ring *et al*. 2002).

At an early stage, neuropsychiatric disturbances could be the presenting picture.

Even though it is known that manganese is a cellular intoxicant that may damage nerve impulse transport systems, enzymatic activities and receptor functions, the exact way that manganese neurotoxicity occurs has not yet been clearly established (Aschner and Aschner 1991). It cannot be concluded that one simple dysfunction is the basic mechanism of manganese neurotoxicity. It appears more probable that the basic mechanism is multifactorial, involving oxidative stress induced by iron and the direct interaction of manganese with the mitochondria in the terminal part of the dopaminergic neurons, leading to selective mitochondrial dysfunction and resultant excito-toxicity (Verity 1999). Mn exposure leads to accumulation of Mn in the pallidum and striatum, and this is likely why these areas are most prominently affected in manganism. In manganism, extrapyramidal parkinsonian signs may appear with rigidity, slowness, gait disturbance, and micrographia. They are similar to, but not identical to IPD.

Based on the hypothesis that free radicals, oxidative stress, and mitochondrial dysfunction contribute to Mn-induced cell damage, antioxidant agents (Fendyur *et al*. 2004) and co-enzyme Q10 have been considered as potentially providing benefit for patients with manganism (Horvath *et al*. 2003; Andersen *et al*. 2001; Ravina *et al*. 2003; Shults *et al*. 2002).

Anti-parkinsonian drugs have been tested in patients with manganism symptoms but are usually ineffective. Any positive effects are generally limited and of short duration. Some authors have attributed these temporary benefits to the placebo effect (Lu *et al*. 1994). Positron emission tomography studies have recently shown that the placebo effect is related to the activation of the limbic circuitry by different neurotransmitters and neuropeptides, perhaps disease-specific, involved in modulating the activity of the limbic system (De La Fuente-Fernandez *et al*. 2004).

Chelation therapy, mainly using $CaNa_2EDTA$, has been used with reports of variable success in acute and chronic cases of manganese intoxication (Discalzi *et al*. 2000; Hernandez *et al*. 2002; Komaki *et al*. 1999; Fitzgerald *et al*. 1999). There are some reports of improvement with chelating treatment and cessation of exposure but, there have been no controlled trials and the treatment is still controversial. Further, it can be complicated by kidney damage. For now, chelation therapy is still considered investigational.

The main treatment therefore consists of stopping exposure in the early phase of the illness, when the signs and symptoms first appear and may be reversible. This requires detection for the early signs; these are detected as early neurofunctional changes, mainly motor.

Workers should also be prevented from harmful occupational exposure to other recognized neurotoxic agents like organic solvents, carbon disulfide, carbon monoxide, cyanide, mercury, lead, etc. (see Mandate 6 for a more complete listing).

Supportive treatment is recommended for any associated sleep problems, mood disturbances, loss of libido, etc. Psychological, cognitive behavioural, physical, speech and occupational rehabilitation therapies should be offered as appropriate.

Treatment outcomes can be measured by subjective rating of therapy satisfaction and also by the usual psychosocial or psychometric tests; some scales can also be useful: "Activities of Daily Living" (ADL) and the motor components of UPDRS for assessment of neurofunctional motor disturbances. However, none of these tests has been validated in manganism.

Since liver diseases, anemia, and alcoholism can affect manganese accumulation in the brain, these conditions should be looked for and treated.

Surgical interventions used in IPD have not been shown to be of value in manganism.

- *Medical monitoring*

Special attention should be given to follow-up of the evaluation of the worker during the first year following the diagnosis. Clinical features of manganism may worsen or improve following withdrawal from the source of exposure. For this reason, the assessment of permanent deficit should be deferred for at least a year.

The physician in charge can do this monitoring, with referral to specialists if there are signs of significant deterioration or change in the progression of the disease.

After the first year, the following examinations should be performed annually:

- Neurological assessment
- Neuropsychological assessment. These tests should not be used too frequently, as learning effect may confound the interpretation. One could use alternate forms
- Functional capacities assessment
- Biological testing: CBC, Blood Mn, iron stores, liver functions

Again, if any negative change occurs in the worker's condition, a multidisciplinary decision as to the treatment, the anatomo-physiological permanent deficit impairment and rehabilitation should be taken.

Although work-related neurotoxic risks today rarely reach the level of the pathologies of previous decades, exposure to manganese may still cause changes in certain higher brain functions. The corollary is that a series of tests should be assembled that defines the cerebral functions that are affected as a consequence of chronic exposure to manganese.

MANDATE 6

Propose safe conditions for keeping workers with manganism at work or for returning them to work

Recommendations

A worker considered as a definite, probable or possible case of occupational manganism and who has the physical capacity to work should be kept from any further significant exposure to manganese in the workplace. Furthermore, he should not be returned to a workplace significantly contaminated with any other recognized neurotoxic agent. The level of Mn exposure should be as low as possible but never exceed 0.03 mg Mn/m^3 (expressed as respirable dust).

Consensus status

These recommendations were agreed upon by consensus.

Rationale

As already discussed in this report, chronic Mn exposure may lead to serious damage of the central nervous system, called manganism. Manganism is a progressive and debilitating syndrome that typically begins with relatively mild nonspecific symptoms that gradually develop. It has been suggested that the health effects, particularly on the central nervous system, occur in a "continuum of dysfunction" which could be dose-related (Mergler *et al*. 1999; ATSDR 2000; ACGIH 2001). Mergler *et al*. (1999) have described neurofunctional alterations attributed to manganese in workers who were otherwise asymptomatic and neurologically intact. There is a concern that these workers are at increased risk of developing manganism whose progression depends on the exposure level, the exposure duration and individual susceptibility.

Furthermore, epidemiological studies suggest that lifetime cumulative exposure is the best indicator, allowing correlation of occupational exposure with the early effects observed on the CNS (Chandra *et al.* 1981; Roels *et al.* 1987a and b, 1992; Iregren 1990, 1992; Chia *et al.* 1993a and b; Mergler *et al.* 1994; Lucchini *et al.* 1995, 1999; Sjögren *et al.* 1996; Gibbs *et al.* 1999; ATSDR 2000; Ostiguy *et al.* 2003). For this reason, it is suggested that a worker who has shown CNS effects be given a work assignment removed from further significant Mn exposures.

Few scientific data are available on the reversibility of the neurotoxic effects associated with chronic Mn overexposure. The researchers believe that the effects are rather irreversible (Ellenhorn and Barceloux 1988). However, there is some evidence that recovery may occur when the exposure stops (Smyth *et al*. 1973). Antiparkinson drugs such as levodopa may be able to reverse some of the neuromuscular signs of manganism (Ejima *et al.* 1992; Rosenstock *et al*. 1971), but these drugs have several side effects, and reports indicate that they do not improve the patients' neurotoxic symptoms (Calne *et al*. 1994; Chu *et al*. 1995; Cook *et al*. 1974; Ellenhorn and Barceloux 1988; Haddad and Winchester 1990; Huang *et al*. 1989). The ATSDR review (2000) reports that symptoms of manganism can be improved by certain medical treatments, but the improvement is generally temporary and damage to the brain permanent.

Huang et *al.* (1993, 1998) documented the progression of manganism in five workers chronically exposed to Mn in the ferroalloy sector. Their results show that the disease continues to progress even 10 years after leaving the workplace. Roels *et al*. (1999) carried out an eight-year longitudinal study on the same cohort as that published in 1992 in order to determine the reversibility of three early neurotoxic effects: hand-eye coordination (HEC), hand steadiness (HS), and simple visual reaction time (SVRT). They concluded that the tests used were reproducible and reliable throughout the study. They also demonstrated that past severity of Mn exposure determined the relative significance of the loss in precision in hand and forearm movement (HEC) in exposed workers as compared to the control group as well as their recovery potential. However, for the two other tests, HS and SVRT, no recovery was noted, suggesting that these conditions are irreversible.

However, when neurological damage is measured, it could be reversible but could also worsen over time, even in the absence of occupational exposure. As a result, it is important to intervene as rapidly as possible, in a phase that is possibly still reversible. Then, any significant additional exposure to manganese or to any other neurotoxic agent could contribute to the acceleration in the progression of the disease.

At the present time, a dose-response relationship cannot be established from all the epidemiological studies available, but early signs of central nervous system injury by inhalation have been observed at levels from 0.027 to 1.0 mg Mn/m^3 in total dusts (Chia *et al*. 1993a, 1993b, 1995; Iregren 1990; Lucchini *et al.* 1995; Mergler *et al*. 1994; Roels *et al.* 1987a, 1992; Wennberg *et al*. 1991), while

cases of manganism have been reported at levels as low as 2 to 22 mg/m^3 in total dusts (Cook *et al.* 1974; Rodier 1955; Saric *et al.* 1977; Schuler *et al.* 1957; Tanaka and Lieben 1969; Whitlock *et al.* 1966). These neurotoxic effects were observed following exposures varying from 1 to 35 years (Schuler *et al.* 1957; Whitlock *et al.* 1966; Tanaka and Lieben 1969; Cook *et al.* 1974; Saric *et al.* 1977; Roels *et al.* 1987a, 1992; Iregren 1990; Wennberg *et al.* 1991; Chia *et al.* 1993a, 1993b, 1995; Mergler *et al.* 1994; Lucchini *et al.* 1995). In the case of manganese, Roels' studies, which were corroborated by several other studies, are the ones most commonly used, and the majority of the organizations use these results as a basis for proposing limit values based on their respective approaches.

Because of the continuous progression of the disease in most cases, a diagnosed worker, even at the possible stage, should be kept away from any significant additional exposure. In 2003, the IRSST and CSST established an interim level of 0.00015 mg/m^3 in total dusts, for clinically probable and definite cases of manganese-induced parkinsonism, which is the WHO recommended level for the general population including newborns and elderly people. This interim level was established while waiting for the expert panel to recommend a more applicable but still safe level of exposure.

In 2000, the American Agency for Toxic Substances and Disease Registry (ATSDR) established a concentration at which no effect (NOAEL) should occur on the CNS or pulmonary system of healthy workers. This level is 0.07 mg Mn/m^3 in respirable dust and represents an average exposure level for a healthy worker.

Based on the level of scientific knowledge and for practical reasons, the experts agreed on the following recommendations for keeping workers with manganism at work or for returning them to work when medical conditions permit: the occupational exposure to manganese should be kept as low as possible and should be accompanied by a ceiling value, a value never to be exceeded of 0.03 mg/m^3, measured in respirable dusts. This value is based on the ATSDR established NOAEL. The ATSDR value of 0.07 is divided by 2 and, rather than being an average value for the work shift, it is converted to a ceiling value. Since the ATSDR level has been established for healthy workers, the experts concluded that half this value, 0.03 mg/m^3, evaluated in respirable dusts and never to be exceeded should not be detrimental to the health of the confirmed (definite and probable) or suspected (possible) diseased worker and should be applied to all those cases where medical diagnosis is such that the worker is judged capable of returning to or staying at work.

The experts also concluded that workers who show some effects of manganism should not be exposed to other neurotoxic agents in the workplace. Human neurotoxicity has already been documented for many chemicals (Costa and Manzo 1998). These substances include metals, solvents, pesticides, gases, and other miscellaneous substances. The metals most frequently associated with neurotoxicity are aluminum, arsenic, lead, manganese, mercury, thallium, trimethyl tin and welding fumes. Many solvents have shown different effects on the central nervous system: carbon disulfide, n-hexane, methanol, methyl n-butyl ketone, perchloroethylene, styrene, toluene, trichloroethylene, 1,1,1-trichloroethane, etc., as did many pesticides including carbamates, chlordecone, chlorophenoxy compounds, cyclodienes including chlordane and aldrin, dithiocarbamates and organophosphates.

Many gases such as carbon monoxide, ethylene oxide, cyanide, hydrogen sulfide, methyl bromide, methyl chloride, nitrous oxide, waste anesthetic gases. Other miscellaneous substances (allyl chloride, acrylamide, dimethylaminoproprionitrile, methyl methacrylate, naphthalene, trinitrotoluene) have also been documented for neurotoxic effects.

MANDATE 7

Evaluate the relevance of a monitoring and/or early screening and intervention program for asymptomatic workers exposed to manganese. Should such a program prove to be relevant, propose an operational strategy that includes defining the target population, organizing follow-up, establishing positivity criteria, and selecting appropriate interventions

Recommendations

There is a consensus for considering clinical manganism as a condition that could severely decrease the quality of life of affected individuals, their ability to work and to fulfil their social role. It is recognized that manganism is a progressive disorder ending up in a severe neurological and neuropsychological impairment.

A wide variety of neuropsychological tests have been used in studies of groups of asymptomatic individuals exposed to low doses of manganese. These tests are considered to be safe and acceptable for workers, affordable and relatively easy to perform. The distribution of values in normal populations not exposed to neurotoxic substances is usually known, and the metrologic characteristics of these tests in terms of precision and reliability have been evaluated. Functional tests are considered to be sensitive indicators of the early neurotoxic effects of Mn. On the other hand, the quantitative relationship between the prevalence rate of abnormal test results and the duration and intensity of different types of environmental exposures to manganese is not precisely known.

None of these functional tests is specific to the neuropsychological effects of manganese, and abnormal results have been associated with other adverse environmental exposures. However, a consistent pattern of abnormalities has been associated with manganese, including deterioration of the rapidity of neurosensorial response, motor function, mood and memory tests. There is no data from longitudinal studies allowing an assessment of the value of any test or combination of tests for predicting the occurrence of clinical manganism. On an individual basis, it is therefore impossible to predict who among asymptomatic workers exposed to low doses of manganese and having some abnormal functional tests will develop a syndrome of clinical manganism. Based on current scientific knowledge and the criteria of the WHO to be fulfilled in order to implement screening program and therefore good medical practice, no recommendation can be made for a screening program targeting asymptomatic workers exposed in the workplace. A prospective longitudinal controlled study could be useful for learning more about the progression from pre-manganism or some preclinical effects of Mn to clinical manganism.

However, in research settings, neuropsychological tests may be useful at the group level, in order to better describe the natural history of pre-manganism, to establish occupational exposure guidelines and permissible levels, and to identify plants, jobs and categories of workers at risk in conjunction with environmental monitoring biomarkers. The only preventive intervention that could be proposed to reduce or eliminate the risk of developing clinical manganism is the reduction of exposure.

Consensus status

These recommendations were agreed upon by consensus.

Rationale

A screening program aiming to detect an asymptomatic person and to implement preventive measures, should meet the following criteria:

- The disease burden is important
- The natural history of the disease including a preclinical stage
- There is a screening test (or battery of tests) that is safe, acceptable, easy to perform, affordable, precise and reliable
- The distribution of values for the test in the normal and risk population is known
- There is a cut-off level providing acceptable sensitivity (capacity to predict disease occurrence, specificity (capacity to exclude disease occurrence), and predictive positive value (proportion of individuals who will develop the disease among those having a positive test)
- There is an effective intervention at the preclinical stage that could reduce or eliminate disease risk or alter the course of the disease

Manganism is a condition that reduces the quality of life of affected individuals and their ability to work and to fulfil their social role. Furthermore, at clinical stage, some effects are irreversible, and the disease may progress towards severe manganism, even if exposure is drastically reduced by removing the affected individual from the workplace (Huang *et al*. 1993, 1998).

There is no prospective follow-up study describing the evolution of manganism from the preclinical to the clinical stage. The early natural history of manganism has to be reconstructed from cross sectional studies of individuals exposed to various levels and durations of manganese exposure, and from interviews with individuals with clinical manganism. It is generally recognized that the central nervous system effects of manganese progressively develop along a continuum of dysfunction, starting with subtle neurofunctional disturbances, evolving initially towards subclinical neurological signs, and thereafter towards the clinical neurological and psychiatric manifestations of manganism (Mergler *et al*. 1999; ATSDR 2000; ACGIH 2001).

A wide variety of neuropsychological tests have been used in epidemiological studies of different groups of asymptomatic individuals exposed to low doses of manganese. These studies have been described in detail elsewhere (Ostiguy *et al*. 2003) and are listed and some are described in Mandate 6 of this report (Chandra *et al.* 1981; Roels *et al.* 1987a and b, 1992; Iregren 1990, 1992; Chia *et al.* 1993a and b; Mergler *et al.* 1994; Lucchini *et al.* 1995, 1999; Sjögren *et al.* 1996; Gibbs *et al.* 1999; ATSDR 2000).

Among the other available studies, Bowler *et al*. (2003) compared the neuropsychological function, emotional status, and psychoneurological symptoms of 76 former and current chemical industry welders primarily involved in steel welding. The welders performed worse than the controls on tests of verbal learning, working memory, cognitive flexibility, visuomotor processing speed, and motor efficiency. They had poorer colour vision and emotional status, and an increased prevalence of illnesses and psychiatric symptoms. Within the group of welders, the number of hours welding was negatively related to scores on verbal learning, auditory span, working memory, cognitive flexibility, and motor efficiency. All the functional tests that were used in the above-mentioned studies are considered to be safe and acceptable for workers. Sophisticated and very expensive technologies are not required and the tests are relatively easy to perform by experienced technicians. Results are generally expressed as a continuous score or ordinal scale. The distribution of values in (normal) populations not exposed to neurotoxic substances is usually known, and abnormal results are defined as a deviance from a mean, median or modal value, either on the basis of a selected

percentile or a standard deviation. The metrologic characteristics of these tests in terms of precision and reliability were also evaluated.

For some tests, significantly higher than expected rates of abnormal results have been reported for exposure concentrations in the air as low as 0.027 mg Mn/m^3 in total dust (Lucchini *et al.* 1995). All these functional tests are generally considered as being sensitive indicators of the early neurotoxic effects of manganese (Mergler *et al*. 1997; Iregren 1999). However, the quantitative relationship between the prevalence rate of abnormal test results and the duration and intensity of different types of environmental exposures to manganese is not precisely known.

None of these functional tests is specific to the neuropsychological effects of manganese. Although there is some inconsistency in the results of the above-mentioned studies, the most consistent (specific) pattern of abnormalities includes deterioration in the rapidity of neurosensorial response, motor function, and memory tests (Iregren 1992, 1999).

The value of these tests in predicting the occurrence of clinical manganism is not documented. To date, only one long-term follow-up study of asymptomatic exposed workers has been conducted and the results published. Roels *et al.* (1999) carried out an eight-year longitudinal study on the same cohort as that published in 1992 in order to determine the reversibility of three early neurotoxic effects: hand-eye coordination (HEC), hand steadiness (HS), and simple visual reaction time (SVRT). They found some recovery in precision in hand and forearm movement after the implementation of better exposure controls or removal from exposure. No recovery was noted for HS and SVRT. Despite the fact that two of these conditions seem irreversible, the authors do not suggest any of the tests as predictive of the development of manganism because none of the workers had or developed clinical features of manganism. On an individual basis, it is thus impossible to predict who among asymptomatic workers exposed to manganese and having some abnormal functional tests will develop a syndrome of clinical manganism.

The majority of cases of manganism reported in the literature came from operations in mines where concentrations were extremely high and could reach 900 mg Mn/m^3 (Flinn *et al*. 1990; Rodier 1955) or in foundries (Whitlock *et al*. 1966; Smyth *et al*. 1973).

Schuler *et al*. (1957) documented chronic Mn poisonings in chronically-exposed miners and in which one third of the air samples exceeded 5 mg Mn/m^3. The latency period varied from a few months to a few decades. Tanaka and Lieben (1969) reported 7 cases of manganism and 15 cases at the diagnosis limit in 144 workers exposed to manganese dusts or fumes at concentrations above 5 mg Mn/m^3. In the literature, no proven case of clinical manganism has been reported for exposure levels below 2 mg Mn/m^3 (Cook *et al.* 1974; Rodier 1955; Saric *et al.* 1977; Schuler *et al.* 1957; Tanaka and Lieben 1969; Whitlock *et al.* 1966). Neurotoxic effects were observed following exposures varying from 1 to 35 years (Schuler *et al*. 1957; Whitlock *et al*. 1966; Tanaka and Lieben 1969; Cook *et al*. 1974; Saric *et al.* 1977; Roels *et al*. 1987a, 1992; Iregren 1990; Wennberg *et al.* 1991; Chia *et al*. 1993a, 1993b, 1995; Mergler *et al.* 1994; Lucchini *et al*. 1995).

The only preventive intervention that could be effective in reducing the risk of developing clinical manganism is a reduction of exposure. In the above-mentioned study of battery plant workers (Roels *et al*. 1999; Crump *et al*. 1999), ambient exposure to manganese was reduced during follow-up. Comparison of workers exposed to the lowest range of initial doses and staying in the workplace and individuals who left the company did not reveal any difference in outcome.

Since there is no evidence of any specific manganese-screening tool, and as we know about the potential adverse consequences that may be associated with a "positive" label, no recommendation

can be made for a screening program targeting asymptomatic workers exposed in the workplace. However, neuropsychological tests may be useful at the group level, in order to describe the natural history of pre-manganism, to establish occupational exposure guidelines and permissible levels, and to identify plants, jobs and categories of workers at risk in conjunction with environmental monitoring of manganese concentration in dust and air, and measures of exposure biomarkers in a research setting. Such a study should be performed on an ad hoc basis and the results could be kept anonymous, with only aggregated data divulged.

CONCLUSION

The IRSST and the CSST are very grateful to the experts on the panel who invested a lot of time and effort to reach consensus on the seven questions that were prepared by the medical committee. Consensus has been reached in all situations.

Occupational manganism has been clearly defined and a severity scale has been proposed. Criteria have been established for the classification and diagnosis of occupational manganism. A plan has also been proposed for the monitoring and treatment of patients. Finally, early screening for asymptomatic workers has not been recommended. Once a worker has been diagnosed with manganism, his exposure to manganese or other neurotoxic substances should be kept as low as possible. Prevention by decreasing the occupational exposure to manganese remains the best approach to prevent the development of the disease.

From this very valuable information on medical aspects, and from additional work that has been done in Québec to document the occupational exposure of workers to manganese, it will be possible to better manage what now seems to be an emerging problem since only two compensation claims came to the CSST before the recent cluster of cases.

Diagnosis should be easier to establish and the management of diseased workers will be greatly facilitated. CSST compensation parameters and management procedures for cases should be reconsidered taking into account the information included in the present report.

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APPENDIX A: Short neuropsychological battery of tests

Function	Test	Duration (min)
Mini Mental State Examination		5
Verbal fluency	COWAT	4
Cognitive flexibility & Info processing	Stroop Color Word &	4
Divided attention	Auditory Conson. Trigrams	4
Information processing & set shifting	Trails A & B	5
Digit Span	Digit Span	3
Verbal learning	Word Lists	5
Motor speed	Finger tapping	3
Tactile ability	Grooved Pegs	2
Gross motor tactile	Santa Ana	3
Grip strength	Dynomameter	1
Graphic tremor	Parallel Lines Tremor	2
Tremometer	9 Hole Tremor Test	3
Visuo-spatial, perceptual motor	Digit Symbol	2
Planning and organizing and Imm. Recall	Rey Osterreith Copy	3
Rey – 15 items		1
Verbal memory	Word lists	5
Visual Attention Test Battery (computer administered)		10-12

APPENDIX B: Thorough neuropsychological battery of tests

Domain	Function	Test	Duration (min)
Motor	Coordination	Santa Ana	5
	Tactile Speed, Coordination	Grooved Pegboard	5
	Fine Motor Speed	Finger Tapping	4
	Grip Strength	Dynamometer	3
	Tremor	Parallel Lines Test	3
		Tremometer	3
		Hand Steadiness Test	5
	Visual Reaction time	Visual Attention test (VAT)	12
	Somatosensory	Luria Motor Items	1
Sensory	Vision	Visual acuity (Snellen)	3
	Vision	Contrast sensitivity (Vistech 6000)	15
	Vision	Color Confusion Index (Lanthony D-15)	5
	Vision	Schirmer Strips	2
Cognitive			
	Perceptual-motor speed	Cancellation H or symbol	3
	Perceptual-motor speed / visual memory	Symbol Digit / Symbol Digit (recall)	3
	Learning / Sustaining Concentration and Memory	Auditory Trigrams (ACT)	10
	Verbal – Reading level	Wide Range Achievement Test-3, Reading Subtest	10
	Verbal Fluency	COWAT	4
	Category Fluency	Animal Naming	2
		Boston Naming Test	
	Auditory memory	Digit Span (forward and backward)	5
	Executive function	D-KEFS Sorting Test	5
WMSIII	Spatial Memory	Spatial Span (forward and backward)	5
	Verbal Learning	Word Lists I &II	10
WAISIII		Block Design	8
		Arithmetic	8
		Picture Completion	8
	Perceptual-motor speed / visual memory	Digit Symbol Coding & Recall	5
	Visual Memory	Rey Osterreith, copy, recall & delay	10
	Information Processing &	Trails A and B	5
	Concept shifting	Stroop Color Word Test	4
	Malingering	Rey 15 Item and/or	3
		Tomm Test of Malingering	10

APPENDIX C: Tests of Affect, Mood

Test	Duration (min)
Symptom Checklist 90 - R	15
Relative Patient Questionnaire	10
Profile of Mood States (POMS)	10
Beck Depression & Beck Anxiety Scales	10
Behavioral. Risk Factor Survey BRFSS (days per month of good mental and physical health	5

APPENDIX D:

Differential diagnosis of Parkinsonism (Hobson, 2003, reproduced with permission)

Primary neurodegenerative disorders with Parkinsonism:

Inherited:

- Genetic Parkinson's disease; [types with confirmed gene site and inheritance type]
- Alzheimer's disease
- Huntington's disease
- Spinocerebellar atrophies (SCA2, SCA3)
- Neuro-acanthocytosis
- Dopa responsive dystonia (DRD)
- Dentato Rubral Pallidal Luysian atrophy (DRPLA)
- Pantothenate kinase-associated neurodegeneration (PKAN) formerly Hallervorden Spatz syndrome
- Familial depression, alveolar hypoventilation and Parkinsonism
- Neuronal intranuclear inclusion disease

Sporadic:

- Idiopathic Parkinson's disease
- Parkinson 'Plus' syndromes:
  - Progressive supranuclear palsy
  - Multiple system atrophy
  - Cortical basal ganglionic degeneration
  - Dementia with Lewy bodies
  - Alzheimer's disease
  - Pick's disease
  - ALS-Parkinson-dementia of Guam
  - Hemiparkinsonism with hemiatrophy

Secondary disorders with Parkinsonism:

Inherited:

- Wilson's disease
- Gauchers disease
- GM1 gangliosidosis
- Chediak-Higashi syndrome

Sporadic:

- Toxic (1-methyl-4-phenyl-1,2-5,6-tetrahydropyridine (MPTP), carbon monoxide, carbon disulfide, cyanide, manganese)
- Hepatocerebral degeneration (non-Wilsonian)
- Endocrine (hypothyroidism, hypoparathyroidism)
- Mass lesions (arteriovenous malformation, neoplasm - primary or metastatic or paraneoplastic syndrome)
- Vascular (vasculitis, infarction, lacunar state)
- Infection related (viral encephalitis, syphilis, HIV, Creutzfeldt-Jakob disease)
- Trauma
- Autoimmune or inflammatory
- Lack of substrate (hypoxia, hypoglycemia)

Others:

- Normal pressure hydrocephalus

Medication induced (direct or withdrawal)

Classic neuroleptics	(e.g. haloperidol, chlorpromazine, perphenazine)
Novel neuroleptics	(e.g. risperidone tartrate, olanzapine)
Dopamine reuptake blockers	(e.g. reserpine, tetrabenazine)
Gastrointestinal dopamine blockers	(e.g. metoclopramide)
Calcium channel blockers	(e.g. flunarizine hydrochloride, verapamil, amlodipine)
Selective serotonin reuptake inhibitors	(e.g. fluoxetine hydrochloride)
Tricyclics	(e.g. amytriptyline)
Anticonvulsants	(e.g. diphenylhydantoin, carbamazepine, valproic acid)
Monoamine oxidase inhibitors	(e.g. phenelzine)
Benzodiazepines	(e.g. diazepam, clonazepam, bromazepam)
Other medications:	Trazodone hydrochloride, buspirone, lithium, amphetamines, cocaine, meperidine, amiodarone, H1 and H2 blockers.