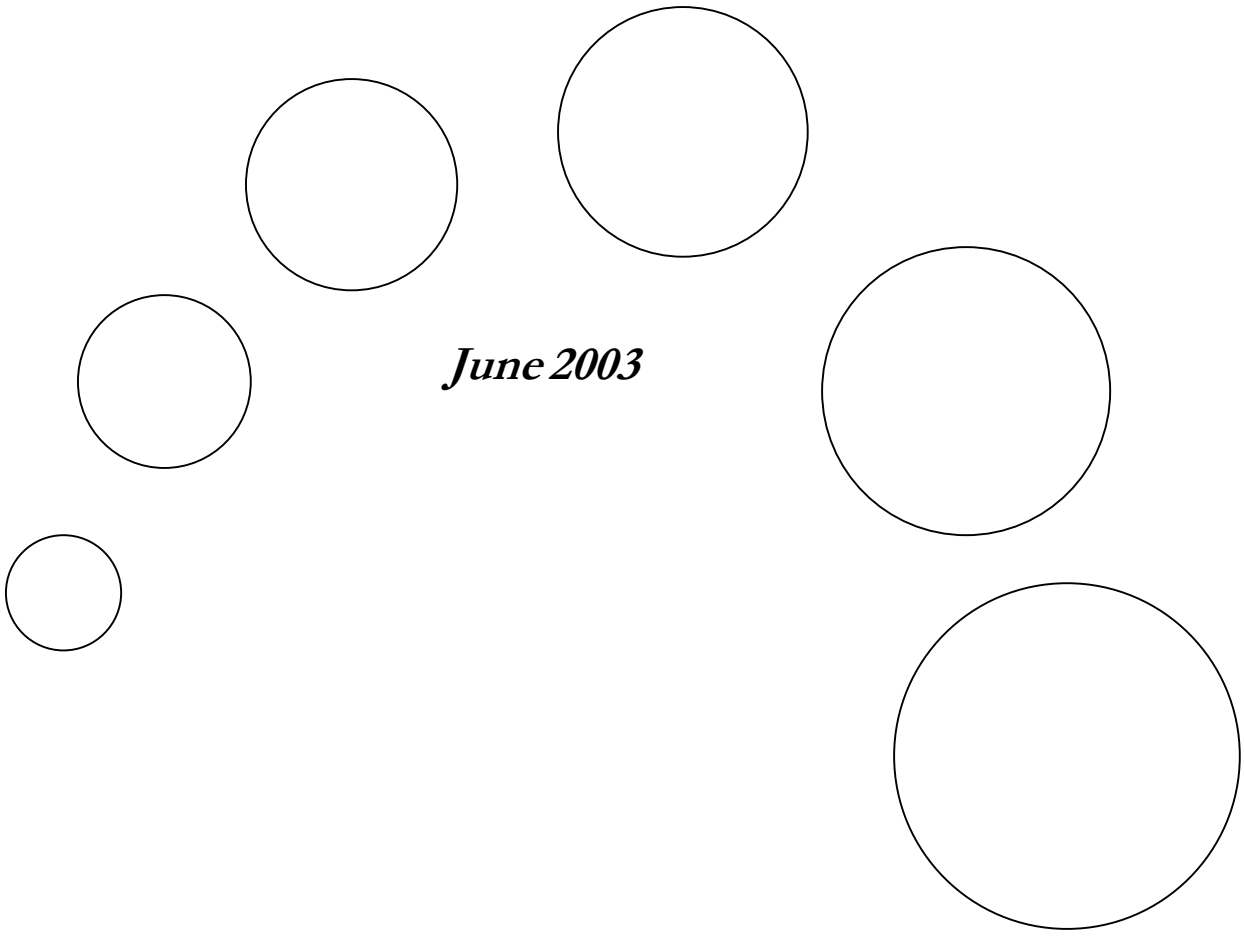
NICNAS

National Industrial Chemicals Notification and Assessment Scheme

Methylcyclopentadienyl Manganese Tricarbonyl (MMT)

Priority Existing Chemical Assessment Report No. 24



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Preface

This assessment was carried out under the National Industrial Chemicals Notification and Assessment Scheme (NICNAS). This Scheme was established by the *Industrial Chemicals (Notification and Assessment) Act 1989* (Cwlth) (the Act), which came into operation on 17 July 1990.

The principal aim of NICNAS is to aid in the protection of people at work, the public and the environment from the harmful effects of industrial chemicals.

NICNAS assessments are carried out in conjunction with Environment Australia and the Therapeutic Goods Administration, which carry out the environmental and public health assessments, respectively.

NICNAS has two major programs: the assessment of the health and environmental effects of new industrial chemicals prior to importation or manufacture; and the other focussing on the assessment of chemicals already in use in Australia in response to specific concerns about their health and/or environmental effects.

There is an established mechanism within NICNAS for prioritising and assessing the many thousands of existing chemicals in use in Australia. Chemicals selected for assessment are referred to as priority existing chemicals.

This priority existing chemical report has been prepared by the Director of NICNAS, in accordance with the Act. Under the Act, manufacturers and importers of priority existing chemicals are required to apply for assessment. Applicants for assessment are given a draft copy of the report and 28 days to advise the Director of any errors. Following the correction of any errors, the Director provides applicants and other interested parties with a copy of the draft assessment report for consideration. This is a period of public comment lasting for 28 days during which requests for variation of the report may be made. Where variations are requested, the Director's decision concerning each request is made available to each respondent and to other interested parties (for a further period of 28 days). Notices in relation to public comment and decisions made appear in the *Commonwealth Chemical Gazette.*

In accordance with the Act, publication of this report revokes the declaration of this chemical as a priority existing chemical; therefore manufacturers and importers wishing to introduce this chemical in the future need not apply for assessment. However, manufacturers and importers need to be aware of their duty to provide any new information to NICNAS, as required under Section 64 of the Act.

For the purposes of Section 78(1) of the Act, copies of assessment reports for new and existing chemical assessments may be inspected by the public at the library of the National Occupational Health and Safety Commission (NOHSC). Summary Reports are published in the *Commonwealth Chemical Gazette*, which are also available to the public at the NOHSC library.

Copies of this and other priority existing chemical reports are available on the NICNAS web site. Hardcopies are available from NICNAS either by using the order form at the back of this report, or directly from the following address:

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AUSTRALIA

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Other information about NICNAS (also available on request and on the NICNAS web site) includes:

- NICNAS Service Charter;
- information sheets on NICNAS Company Registration;
- information sheets on the Priority Existing Chemicals and New Chemical assessment programs;
- safety information sheets on chemicals that have been assessed as priority existing chemicals;
- details for the NICNAS Handbook for Notifiers; and
- details for the *Commonwealth Chemical Gazette*.

More information on NICNAS can be found at the NICNAS web site:

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Other information on the management of workplace chemicals can be found at the web site of the National Occupational Health and Safety Commission:

http://www.nohsc.gov.au

Overview

Anti-valve seat recession (AVSR) fuel additives were declared as Priority Existing Chemicals for full assessment under the *Industrial Chemicals (Notification and Assessment) Act 1989* on 5 December 2000. They were nominated by the public because of health and environmental concerns due to their increasing widespread use in automotive lead replacement petrol (LRP). Four AVSRs have been notified for assessment: methylcyclopentadienyl manganese tricarbonyl-based, phosphorous-based, sodium-based and potassium-based additives.

AVSR fuel additives are available for both industrial and consumer use and are delivered either by pre-blending to unleaded petrol at the oil refinery (LRP) or purchased and added to unleaded petrol by the vehicle owner (known as aftermarket addition). Methylcyclopentadienyl manganese tricarbonyl (MMT) (CAS # 12108-13-3) is a manganese (Mn)-based AVSR imported predominantly for addition to LRP and in smaller quantities for formulation of aftermarket fuel additives.

The natural attrition of older cars requiring AVSR additives means a decreasing AVSR market and consequently the use of AVSR additives including MMT is likely to decline with time. The production and infrastructure support of LRP will eventually become economically unviable and aftermarket addition of AVSR additives will be the sole method of providing valve seat protection through fuel. This report considered the occupational health and safety, public health and environmental consequences of two separate scenarios for the use of MMT – a Present Use scenario assuming 100% market share and present delivery modes and levels of demand, and a 2004 scenario assuming attrition of the AVSR vehicle fleet, reduced demand and delivery of MMT via aftermarket addition only.

MMT is highly toxic to aquatic organisms. Spill incidents and leaks to water bodies and land may potentially occur during shipment into Australia, bulk handling and storage and leaks from underground storage tanks. These should be managed through existing Federal, State and Territory legislative frameworks and protocols to mitigate adverse effects to the aquatic environment.

Manganese, a by-product from combustion of MMT, is naturally occurring and ubiquitous in the environment. It is an essential nutrient of plants and animals. Environmental exposure to manganese compounds arising from combustion of MMT will mostly arise through the gaseous phase. Eventually, these will deposit to land and waters. The emission of manganese into the environment from use of fuels containing MMT is unlikely to develop to levels of concern for terrestrial or aquatic environments. As such, the findings of this assessment have not identified any significant risk to the environment given the considered current use pattern of fuels containing MMT as an AVSR.

MMT is highly toxic in animals and humans. It is absorbed by all routes of exposure and metabolised predominantly in the liver. Metabolites are excreted in urine and faeces. The liver, kidney, brain and lung are the primary sites of Mn accumulation following MMT absorption. The critical effects from acute exposure to MMT are neurological and pulmonary dysfunction. Acute lethal exposure to MMT in animals is associated with damage to the lungs by all routes, kidney, liver and spleen effects, tremors, convulsions, dyspnea and weakness. In humans, giddiness, headache, nausea, chest tightness, dyspnea

and paresthesia are reported in anecdotal cases of acute occupational exposure. Repeated inhalation exposure to MMT in animals results in degenerative changes in liver and kidneys.

MMT (as Mn) is currently listed in the NOHSC *List of Designated Hazardous Substances* with no classification. Based on assessment of health effects, this report has concluded that MMT meets the NOHSC *Approved Criteria for Classifying Hazardous Substances* for classification on the basis of acute lethal effects by all exposure routes and severe effects after repeated or prolonged exposure via inhalation. The following risk and safety phrases are recommended: R26 - Very Toxic by Inhalation; R28 – Very Toxic if Swallowed; R24 – Toxic in Contact with Skin; R48/23 – Toxic: Danger of Serious Damage to Health by Prolonged Exposure Through Inhalation; S36 - Wear Suitable Protective Clothing; S38 - In Case of Insufficient Ventilation Wear Suitable Respiratory Equipment.

As MMT is combusted to a number of inorganic Mn species, the health hazards associated with the use of MMT also include those associated with inorganic Mn. In animals and humans, neurological dysfunction is the critical effect following acute exposure to Mn compounds. Decreased activity, alertness, muscle tone, touch response and respiration are reported in animal studies. In humans, chronic occupational exposure to respirable Mn dusts is associated with subclinical nervous system toxicity through to overt manganism, a progressive neurological disorder characterised by altered gait, tremor and occasional psychiatric disturbances.

Minimal occupational exposure to MMT is likely for workers involved in formulating and distributing LRP or aftermarket fuel additives and those involved in automotive maintenance. Overall, a low occupational risk associated with MMT was concluded.

Occupational exposure to Mn, mainly via inhalation, may occur also for these and other workers associated with or in the vicinity of automotive usage. Where automotive usage is ubiquitous, chronic inhalation of inorganic Mn species may result. In the absence of Australian occupational exposure data, a worst-case scenario was considered for Mn exposure of Australian auto mechanics from the use of MMT using overseas personal inhalational exposure estimates. A low occupational risk associated with Mn exposure from MMT combustion was concluded.

Minimal public exposure to MMT is likely as a result of spills and splashes of LRP and aftermarket additives. A low risk is concluded. A similar low risk is envisaged from MMT in LRP given the lower concentrations of MMT compared to aftermarket additives.

Acute health effects could occur as a result of accidental ingestion of MMT by a child or by adults when siphoning fuel. The health risk to adults from accidental ingestion of LRP containing MMT during siphoning or to children following ingestion of LRP stored inappropriately around the home is considered low, given the low level of MMT in LRP. However, a comparison between the potential oral dose of MMT from accidental ingestion of aftermarket additive by a child and animal oral LD50 values indicates that MMT represent a significant acute health risk for children.

Although the public use of MMT may increase ambient air Mn levels and therefore doses received by inhalation, given that the predominant sources of Mn for humans via food and water are unlikely to be altered significantly by the use of MMT, overall chronic Mn exposures (from all sources combined) are unlikely to change significantly. The margins of exposure for the public are greater than 1000. The estimated ambient air concentration of Mn due to MMT combustion according to the Present Use scenario is less than a range of

overseas inhalation health standards and guidance values. Given the conservative assumptions used in the exposure assessment, the overall public health risk from the use of MMT as an AVSR is low.

This report has identified the need particularly to reduce public exposure to MMT as much as practicable. Given its toxicity profile and consumer use, it is recommended that the National Drugs and Poisons Schedule Committee (NDPSC) consider scheduling MMT on the *Standard for Uniform Scheduling of Drugs and Poisons* (SUSDP). It is recommended also that consumer packaging be of a design to facilitate the accurate addition of additive to fuel tanks without spillage and incorporate an automatic measuring and dispensing capacity and child-proof closures.

This report encourages the monitoring of ambient air Mn to more accurately estimate the risk to the public. It also supports research into the effects of fuel-related Mn emissions especially on susceptible subpopulations such as children.

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Abbreviations

ACGIH	American Conference of Governmental Industrial Hygienists
ADG Code	Australian Code for the Transport of Dangerous Goods by Road and Rail
AMSA	Australian Maritime Safety Authority
ANZECC	Australian and New Zealand Environment and Conservation Council
AOAA	aminooxyacetic acid
aq	aqueous
ARMCANZ	Agriculture and Resource Management Council of Australia and New Zealand
ATSDR	Agency for Toxic Substances and Disease Registry
ABS	Australian Bureau of Statistics
AVSR	anti-valve seat recession
bw	body weight
CAA	Clean Air Act
CAS	Chemical Abstracts Service
CC16	Clara cell protein
CID	cubic inch displacement
C_{max}	maximum concentration
CMT	carboxycyclopentadienyl manganese tricarbonyl
DNA	deoxyribonucleic acid
DOPAC	3,4-dihydroxyphenylacetic acid
EA	Environment Australia
EC50	median effective concentration
EINECS	European Inventory of Existing Commercial Chemical Substances
FORS	Federal Office of Road Safety
g	gram

GABA	4-aminobutyric acid
h	hour
HAPS	hazardous air pollutants
HMT	hydroxymethylcyclopentadienyl manganese tricarbonyl
HQ	hazard quotient
HVA	homovanillic acid
IC25	25th percentile inhibitory concentration
IC50	median inhibitory concentration
IIWL	interim indicative working level
IMO	International Maritime Organisation
ip	intraperitoneal
IPCS	International Programme on Chemical Safety
iv	intravenous
kg	kilogram
K_m	Michaelis constant
L	litre
LC50	median lethal concentration
LD50	median lethal dose
LOAEL	lowest-observed-adverse-effect level
LRP	lead replacement petrol
LT50	median lethal time
µg	microgram
µm	micrometre
MATC	maximum acceptable threshold concentration
ML	megalitre
mg	milligram
mL	millilitre
MMT	methylcyclopentadienyl manganese tricarbonyl
Mn	manganese
MOE	margin of exposure

MSDS	Material Safety Data Sheet
m^3	cubic metre
NAPS	National Air Pollution Surveillance
NDPSC	National Drugs and Poisons Schedule Committee
NEPC	National Environment Protection Council
NEPM	National Environment Protection Measure
ng	nanogram
NHMRC	National Health and Medical Research Council
NICNAS	National Industrial Chemicals Notification and Assessment Scheme
NOAEL	no-observed-adverse-effect level
NOEC	no-observed-effect concentration
NOEL	no-observed-effect level
NOHSC	National Occupational Health and Safety Commission
NOS	not otherwise specified
NPI	National Pollution Inventory
OECD	Organisation for Economic Cooperation and Development
PEC	predicted environmental concentration
PNEC	predicted no-effect concentration
PPE	personal protective equipment
ppm	parts per million
RfC	reference concentration
ROS	reactive oxygen species
SEM	scanning electron microscopy
SUSDP	Standard for the Uniform Scheduling of Drugs and Poisons
$T_{1/2}$	half-life
TBOB	t-butylbicycloorthobenzoate
TGA	Therapeutic Goods Administration
TLm	median threshold limit
T_{max}	maximum time

TWA	time-weighted average
UKDETR	United Kingdom Department of Environment, Transport and Regions
USEPA	United States Environmental Protection Agency
V_{max}	maximum enzymatic velocity
VSR	valve seat recession
WHO	World Health Organisation

1. Introduction

1.1 Declaration

Anti-valve seat recession (AVSR) fuel additives were declared as Priority Existing Chemicals for full assessment under the *Industrial Chemicals (Notification and Assessment) Act 1989* on 5 December 2000. They were nominated because of their increasing widespread use in lead replacement petrol (LRP) and potential adverse effects on the environment and human health.

Applications for the following AVSRs in use in Australia were received:

- Methylcyclopentadienyl Manganese Tricarbonyl (MMT)-based;
- Phosphorous-based;
- Sodium-based; and
- Potassium-based.

Each AVSR fuel additive has been assessed individually and separate reports are prepared for each. This present report addresses the use of MMT (CAS # 12108-13-3) as an AVSR.

1.2 Objectives

The objectives of this assessment are to:

- Characterise the chemical and physical properties of MMT;
- Determine the current and potential occupational, public and environmental exposure to MMT as an AVSR;
- Characterise the intrinsic capacity of MMT to cause adverse effects on persons or the environment;
- Characterise the risk to humans and the environment resulting from exposure to MMT as an AVSR;
- Determine the extent to which any risk is capable of being reduced and make recommendations for the management of these risks.

1.3 Sources of information

Consistent with these objectives, the report presents a summary and critical evaluation of relevant information relating to the potential health and environmental hazards from exposure to MMT. Relevant scientific data were submitted by the applicants listed in Section 3, obtained from published papers identified in a comprehensive literature search of several online databases up to August 2002, or retrieved from other sources such as the reports and resource documents prepared by overseas regulatory bodies.

Due to the availability of detailed overseas regulatory reviews e.g. *Risk Assessment for the Combustion Products of Methylcyclopentadienyl Manganese Tricarbonyl (MMT) in Gasoline* (Wood and Egyed, Health Canada, 1994), *Reevaluation of Inhalation Health Risks Associated with Methylcyclopentadienyl Manganese Tricarbonyl (MMT) in Gasoline*, (USEPA 1994c), Environmental Health Criteria 17: *Manganese* (WHO 1981), Concise International Chemical Assessment Document 12 – *Manganese and Its Compounds* (WHO 1999) and *Toxicological Profile for Manganese (Update)* (ATSDR 2000), not all primary source data were evaluated. However, relevant studies published since the cited reviews were assessed on an individual basis.

The characterisation of health and environmental risks in Australia was based upon information on use patterns, product specifications, occupational exposure and emissions to the environment made available by the applicant and relevant State and Federal authorities. Information to assist in the assessment was also obtained through site visits and telephone interviews.

1.4 Peer review

During all stages of the preparation, the report has been subject to peer review by NICNAS, Environmental Australia (EA) and the Therapeutic Goods Administration (TGA). In addition, selected parts of the report were peer reviewed by overseas authorities. Dr. J. Michael Davis of the National Centre for Environmental Assessment-RTP, Office of Research and Development, United States Environmental Protection Agency and Dr. Barry Jessiman, Air Health Effects Division, Air and Fuel Assessment Section, Health Canada provided valuable comment focussing on exposure and risk characterisation.

2. Background

Methylcyclopentadienyl manganese tricarbonyl (MMT) was first developed in the 1950s by the Ethyl Corporation. MMT is an organometallic compound produced either by the reaction of manganous chloride, cyclopentadiene, and carbon monoxide in the presence of manganese carbonyl and a group II or IIIA element, or the reaction of methylcyclopentadiene with manganese carbonyl. MMT is used as an antiknock agent in internal combustion engine fuels (Davis 1998). In more recent times, MMT has also been marketed as an anti-valve seat recession (AVSR) additive for lead replacement petrol (LRP).

2.1 What is an anti-valve seat recession additive?

Anti-valve seat recession fuel additives are added to petrol to stop excessive valve seat wear and recession of the valve seat into the automotive engine cylinder head (Figure 1).

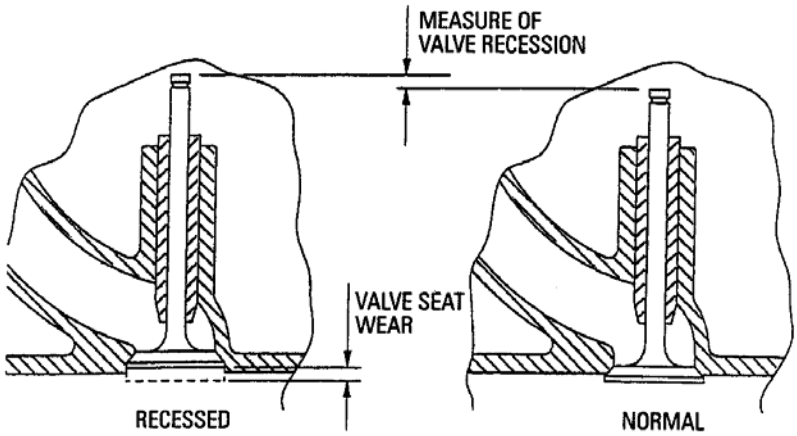

Figure 1. Exhaust valve recession into the cylinder head. From: Barlow (1999)

Although valve seat recession (VSR) occurs as part of the normal wear of an engine, premature erosion of the valve seats observed as excessive VSR occurs when vehicles with soft exhaust valve seats normally designed to operate on leaded petrol are operated on unleaded petrol.

Valve seats in engines designed for leaded fuel are generally relatively soft. With leaded fuels, lead oxide formed by the combustion of lead alkyls forms a thin layer of lead oxide on the valve and valve seat, so acting as a solid lubricant and preventing erosion of the valve seats in the cylinder head of the engine (Figure 1). VSR can cause valve burning and loss of compression and if allowed to progress result in serious loss of performance and ultimately engine failure. Lead replacement petrol uses AVSR additives to provide the lubricating qualities previously provided by lead. During fuel combustion, the AVSR additive burns and forms an oxide coating on the exhaust valve seats providing similar protective lubrication to lead oxide.

Since the early 1970s, increasing environmental and health concerns have resulted in the reduction of lead levels in petrol and the complete removal of leaded gasoline in several countries (Lovei, 1998). In 2000, the World Bank reported that 36 countries had already phased out the use of leaded petrol and this was expected to increase to 55 countries by 2005 (Benbarka, 2000). In addition, the use of catalytic converters in automotive exhaust systems required the introduction of unleaded fuels as lead destroys the capacity of catalytic converters to reduce other pollutants (Lovei, 1998).

A consequence of the removal of lead from petrol is that engine designers have been required to use harder exhaust valve seat materials that maintain integrity without lead lubrication. For existing cars with soft valve seats, the removal of lead has required motorists to use lead replacement petrol containing an AVSR additive or to modify their engine by fitting hardened exhaust valve seats suitable for unleaded petrol with no AVSR fuel additive (Lovei 1998).

The use of AVSR additives has risen with the demand for lead replacement petrol resulting from the lead phase-out worldwide. The demands for lead replacement petrol and hence AVSR additives in individual countries have been determined largely by policy decisions regarding the import, sale and retirement of older vehicles, the encouragement of new technology environmentally cleaner engines and improved petrol standards. Consequently, the population of VSR sensitive cars and thus demand for AVSR additives in lead replacement petrol vary from country to country.

2.2 International perspective

MMT has been used in internal combustion engine fuels in the United States since 1976. In 1977, the passing of the Clean Air Act in the United States (US Congress 1977) limited the use of MMT to leaded gasoline. The basis of this decision was that MMT had detrimental effects on catalytic converters in unleaded vehicles, resulting in increased hydrocarbon emissions. Between 1977 and 1993 Ethyl Corporation unsuccessfully applied to the United States Environmental Protection Agency (USEPA) on several occasions for a waiver to use MMT in unleaded fuel in the United States. Based on extensive additional emission data submitted by Ethyl Corporation, the USEPA concluded in November 1993 that MMT did not increase hydrocarbon emissions. However, in July 1994 the USEPA again denied the waiver application by Ethyl Corporation, based on possible adverse health effects of an increase in airborne manganese (Mn) resulting from MMT use (USEPA 1994a). Ethyl Corporation subsequently challenged this decision in the United States Federal Court (Ethyl Corporation v. USEPA 1995a). The Federal Court ruled that the USEPA had no grounds to deny Ethyl Corporation's application except if MMT caused or contributed to the failure of any emission device or system.

In May 1994, the fuel or fuel additive rule (USEPA 1994b), as mandated in the Clean Air Act (US Congress 1977), was issued by the USEPA requiring all fuel or fuel additive manufacturers to provide specific mammalian toxicity studies. Furthermore, the marketing of products not registered by the USEPA was prohibited until the specific toxicity studies were provided. The USEPA subsequently claimed that MMT was not registered, but Ethyl Corporation successfully challenged this position (Ethyl Corporation v. USEPA 1995b) and has been marketing MMT in the United States since December 1995. However, the studies specified by the USEPA on MMT as well as other fuel additives must still be conducted (Wood and Egyed 1994; Davis 1998). At

the time of writing, according to Ethyl, some studies have been completed. The use of MMT, especially in the United States, remains controversial (Landrigan 2001).

The use of MMT in combustion engine fuels has been permitted in Canada since 1978. At this time a review of MMT by the Canadian Department of Health and Welfare concluded that its use as a fuel additive did not constitute a hazard to human health (Health and Welfare Canada 1978). In 1985, the Canadian Royal Commission on Lead in the Environment examined MMT as part of a review on lead additives and lead substitutes in combustion engine fuel. The conclusions reached were similar to those in 1978 (Royal Society of Canada 1986). During the next two years, two independent studies were prepared under contract from Health and Welfare Canada. The first incorporated recently completed toxicity studies (Midwest Research Institute 1987) while the second completed an exposure assessment (Hill 1988). Again, both reports reached similar conclusions to those formed in 1978.

In 1994, Health Canada performed a risk assessment of the health issues arising from the use of MMT in fuel in Canada, focusing on new epidemiological studies and Canadian exposure data (Wood and Egyed 1994). These authors concluded that the use of MMT in fuel posed no added health risk to the general population. However, in 1997, trade in MMT was restricted in Canada under the Manganese-based Fuel Additives Act that effectively banned the importation of MMT into Canada. This Act was subsequently and successfully challenged on the grounds that it contravened the Agreement on Internal Trade (AIT). The AIT is an agreement between the federal and provincial governments designed to prevent arbitrary trade barriers within the country. In 1998, the Government of Canada announced that it had removed restrictions on inter-provincial trade and import of MMT (Davis 1998). However, the use of MMT in Canadian fuel is still the subject of debate and health and environmental uncertainties remain (Zayed et al., 2001).

In addition to the US and Canada, the use of MMT is permitted in France (Minestre de L'Amenagement du Territoire et de L'Environment 1999), UK (British Standards Institute 1999), China (China State Bureau of Quality and Technology Supervision 2000), Russia (Ministry of Fuel and Energy of Russian Federation 1997), and Argentina (Norma Argentina 1999).

In New Zealand, as a result of promulgation of the *Petroleum Products Specifications Regulations* 2002, effective from 1 September 2002 automotive fuel must contain no more than 2.0 mg/L Mn. The background behind this decision is not known. The limitation on Mn content of fuels is to be reviewed by 2006. This law effectively severely restricts the use of MMT in automotive fuels in New Zealand.

2.3 Australian perspective

In Australia, under the *Fuel Quality Standards Act 2000 (Cwlth)* lead was removed from automotive fuel from 1 January 2002 requiring the use of alternative additives for valve seat protection. Under this Act, provision is made for listing of prohibited fuel additives. MMT is not currently listed.

An Australian Standard AS 4430.1 - 1996 (Standards Australia, 1996) exists for the evaluation of devices and additives which claim to improve vehicle performance. Part 1 of AS 4430.1 – 1996 is noteworthy for the present report as it considers engines

designed for leaded fuel to operate on unleaded fuels and includes assessment of valve seat recession.

An environmental and epidemiological study of Mn from MMT use is currently being conducted in Australia. The objectives of the project are to determine the contribution of MMT use to Mn levels in air, dust, soil and water and also blood and urine Mn levels in children aged 1-5 years.

2.4 Assessments by other national or international bodies

Reviews of the health and environmental effects associated with the use of MMT in combustion engine fuels were released in 1994 by the Environmental Health Directorate, Health Canada (Wood and Egyed 1994) and the USEPA (USEPA 1994c). Further, detailed overseas regulatory reviews of Mn have been conducted e.g. Environmental Health Criteria 17: Manganese (WHO 1981), Concise International Chemical Assessment Document 12 – Manganese and Its Compounds (WHO 1999) and Toxicological Profile for Manganese (Update) (ATSDR 2000).

3. Applicants

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Wynn's Australia Pty Ltd

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French's Forest Delivery Centre NSW 1640

Nulon Products Australia Pty Ltd

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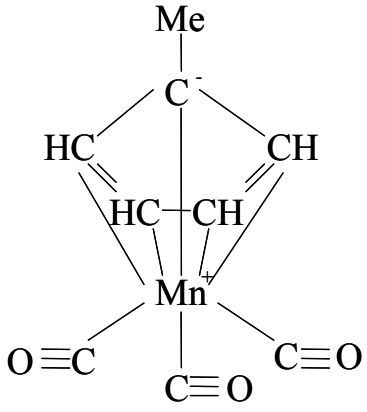
Belrose NSW 2085

4. Chemical Identity and Composition

4.1 Chemical identity

Chemical Name:	Manganese tricarbonyl [(1,2,3,4,5-eta)-1-methyl-2,4-cyclopentadien-1-yl]-
CAS No.:	12108-13-3
EINECS No.:	235-166-5
Synonyms:	MMT, Methylcyclopentadienyl manganese tricarbonyl, Methylcymantrene
Trade Names:	AK-33X, Antiknock-33, CI-2, Combustion Improver-2.
Molecular Formula:	$C_9H_7MnO_3$
Structural Formula:	
Molecular Weight:	218

4.2 Composition of commercial products

The Ethyl Asia Pacific Company markets two MMT-containing products. HiTEC 3062 contains 62% MMT w/w in a mixed aromatic and aliphatic solvent and HiTEC 3000 contains neat MMT. At the time of writing, HiTEC 3000 is not being imported to Australia.

Wynn's Australia Pty Ltd markets two MMT-containing products. Spitfire Octane Boost and Race Formula Octane Boost both contain < 5% w/w MMT in petroleum distillate.

Nulon Products Australia Pty Ltd markets three MMT-containing products. Octane Boost and Clean and Total Fuel System Cleaner both contain < 5% w/w MMT whilst Pro Strength Octane Booster contains < 10% w/w MMT, all in petroleum distillate.

5. Physical and Chemical Properties

5.1 Physical state

MMT is a dark orange or yellow liquid with a faintly pleasant or herbaceous odour (Lewis 1996).

5.2 Physical properties

Table 1. Physical properties of MMT

Property	Value	Reference
Boiling point	231.67°C	ACGIH, 1991
Melting point	2.22°C	Ethyl Submission
Density at 20°C	1390 kg/m^3	ACGIH, 1991
Water solubility at 25°C	0.029 g/L	Ethyl Submission
Vapour pressure at 100°C	1.24 kPa	Zenz , 1988
at 20°C	0.01 kPa	Ethyl Submission
Henry's law constant	<10^{-9} Pa m^3/mol	Ethyl Submission
Partition coefficient (log P_{ow})	3.4	Ethyl Submission
Autoignition temperature	257°C	Ethyl Submission
Flammability Limits	Lower: 0.3% at 153°C	Ethyl Submission
	Upper: 26% at 175°C	
Flash point (closed cup)	96°C	Zenz, 1988

5.3 Chemical properties

Solubility: MMT is miscible in most hydrocarbon solvents (Kirk-Othmer 1967).

Stability: MMT decomposes when exposed to light (Kaufman et al., 1961).

Polymerisation: MMT will not undergo hazardous polymerisation.

5.4 Conversion factors (at 25°C)

1 mg/m^3 = 8.93 ppm 1 ppm = 0.11 mg/m^3

6. Methods of Detection and Analysis

6.1 Identification

The detection and determination of MMT is usually achieved by using chromatography together with spectrophotometry. In addition, a number of methods have been described for indirect MMT determinations based on total Mn concentrations.

6.2 Atmospheric monitoring methods

A gas chromatographic protocol has been developed to determine MMT in ambient air. The limit of detection using this protocol is 0.05 ng/m^3. MMT is trapped on Teflon-lined U-tubes packed with 3% OV-1 on Chromosorb W. During sampling the U-tubes are placed in a water-ice cooling bath and air is pumped through the U-tube at approximately 70 mL/min using a vacuum pump. Determination is made by gas chromatography with an electrothermal atomic absorption detector (Coe et al., 1980).

A similar procedure to Coe et al. (1980) for the determination of MMT in ambient air is described by Gaind et al. (1992). Airborne MMT is collected in XAD-2 containing tubes using an air-sampling pump. Determination is made by gas chromatography with an electron capture detector. The limit of detection using this protocol is 0.001 mg/m^3 from a 10 L air sample.

A procedure for the determination of organic Mn in personal air samples has been described by Albemarle Corporation (1994). Determination is achieved by adsorption onto activated charcoal, followed by desorption by nitric acid, and then atomic absorption spectrophotometry. This protocol is applicable to organic Mn concentrations below 3 μg Mn/mL nitric acid. The method does not distinguish between different organic Mn species. A glass fibre filter is attached to the front of the charcoal tube to remove inorganic (particulate) Mn.

A number of methods have been described for the determination of inorganic Mn in ambient air. These include x-ray fluorescence and inductivity coupled plasma atomic emission spectrophotometry (ATSDR 2000).

6.3 Biological monitoring methods

A gas chromatography protocol has been developed to determine MMT in biological tissues or fluids. MMT present in small biological samples or fluids is extracted into hexane containing biphenyl as an internal standard followed by gas chromatography utilising a flame ionisation detector. As little as 1-2 ppm MMT can be quantified using this method (Hanzlik et al., 1979).

More recently, Walton et al., (1991) have described a method that combines high-performance liquid chromatography with laser-excited atomic fluorescence for the

detection of MMT in urine. The limit of detection was 1.6 ng/mL. This method was also able to distinguish MMT from several MMT-derived metabolites.

A number of techniques have been described for the determination of inorganic Mn in biological fluids and tissues. These include flame atomic absorption analysis, furnace atomic absorption analysis, neutron activation analysis, spectrophotometry, mass spectrometry, and x-ray fluorimetry (ATSDR 2000).

6.4 Water monitoring methods

A gas chromatography protocol has been developed to determine trace amounts of MMT in water. This protocol is applicable to MMT concentrations in water of 0.05-10 ppm (the solubility limit of MMT). All samples and standards must be protected from light because solutions of water (and other solvents) are photolytic. A water sample is mixed with carbon disulfide, the carbon disulfide layer is then removed, and the MMT quantified by gas chromatography (Ethyl Corporation 1989).

A number of techniques have been described for the determination of inorganic Mn in water samples. These include inductivity coupled plasma atomic emission analysis, atomic absorption spectrophotometry, catalytic kinetic analysis and colourmetric analysis (ATSDR 2000).

6.5 Petrol monitoring methods

A number of procedures have been described for the determination of MMT in petrol. All utilise gas chromatography, with either an electron capture detector (Giand et al., 1992), argon plasma emission detector (Uden et al., 1978; Ombana and Barry 1994), flame photometric detector (Aue et al., 1990), or atmospheric pressure helium microwave detector (Quimby et al., 1978).

A gas chromatography atomic emission spectroscopy protocol has been developed to determine organic Mn in petrol. This protocol requires minimal sample preparation and is able to quantify and speciate trace organic Mn levels (Swan 1999).

6.6 Soil monitoring methods

An atomic absorption spectrophotometic protocol has been developed to determine MMT in soil at concentrations above 2 ppm. A soil sample is extracted with isooctane and bromine is added to decompose the MMT. Manganese is then extracted using a dilute hydrochloric acid solution and quantified by atomic absorption spectrophotometry (Albemarle Corporation 1976).

Methods have been described for the determination of inorganic Mn in soil, sediments, and sludge. In general these procedures require acid extraction/digestion prior to analysis by atomic absorption spectrophotometry or inductivity coupled plasma atomic emission spectrophotometry (ATSDR 2000).

7. Importation and Use of MMT

7.1 Importation

MMT is imported only. The manufacture of MMT does not occur in Australia.

Three companies import AVSR products containing MMT into Australia. The products are imported in bulk as a 62% MMT petroleum distillate solution in 10 000 L isotanks (HiTEC 3062) and as similar 60 and 62% MMT solutions (Wynn's Octane Booster Concentrate and TK-660 respectively) in 205L steel drums. Solutions are less commonly imported in 450 L steel cylinders. Drummed concentrates are blended into aftermarket fuel additives in 300, 350 or 500 mL plastic bottles. MMT is also imported in pre-packaged aftermarket fuel additive products in 350 mL plastic bottles.

A total of less than 180 tonnes/year of MMT are imported into Australia with less than 10 tonnes/year imported pre-packaged or for formulation into aftermarket fuel additives.

7.2 Uses

MMT is a multifunctional fuel additive and is commonly added to internal combustion engine fuels as a smoke abatement agent, an octane enhancer and inhibitor of valve seat recession. MMT is also reported to reduce particulate smoke emissions from household, commercial, industrial, and marine burners. This report only considers the use of MMT as an AVSR in Australia. MMT is currently not sold in Australia solely as an octane enhancer.

In LRP, MMT is recommended for use at treat rates of 72.6 mg MMT (18 mg Mn)/L (< 0.01% MMT/L fuel). Aftermarket fuel additives contain MMT at < 10% w/w and at recommended treat rates, treated fuel will contain MMT at < 150 mg MMT (38 mg Mn)/L (< 0.02% MMT/L fuel).

7.2.1 Demand for anti-valve seat recession additives

Anti-valve seat recession fuel additives are available for both oil refinery/terminal and consumer use. AVSR fuel additives may be delivered either by pre-blending to unleaded petrol at the oil refinery or terminal (LRP) or purchased separately and added to unleaded petrol by the vehicle owner. The total Australian AVSR additive market will be referred to as the "LRP market" in this report.

Following the declaration of AVSR fuel additives as a Priority Existing Chemical, importers and manufacturers of various AVSR fuel additives provided information on the import/manufacturing quantities and uses of their chemicals for 2000 and 2001. This information was used to estimate a total LRP market for 2001 of approximately 2500 ML, calculated using AVSR additive treatment doses for LRP and AVSR import/manufacturing volumes as recommended by AVSR additive manufacturers. The calculated figure of 2500 ML is slightly higher than the bulk LRP sales volumes for

July 2000 to June 2001 of 1848 ML (Department of Industry, Science and Research, 2001).

The market share of individual AVSR fuel additives in Australia has not been disclosed in this report due to commercial-in-confidence considerations. An analysis of the import and manufacturing data demonstrated that the aftermarket application of AVSR additives in Australia was less than 10 % of the total LRP market in 2001.

In Australia, vehicles requiring leaded petrol are the major consumers of LRP. These vehicles requiring leaded petrol include passenger vehicles, light commercial trucks, rigid trucks, articulated trucks, non-freight carrying trucks, buses and motorcycles (Australian Bureau of Statistics (ABS), 2001). It is likely there are also other VSR sensitive vehicles requiring AVSR additives, e.g., tractors and some plant and equipment engines, not included on the Australian Motor Vehicle Census. However, these vehicles and engines are not expected to represent a significant component of the AVSR market.

There is a declining Australian market for LRP sales (Australian Institute of Petroleum, 1999) and hence AVSR additives. This is due to attrition from the Australian motor fleet of vehicles designed to run on leaded petrol (Figure 2).

By 2004, bulk sales of LRP are expected to decline to less than 5 % of total petrol sales (Australian Petroleum Gazette, 1999). This may render the general provision and sale of bulk LRP by the oil refineries and terminals uneconomical. Phase-out by the oil refineries and terminals of the provision of bulk LRP is yet to be announced by the Australian petroleum industry.

Aftermarket addition of AVSR fuel additives rather than bulk treatment by the oil refineries and terminals is likely to eventually become, therefore, the only option for motorists with vehicles designed to run on leaded petrol. This may occur as early as 2004 as the supply of LRP from the oil refineries and terminal diminishes significantly. Implementation of any partial or total changeover from bulk to aftermarket supply of LRP would, no doubt, require a broad consensus among stakeholders, entailing consideration of technical and practical needs of the program and understanding and acceptance by the public.

7.2.2 Use scenarios

Two use (exposure and emission) scenarios have been assessed in this report – the present state of the market, and that likely to occur at 2004. Both scenarios are considered because of anticipated changes in occupational health and safety, public health or environmental exposure as a result of a decreasing supply of bulk LRP and the consequent increasing use of aftermarket AVSR products and also the attrition from the Australia motor vehicle population of VSR sensitive vehicles. Details of the AVSR additive use-scenarios are presented in Table 2.

Table 2. Summary of the AVSR additive use scenarios

Present Use Scenario
Present AVSR additive LRP market: 2 500 ML for 2 500 000 vehicles.
10 % aftermarket: 90 % bulk AVSR additive market.
2004 Scenario
AVSR additive LRP market in 2004: 1 000 ML for 1 000 000 vehicles.
100 % aftermarket AVSR additive market.

The Present Use scenario was based upon import and manufacturing data provided by industry for the calendar year 2001. The calculation of 2,500,000 vehicles is based upon 2001 calendar year total AVSR additive import and manufacturing data and a petrol fill-up rate of 19.4 L/week/leaded vehicle (Appendix 1).

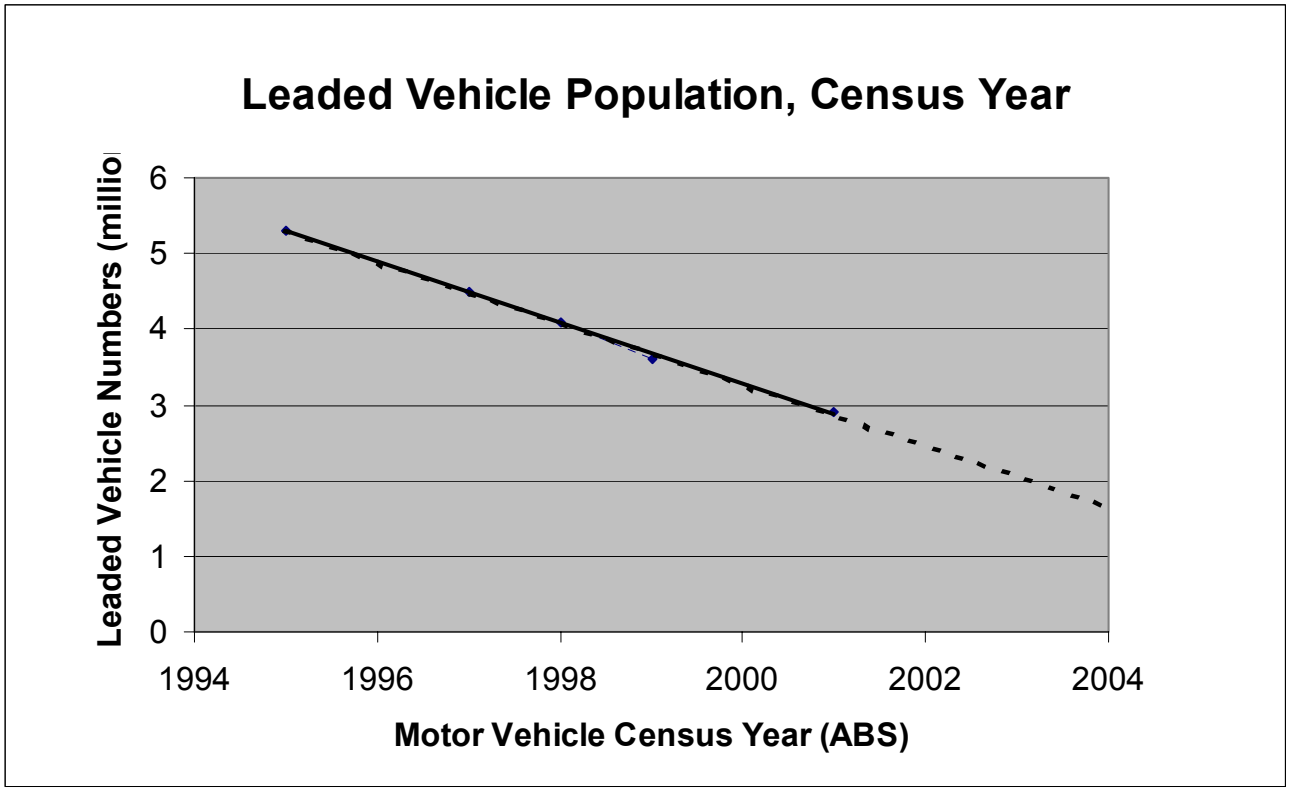
The calculated figure of 2 500 000 vehicles for the Present Use scenario (Table 2) is slightly lower than the ABS Motor Vehicle Census 31 March 2001 of 2 904 342 vehicles. This is attributed to the inclusion in the ABS data of all leaded vehicles irrespective of the requirement for or use of an AVSR additive. For example, not all vehicles requiring leaded petrol are VSR susceptible and require an AVSR additive. In 2000, more than 30 % of cars built before 1986 were estimated to run efficiently on normal unleaded petrol, with the remaining 70 % requiring an AVSR additive (Hill 2000).

The forecast 1 000 000 vehicles for the 2004 Scenario were derived from Australian Bureau of Statistics motor vehicle census data (Australian Bureau of Statistics, 1998, 2001). One million VSR susceptible vehicles equates to a demand for LRP of approximately 1 000 ML in 2004. A description of the calculation for LRP demand in 2004 is also given in Appendix 1. The calculated LRP demand of 1 000 ML in 2004 is slightly higher than the Australian Institute of Petroleum AIP sales forecast made in 1999 of nil to 800 ML (Australian Petroleum Gazette, 1999).

In 2010, a remaining niche market of VSR-sensitive older vehicles and engines requiring leaded petrol is expected (National Heritage Trust, 2000).

For the purposes of commercial-in-confidence and changes in market share, it has been assumed that only one AVSR additive has 100 % market share in each use scenario. Across the assessments of all AVSR additives, the same bulk to aftermarket share is assumed for each AVSR additive.

Figure 2. The Number of Vehicles Requiring Leaded or Lead-Replacement Petrol



(—) 1995-2000

(–·–·) 2001-2004 (Forecast)

(Australian Bureau of Statistics, 1998, 2001)

8. Exposure

The use of MMT as an AVSR agent additive for use in LRP involves relatively small releases of the compound to the environment (details in Section 8.1.2). In general, these releases are of a very diffuse nature since the motor fuel is used throughout Australia. Further, the compound is susceptible to abiotic (physico-chemical) degradation mechanisms, particularly through indirect photolysis, and consequently the MMT released to the environment is not expected to be persistent where sunlight is prevalent. However, leakages from underground fuel storage tanks (UST) where LRP is stored provide a potential process for point source releases of MMT into soils and groundwater and potentially other environmental media (eg. surface waters, air). In these environments, MMT may be persistent and may not readily degrade since photolysis is the main degradation route.

Most of the MMT is destroyed in the cylinders and exhaust trains of motors with production of a variety of inorganic salts and oxides of Mn. A proportion of this inorganic material is released to the atmosphere from the exhaust systems in association with small particles in the respirable size range. Certain adverse human health effects may be associated with inhaled Mn compounds (Davis, 1999; IPCS, 1999) and so the nature of the emitted particles is of importance.

The emissions of exhaust gases such as unburnt hydrocarbons, oxides of nitrogen and particulate material are also pertinent to the overall environmental effect of fuel combustion, and available data on the influence of MMT on these exhaust emissions is briefly reviewed.

8.1 Environmental exposure

Based on the current total AVSR additive LRP market (see Section 7) and assuming a dose rate of 72.6 mg/L of MMT, the amount of MMT in this market in Australia is expected to be less than 180 tonnes per year. The majority of this importation is for formulation of LRP. Imports of MMT solutions for aftermarket use are less than 10 tonnes per year.

8.1.1 Use of MMT as an AVSR Agent

Most of the MMT used in Australia will be imported in 10 000 L isotanks as a 62% solution in a mixed hydrocarbon solvent (HiTEC 3062) for blending into LRP at refineries. Significantly smaller quantities will be imported as solutions intended for formulation into aftermarket additives to be used as fuel supplements by individual vehicle owners. Small volumes of MMT are imported as pre-packaged additives.

The bulk HiTEC 3062 imported in isotanks will be transported to petrol refineries where metered quantities of HiTEC 3062 will be blended into fuel to give a final concentration of MMT of around 72.6 mg/L which corresponds to approximately 18 mg/L Mn.

Since the addition of AVSR agents is only required in LRP for older petrol vehicles that are expected to be progressively retired, the use of LRP is expected to decrease with a concomitant decrease in MMT usage.

8.1.2 Release of MMT

At petrol refineries, all pumping and metering of the MMT into blending tanks is conducted under automatic control. Isotanks, other storage tanks and pumping/control equipment associated with the transfer of the MMT solutions are installed in bunded areas to contain all leaks or spills. Due to these engineering controls very little release of MMT during routine blending operations is expected, and while the applicants provided no information on likely releases, previous experience in assessing other fuel additives suggest that these losses are unlikely to exceed 0.1% of the HiTEC 3062. Based on an annual import of 180 tonnes of MMT, and assuming all this is used at the refineries, an anticipated maximum annual release of no more than 180 kg would be apportioned between those fuel refineries producing LRP.

Any spillage resulting from the transfer activities would most likely be diverted to on site waste treatment plants where the organic materials would be recovered into a sludge which would be incinerated or possibly be placed into a landfill.

Spillage of petrol during transfer from the tanker trucks to underground storage at consumer petrol outlets or from bowsers to consumer vehicles would also result in small releases. While no definitive data were supplied, previous experience in the assessment of fuel additives indicates that losses are not expected to amount to more than 0.5% of petrol volume, equating to an (estimated maximum) annual release of around 900 kg.

Like other fuels, LRP is typically stored in underground storage tanks (USTs). USTs have a tendency to begin leaking over time, resulting in release of fuel to groundwater. USTs have been installed throughout Australia at terminals and refineries, fuel depots, service stations, and many private facilities and organisations have USTs for fuel storage.

Not all USTs leak, and not all leaks pose an unacceptable risk to the environment. However, many have and have required decommissioning and land remediation. The length of service of the tank is one of a number of factors increasing the risk of UST leakage. Other factors include the type of construction materials, presence of liners, fuel type, fittings/pipes and environmental conditions surrounding the UST. Major fuel suppliers generally have tank decommissioning and replacement programs and install leak detection equipment on their tanks to prevent leaks from occurring and to trigger pollution abatement procedures to minimise risks to the environment where leaks are detected.

A relatively small quantity of MMT is imported in 205 L drums for formulation into after market fuel additives containing < 10% w/w MMT. This will be sold through consumer outlets in plastic bottles up to 500 mL capacity to be added to the fuel in the vehicle tanks by the owners. While losses of MMT through formulation into the aftermarket products are expected to be small (not exceeding 0.1%), the use patterns of these products and the small package sizes indicate higher release rates from spillage and remnants of additive left in the bottles. No information on this issue was provided, but it is not unreasonable to assume that up to 5% of the formulation could be spilt or be left in the bottles after the majority of the contents has been added to the fuel,

equating to an annual release of approximately 500 kg. The emptied bottles are expected to be placed into landfill and due to the Australia-wide use of these additives, the associated release of MMT from disposal of the emptied bottles overall will be diffuse and at low levels.

All emptied isotanks used for importing the bulk HiTEC 3062 into Australia will be returned to the USA for refurbishment and refilling, so there will be no local release of residuals remaining in empty bulk shipment containers. Drums containing MMT for formulation of aftermarket additives are cleaned at drum recycling facilities and any residual MMT becomes incorporated into waste sludge. This is either placed into landfill or incinerated.

MMT has a much lower vapour pressure at 0.01 kPa (at 20°C) compared with approximately 70 kPa for the hydrocarbon constituents of petrol (Environment Australia, 2000). Consequently, spilt MMT is likely to be left on the concrete aprons of service stations following evaporation of the more volatile fuel components, and while it is possible that this residual MMT could be washed from the concrete aprons into stormwater drains or onto surrounding soil, the compound is not stable to light (Section 9.2.1), and in reality very little is expected to enter the water or soil compartments. In any case, since use of the petrol is expected to be nationwide these releases will be very diffuse and at low concentrations.

Experimental data indicate that at least 99.5% of the MMT present in the fuel is destroyed during combustion with a maximum of 0.5% of unconverted compound emitted with exhaust gases (Ter Haar et al., 1975). Assuming imports of 180 tonnes of MMT per annum, this equates to an annual release of 900 kg to the atmosphere, again in a very diffuse manner and at low concentrations. Due to rapid degradation of MMT through direct photolysis and/or reaction with atmospheric hydroxyl radicals (Section 8.2.1) the atmospheric concentration of un-degraded MMT is expected to be negligible. Some MMT may enter the atmospheric compartment through evaporation from fuel, but measurements of the concentration in air in the vicinity of filling stations suggest that these amounts are very small (Zayed et al., 1999a).

Overall, the blending of HiTEC 3062 into LRP and the transfer of fuel to consumer vehicles are expected to release a maximum of around 2000 kg/year of MMT, with about half this becoming associated with soil or possibly stormwater. However, this release will be nationwide and at low concentrations and the sensitivity of the compound to light and other degradation mechanisms precludes environmental persistence. The remainder would be released to the atmosphere and is expected to rapidly degrade.

8.1.3 Exhaust release of manganese compounds from combustion of MMT

Most of the MMT used each year will be destroyed during combustion in the engine cylinders, and recent data indicate that the Mn component is converted to a mixture of Mn oxides (e.g. Mn_3O_4) and salts such as Mn phosphate ($Mn_3[PO_4]_2$) and Mn sulphate ($MnSO_4$) – see for example Colmenares et al. (1999) and Ressler et al. (2000). A proportion of these inorganic derivatives are released in association with particulate material in the exhaust emissions. The chemical nature and physical form in which these Mn-containing decomposition products are released in engine exhaust gases is of importance and will be discussed in further detail in following subsections.

8.1.4 Emission rate and physical form of manganese in exhaust gases

Emission rates

While it could be expected that almost all the Mn added to the fuel would be emitted in the exhaust gases, recent monitoring of the Mn levels in vehicle exhaust gases suggests that this is not the case, with only part of the fuel Mn manifesting itself in the tailpipe emissions (Ardeleanu et al., 1999; Roos et al., 2000). The actual proportion of Mn emitted is very variable and appears to depend on various factors including the overall distance that the vehicle has been driven using MMT supplemented fuel. Also, for a given vehicle, the Mn emission rate is particularly sensitive to the driving conditions – for example urban versus highway driving (Ardeleanu et al., 1999). In dynamometer tests on 8 different vehicles which had previously been driven using MMT supplemented fuel between 3 700 km and 124 000 km, and then "driven" for the equivalent of approximately 17 km on the dynamometer equipment, Ardeleanu et al. (1999) determined Mn emission rates of between 4 and 41%. In all cases, more Mn was emitted when the vehicle was run under the conditions of an urban driving cycle (i.e. stop, idle and start) compared to highway driving conditions. When averaged over all vehicles, with each vehicle "driven" for approximately 17 miles (27.4 km) under each driving regime (i.e. urban and highway), the mean Mn emission rate was around 12.3%. However, there was a positive correlation between the rate of Mn emission and the overall length of service of the vehicles, with those cars that had accumulated the highest driving time prior to the test emitting higher exhaust concentrations of Mn. This correlation was stronger for the data collected during the urban driving cycle than the highway cycle.

Experimental determination of Mn exhaust emissions have been reported by other authors with emission rates determined between 6 and 45%. These earlier results have been summarised in the paper by Ardeleanu et al. (1999) and are in general agreement with the results of their own study. A second recent study also comprehensively summarised emission data from a number of tests using a variety of test vehicles with 4-8 cylinder motors, and concluded that the proportion of Mn emitted under open road (highway) conditions is 6-8% of the Mn contained in the MMT compared with 12-16% emitted during urban driving, with these results showing no dependence on motor size or type (Roos et al., 2000). This study also reported results from Lynam et al (1994) that approximately 27% of the Mn in the fuel of three light duty trucks was emitted in the exhaust after an accumulated 20,000 mile (32,000 km) urban driving test.

It should be noted that all these data indicate that Mn emissions from vehicle exhausts (with concomitant exposure potential through particulate inhalation) are expected to be significantly higher in areas of high traffic density where the vehicles are undergoing alternate periods of acceleration and braking – i.e. typically under conditions of urban driving during business hours.

The balance of the Mn introduced in the fuel (approximately 87.7%) is apparently accumulated in the engines or the exhaust systems of the vehicles (Ardeleanu et al., 1999). Similar conclusions were reached by Roos et al. (2000). While no details of this were discussed, the authors also indicated that some of the Mn becomes associated with the engine lubricating oil.

The work by Ardeleanu et al., (1999) appears to have been well designed and executed, and the average Mn exhaust emission figure of 12.3% of fuel Mn (as MMT) derived in

this work appears to be an appropriate emission figure. However, this may underestimate the Mn emission rate from particular vehicles under certain driving conditions, and due to the considerable spread in the available emission data (i.e. 4-41%), a figure of 20% will be used in the present report when estimating likely Mn emissions from vehicles using MMT supplemented fuel within Australia.

Since it is anticipated that annually around 180 tonnes of MMT (containing approximately 45.4 tonnes of Mn) may be used in petrol as an AVSR agent within Australia, and assuming 20% of the Mn is released in exhaust emissions, this equates to an annual release of approximately 9.1 tonnes of Mn to the atmosphere. These emissions will be in the form of inorganic Mn compounds associated with fine particulate matter, and while this release will be diffuse, higher atmospheric concentrations of the emitted particulates are expected in urban areas where traffic density is high.

Nature of particulate emissions in vehicle exhaust streams

The Mn released in exhaust emissions appears to be primarily associated with small particles composed of soot and unburnt hydrocarbons. It is recognised that most of the Mn is associated with particles of respirable size (< 2.5 μm), and in a recent study the distribution of Mn through the size fractions of exhaust particulate emissions was determined over the 0.056 to 3.1 μm size range (Roos et al., 2000). The exhaust particulate emissions from eight vehicles which had been subjected to the standard urban driving test regime over the equivalent of 40 000 miles (64 000 km) were collected and on average it was found that approximately 80% of the emitted Mn was associated within particles of diameter < 1.8 μm, with a peak in the 0.32-1.8 μm range which accounted for roughly 40% of the Mn.

The particle size distribution in engine exhausts from a number of vehicles was also determined using Scanning Electron Microscopy (SEM) to count the actual particle frequency in particular size ranges (Ardeleanu et al., 1999). This study found that more than 96% of the particulate matter was in the < 2.5 μm range with 86% having diameters < 1 μm and 39.2% having diameters < 0.5 μm. In an associated paper it was found that SEM studies indicated that the Mn-containing particles are amorphous, and the chemical forms of the Mn compounds present were also characterised (Zayed et al., 1999b). Another recent study also determined that 80-90% of the Mn emitted from vehicle exhausts was associated with particles < 2.5 μm (Colmenares et al., 1999).

Chemical speciation of emitted manganese

In early work on this topic, it was considered that all the Mn emitted in vehicle exhaust streams was in the form of oxides, primarily Mn_3O_4 (Ter Haar et al., 1975). This conclusion was reached apparently on the basis of X-ray diffraction data alone, and although no experimental details were given in the paper, the assertion that Mn_3O_4 is the major emitted product has since often been made in the literature, e.g. Abbott (1987).

However, a number of recent studies using sophisticated X-ray spectroscopy and other spectroscopic techniques have shown that while Mn_3O_4 is a minor component of exhaust emissions, most of the emitted Mn is in the form of Mn phosphate – either $Mn_3(PO_4)_2$ or possibly $Mn_5(PO_4)_2(H_2PO_4)_2$ – and Mn sulphate - $MnSO_4$. It is important to note that the oxidation state of the Mn in the exhaust emissions is essentially +2, with only the small amount of Mn_3O_4 having some Mn in higher oxidation states.

Electron spectroscopy together with L-edge X-ray absorption spectroscopy was used in an analysis of the Mn-containing particulate matter in motor vehicle exhausts, and it was concluded that Mn phosphates and Mn sulphate are the major Mn compounds present (Colmenares et al., 1999). Interestingly, these authors stated that Mn phosphate is the primary combustion product formed in the cylinders since these compounds have very high thermal stability, but as the exhaust gases cool some of this is converted to Mn sulphate – presumably through reaction with SO_2. In a separate study it was also found that Mn phosphates and Mn sulphate were the major Mn compounds present in the exhaust particulates with some Mn_3O_4 (Ressler et al 2000). The percentage of emitted Mn was 42.4% as Mn phosphate, 35.5% as Mn sulphate with the remainder (22.1%) as Mn_3O_4. Another study also found that the primary Mn species in exhaust particulates was a manganous phosphate together with some manganous sulphate (Zayed et al., 1999b). In an associated paper the authors also make the point that most of the Mn in the exhaust particles is water soluble (Ardeleanu et al., 1999). The presence of Mn sulphate, phosphate and oxide in exhaust emissions of vehicles fuelled with MMT containing petrol has also been confirmed in a more recent study using Mn K edge X-ray adsorption techniques (Molders et al., 2000).

In many of these studies on Mn speciation the source of the phosphorus was stated as being from zinc dialkyl dithiophosphate, which is a minor component of some lubricating oils (Colmenares et al., 1999, Ressler et al., 2000 and Molders et al., 2001).

8.1.5 Effect of MMT on exhaust gases (NOx, CO, CO_2, hydrocarbons, particulates) and onboard pollution control equipment

There have been several studies conducted to evaluate the impact of MMT in fuel on exhaust gases, and there remains a dispute at this point in time as to the effect of MMT on vehicle exhaust gases and fuel efficiency.

In an extensive comparative test of the exhaust gas emissions from 24 vehicles (3 examples of 8 different 1987 models) fuelled with petrol containing MMT at a level of 8.27 mg Mn/L, Lenane et al. (1994) found lower nitrogen oxides (NOx) and carbon monoxide (CO) emissions in the exhaust gases of these vehicles than in the emissions from a fleet of 24 similar vehicles fuelled with the baseline petrol alone. Each vehicle was run over a 75 000-mile (121 000 km) course according to a test protocol based on a USEPA test procedure, and exhaust emissions for hydrocarbons, NOx and CO were determined for each vehicle throughout the test. In total some 2500 emission tests were conducted, almost all of which were used in the subsequent analysis. The results averaged over the 121 000 km course are summarised in Table 3 and strongly indicate that the emissions of NOx and CO were significantly less for those vehicles fuelled with the petrol containing MMT, with reductions of up to 20% for NOx and around 6% for CO. However, the hydrocarbon emissions were approximately 6% higher in the emissions from the MMT supplemented vehicles, than for those running on the base petrol and once established (over the first 4000 miles of the test) this increase appeared to be fairly constant over the test duration. No further discussion on this result was offered in the paper.

Table 3. Emission data for MMT use (Lenane et al., 1994)

	MMT (8.27 mg Mn/L)	Base Petrol	% Change of MMT Fuelled Vehicles Relative to Base Petrol Fuelled Vehicles
NOx Emissions	0.43 (g/mile)	0.55 (g/mile)	- 20%
CO Emissions	3.08 (g/mile)	3.30 (g/mile)	-6%
Hydrocarbon Emissions	0.307 (g/mile)	0.289 (g/mile)	+6%

In another paper the authors describe the results of an extensive fleet test in which more than 100 vehicles accumulated over 8.5 million kilometres, and where monitoring of the exhaust emissions showed that the presence of MMT in the fuel (8.27 mg Mn/L) leads to an average reduction of 20% in NOx emissions and 5-6% reduction in CO emissions, which are similar to the results above (Roos et al., 1994). This study appears to be an extension of that discussed by Lenane et al. (1994).

In another recent publication the authors also indicate decreased emissions of hydrocarbons, NOx, CO and benzene from a vehicle fuelled with a "low aromatic" petrol containing MMT (equivalent to 18 mg/L Mn) compared with those from when the vehicle was fuelled with a base petrol which contained 3% more aromatics in order to give the fuel the same octane rating (Hollrah and Roos, 2000). While the bar charts presented in this paper indicated definite reductions in pollutant emissions from the MMT fuel, no actual figures were given. However, in respect of this, the lower emissions of hydrocarbons and benzenes can be directly attributable to the lower aromatic content of the MMT-containing fuel.

A very recent study released by the Alliance of Automobile Manufacturers, the Association of International Automobile Manufacturers and the Canadian Vehicle Manufacturer's Association of the effects of MMT on vehicle emissions (Alliance of Automobile Manufacturers; AAM, 2002) purports to show different results to those above. Vehicles were powered either with regular grade unleaded gasoline or similar gasoline plus MMT at a treat rate of 8.3 mg/L. Emissions were sampled directly from the engine via an engine-out sample tap and also at the tailpipe after exhaust system emissions control. This study reports increased emissions from MMT use (Table 4).

Table 4. Emission data for MMT use (AAM, 2002)

	% Change of MMT Fuelled Vehicles Relative to Base Petrol Fuelled Vehicles
NOx Emissions	Engine-out +1%
	Tailpipe –10%
CO Emissions	Engine-out +1%
	Tailpipe +6%
CO_2 Emissions	≤ 1%
Hydrocarbon Emissions	Engine-out +14%
	Tailpipe +13%

However, the above results of AAM (2002) themselves are the subject of subsequent critique (Roos et al, 2002a; Roos et al, 2002b). These disparate findings indicate

ongoing uncertainty regarding the actual effects of MMT on vehicle exhaust emission quality.

8.2 Fate

Although it is expected that little MMT will be released into the environment from its use as a fuel additive (Section 8.1.2) there are a number of relevant papers in the literature addressing the environmental fate of this compound, and these are briefly summarised in the following subsections. As indicated previously, most of the MMT will be destroyed during combustion of the fuel with release of inorganic Mn compounds (Mn phosphates, sulphates and oxides), with almost all the released Mn being associated with and incorporated in small particles.

8.2.1 Atmosphere

MMT is unstable to photochemical degradation in the atmosphere, with a reported atmospheric half-life of 8-18 seconds determined from direct measurement of the content of organic and inorganic Mn (apparently Mn oxides and Mn carbonates) down wind of a device designed to release MMT at a controlled rate (Ter Haar et al., 1975). However, the authors indicated that experimental uncertainties precluded a more precise determination, and while they endeavoured to obtain more accurate measurements through direct photolysis of an MMT/air mixture in a quartz tube under well-controlled conditions, this effort was confounded by deposition of photolysis products on the surface of the tube. Nevertheless, the conclusion from these experiments was that MMT decomposes quickly in the atmosphere and the decomposition mechanism was reported to involve both light (wavelength 340-440 nm) and atmospheric oxygen. However, a more recent study indicated that the first step in the degradation process involves adsorption of a visible-UV photon, which then weakens the bonds between Mn and the CO groups leading to ejection of a CO molecule (Vreugdenhil and Butler, 1998). Regardless of the detailed mechanism for photo-degradation, the ultimate degradation products would most likely be water, CO_2 and MnO_2.

A recent study determined the rate constant for reaction of atmospheric MMT for direct photolysis (with visible-UV light), with hydroxyl radicals and with ozone, and found these to be $(1.3\pm0.1) \times 10^{-2}$, $(1.1\pm0.3) \times 10^{-10}$ and $7.7\pm1.9 \times 10^{-18}$ cm^3 $molecule^{-1}$ sec^{-1} respectively. These rate constants provided half-lives of 80 sec, 1.3-2.5 hours and 14-72 hours for photolysis, reaction with OH radicals and ozone respectively (Wallington et al., 1999).

8.2.2 Water

In a determination of the ready biodegradation of MMT in a closed bottle test, while 46% degradation was observed after 15 days, no further degradation was observed after this time (Analytical Biochemistry Laboratories Inc., 1990). The test was conducted according to the protocols of OECD TG 301 D by incubating samples of the MMT (equivalent to 2 mg/L carbon) with sewage bacteria, and monitoring the residual biochemical oxygen demand (BOD) after 5, 15 and 28 days. The result of this test indicates that the compound cannot be classified as readily biodegradable.

The rate of photolytic decomposition of MMT in distilled water was determined and found to be characterised by a half-life of approximately 1 minute when a solution of

the compound was exposed to midday sunlight (Garrison et al., 1995). The authors remarked that this was similar to the result obtained by Ter Haar et al. for direct atmospheric photolysis. A separate part of this study also examined the possibility of degradation of MMT (in the dark) by direct hydrolysis, and found that this process was very slow if indeed it happens at all, with an estimated minimum half-life (at 25± 2°C) of 500 days (Garrison et al., 1995).

It is also of interest that these authors (Garrison et al., 1995) indicated that literature values for water solubility and the n-octanol/water partition coefficient were uncertain. Since these two physico-chemical parameters are important for the determination of environmental fate, these authors presented their own measured values and determined the water solubility at 25°C as 29±3 mg/L and Log K_{ow} as 3.7 (again at 25°C). This water solubility together with the vapour pressure of MMT ($1.1x10^{-2}$ kPa at 25°C - Ethyl Corporation) were used to calculate the Henrys Law Constant as 82 $Pa.m^3.mol^{-1}$, indicating that any MMT entering the water compartment (and not degraded through photolysis) would evaporate and would be destroyed through photolysis in the atmosphere (Lyman, Rheel and Rosenblatt, 1990).

8.2.3 Soils and sediments

The relatively large value for Log K_{ow} (3.7) indicates that MMT would have significant affinity for the organic component of soils and sediments, although the water solubility (29 mg/L) could bestow some mobility to any MMT that enters the soil/sediment compartment. However, in an investigation of the adsorption of MMT to a variety of soil types as well as to the important soil minerals alumina and silica, Vreugdenhil and Butler (1998) found that MMT binds to soils. The mechanism appears to be due to interaction of the carbonyl groups of MMT with silica or alumina surfaces of clay minerals rather than through association of the compound with the organic component of the soils. These authors concluded that MMT can adsorb to and become immobilised in soils and that this would reduce its potential for photo-degradation.

Degradation of MMT spiked into a natural anaerobic aqueous sediment was also studied by Garrison et al. (1995), and although the sediment was kept in the dark to prevent photolytic degradation, no measures were taken to either encourage or hinder biodegradation. In this experiment, the rate of disappearance of the MMT was very slow with data fitted to first order kinetics providing a degradation half-life of 0.5-1.5 years (Garrison et al., 1995).

8.2.4 Fate of inorganic compounds from combustion of MMT

Most of the MMT used as an AVSR in fuel within Australia will be combusted and as described above will be converted to inorganic Mn compounds (oxides, sulphate and phosphate), most of which apparently remain in the exhaust train. However, around 20% of these Mn compounds (approximately 9.1 tonnes) could be expected to be emitted with exhaust gases associated with very fine particles (< 2.5 μm). These small particles have very low quiescent air sedimentation velocities of around 1-2 cm/hour and less, and are consequently not expected to settle under gravity prior to being precipitated.

For example, the settling velocity of the particles in non-turbulent air can be estimated using Stokes law (CRC, 1977), which gives the settling velocity for a particle of radius r (cm) as:

$$V_{set} = 2gr2d/9\eta$$

where g is the acceleration of gravity, d is the density of the particle (gm/cm^3) and η is the viscosity of air, which is around 180 x 10^{-6} gm/cm-sec at 25°C. Taking r as 1.5 μm (= 1.5 x 10^{-4} cm), and assuming d is $2gm/cm^3$, Vset is calculated as 3.75 x 10^{-4} cm/sec (= 1.35 cm/h).

Consequently, the small particles emitted from the exhaust pipes are expected to remain suspended in the air for prolonged periods.

Ultimately these fine particles would be precipitated to the ground with rain or through becoming associated with larger particles with higher sedimentation velocities, and would become associated with soils and aquatic sediments. The inorganic Mn residues remaining in the engines and exhaust systems of vehicles would ultimately be placed into landfill with discarded cars and exhaust systems, or if these are recycled for metal recovery, the residues would become associated with slag and other products from the blast furnaces.

8.3 Environmental concentrations of MMT and manganese

8.3.1 MMT

The atmospheric concentration of MMT is expected to be very low due to the diffuse nature of the releases and the rapid photochemical decomposition of the compound. Recent data support this conclusion, and in a monitoring program in Montreal a mean atmospheric MMT concentration of only 5 ng/m^3 was determined compared with a mean total atmospheric Mn concentration of 103 ng/m^3 – see Section 8.3.2 – (Zayed et al., 1999a).

Although the chemical may be persistent in soils and sediments, except in the cases of gross spillage of HiTEC 3062 or petrol containing the chemical (eg. leakage from USTs or aboveground spillages), very little release to this compartment is likely and apart from areas in the vicinity of such spills and leaks no accumulation of MMT is likely in soils and groundwater.

In the immediate vicinity of leaking USTs, and at LRP spill sites, the MMT concentration may approximate that of MMT in LRP (eg. 72.6 mg/L). Site-specific conditions will determine the environmental concentration of MMT in groundwater with distance away from leaking UST sources. In groundwater, MMT is likely to be relatively persistent and its water solubility indicates it may be mobile in groundwater.

8.3.2 Manganese in the atmosphere in Canada

The most significant effect from the use of MMT in petrol is the generation and release of small respirable particles (< 2.5 μm in diameter) containing inorganic Mn, most of which is expected to be in the +2 oxidation state. Canada has been using MMT as a replacement for tetraethyl lead in fuel since 1976 and it may be expected that in general (i.e. not in the vicinity of steel works, battery factories or other possible point sources of Mn) atmospheric Mn could originate from combustion of MMT.

Several studies measuring atmospheric concentrations of Mn have been conducted in Canada. In a study of combustion products from MMT use is gasoline, Wood and

Egyed (1994) published ambient air Mn PM_{10} and $PM_{2.5}$ concentrations for a range of Canadian cities for 1986-1992 from data from the Environment Canada National Air Pollution Surveillance and the Ontario Ministry of the Environment and Energy air-monitoring network. Generally, levels of approximately 5-50 ng/m^3 were recorded with most cities having ambient air $PM_{2.5}$ concentrations in the range of 10-20 ng/m^3. Unsurprisingly, the highest levels were measured in cities with identifiable Mn emitting industries.

Loranger and Zayed (1997) measured the average air concentration of respirable Mn (PM5) in two urban sites in Montreal. Levels measured in a low traffic area (botanical gardens) were approximately 15 ng/m^3 whilst at a high traffic area (waterworks) levels were approximately 24 ng/m^3.

An exposure assessment of airborne Mn was conducted in Toronto from June 1995 to September 1996 by Pellizzari et al (1999) and further analysed by Crump (2000). In this study, personal exposure levels and static residential indoor and outdoor and ambient levels at fixed sites were measured. The mean concentration of $PM_{2.5}$ Mn measured at a ground level residential outdoors site was 9.7 ng/m^3. Levels measured at two other outdoor sites, one at ground level and one on the roof of a 4 storey building downwind from a major freeway averaged 17.1 and 11.4 ng/m^3 respectively. In contrast, $PM_{2.5}$ levels measured indoors at residential sites were lower with an average of 5.5 ng/m^3 (Crump 2000).

Another recent Canadian study determined the atmospheric concentrations of total Mn (Mn_T), respirable Mn (Mn_R) and MMT itself in five urban microenvironments in Montreal (Zayed et al., 1999a). In this study, the respirable Mn was taken as the Mn associated with particles with diameter < 5 μm, and measurements were made at a petrol station, an underground car park, the centre of Montreal, the vicinity of an expressway and the vicinity of an oil refinery. The results of a 36-hour sampling campaign (12 hours for each of three consecutive days) are summarised in Table 5. As indicated in Table 5, the figures for total atmospheric Mn at different microenvironments in Montreal are all of similar magnitude, with the petrol station site showing the highest air MMT levels.

Table 5. Outdoor monitoring levels of microenvironmental Mn and MMT in Montreal, Canada (Zayed et al; 1999a)

Sampling Location	Manganese concentrations (ng/m^3)		
	Mn_T	Mn_R	MMT
Petrol station	141	35	12
Mid city	103	44	7
Expressway vicinity	127	53	6
Refinery vicinity	66	18	2
Underground car park	78	30	0.4
MEAN	103	36	5

Mn_T = total atmospheric Mn;
Mn_R = respirable atmospheric Mn associated with particles with aerodynamic diameter < 5 μm.

Data have been collected between 1981 and 1996 for 10 cities in Ontario (Ontario Ministry of Environment and Energy, undated, cited in Roos et al., 2000). As an example of these data, the annual geometric mean total atmospheric Mn levels in

Toronto had a minimum of 24 ng/m^3 (1982, 1986) and a maximum of 44 ng/m^3 in 1990. Interestingly, the data for all 10 cities showed a steady increase in average atmospheric Mn levels from 1981 to 1990, and then a gradual decline in subsequent years.

8.3.3 Manganese in the atmosphere in Australia

Data are available for Mn content of atmospheric particulates for several Australian capital cities. In contrast to the Canadian data, recent surveys of the nature and chemical composition of atmospheric particles in 6 cities (Adelaide, Brisbane, Canberra, Launceston, Melbourne and Sydney) show much lower ambient Mn concentrations (Ayers et al., 1999). Except for Launceston, the Australian atmospheric Mn concentrations are roughly one third to one fifth of Mn_T and Mn_R levels measured in Montreal or $PM_{2.5}$ levels measured outdoors in Toronto. The relevant Australian data are summarised in Table 6.

Table 6. Mn content of particulate matter (PM) in the atmosphere of Australian cities (Ayers et al., 1999)

CITY (Sampling period)	Mn in PM_{10} (ng/m^3)	Mn in $PM_{2.5}$ (ng/m^3)
Adelaide (August, 1997)	10 ± 2.4	3.3 ± 2.0
Brisbane (Sept., Oct., Nov. 1996)	7 ± 4	3 ± 2
Canberra (May 1997)	5.5 ± 3.3	0.6 ± 0.9
Launceston (June, July 1997)	79 ± 102	24 ± 28
Melbourne (April 1997)	12 ± 1.7	3.3 ± 2.3
Sydney (August 1996)	13 ± 11	3.0 ± 3.3

In the above Australian data, the Mn determinations were for composite samples taken each day of sampling. The results tabulated are the mean and standard deviations of the individual daily Mn determinations. Samplers were operated on a 6-day cycle (ie. 24 hour samples taken each 6th day) over approximately a one to two month period in each city. In total, five 24 hour samples were taken for Sydney, Melbourne, Canberra and Adelaide and 8 samples for Brisbane and Launceston.

The Launceston Mn data are higher than for the other cities monitored. Whilst a large manganese-alloy smelter is located approximately 50 km to the northwest of Launceston, the contribution of this industry to Mn levels in Launceston is not known. Both the mean and standard deviation results are greater than those for other cities suggesting elevated atmospheric Mn levels only at certain periods.

It is also relevant to note that in general, most of the detected Mn is associated with the PM_{10} fraction. Since MMT was apparently not used in Australian petrol during the period of this study, the origin of the particulate Mn is probably in terrestrial dust. Although these data were collected over only one to two months in each city, in the absence of more comprehensive data the results may be used as a baseline reference set for any future monitoring of atmospheric Mn levels in Australia after introduction of MMT. However, there are some much more extensive published data on the nature and composition of airborne particulate matter in Sydney collected bi-weekly over the 7-year period January 1992 and December 1998 (Cohen, 1999). These data indicated the ambient particle-associated Mn concentration as 10 ± 15 ng/m^3 at Mascot in Sydney, with the Mn comprising approximately 0.1% of the weight of the particulate matter.

The level of atmospheric Mn resulting from emissions of Mn from the combustion of MMT-treated fuel obviously depends on the extent of fuel usage as well as meteorological conditions in the areas where the fuel is used. There are uncertainties associated with both these factors and in order to make some estimates of the likely level of atmospheric Mn resulting from future use of MMT in Australian fuel, it is necessary to make some assumptions based on the following considerations.

All estimates are made for Sydney with a population of 3 800 000, which comprises 20% of the total Australian population (19 000 000), and covers an area of approximately 1550 square kilometres. Two scenarios (see Section 7) are examined corresponding to:

Present use:

Where the total Australian import volume of MMT is constant at 180 tonnes per annum and this is added to petrol for use as an AVSR agent in lead replacement petrol, and

2004:

Where the import volume is reduced to 72.6 tonnes per annum to reflect the expected decreased demand for LRP (and hence for MMT as an AVSR agent) as the older vehicles are retired.

Since it is reasonable to assume that fuel use would roughly reflect population density, it will be assumed that 20% of all petrol in Australia would be used in Sydney.

An atmospheric box model approach has been used to estimate Mn air concentrations in MMT use areas. Implicit in the box model approach is that emissions are expected to behave as if they are released into a box with horizontal dimensions of the urban area (selected so that there is no significant influx of emissions into the box). Various assumptions can then be made about Mn accumulation and dispersion of Mn from the atmospheric box.

Two predicted environmental exposure concentrations for Mn in the air have been estimated resulting from the future use of MMT in Australian fuel. These include an average (AVE) estimate and a reasonable maximum exposure (RME) estimate.

For the calculation of the AVE air Mn concentration representing a long-term average exposure concentration, total yearly MMT use is used to calculate Mn emissions over each day with assumed daily clearance of accumulated air Mn from the atmospheric box.

The RME calculation represents the Mn concentration that may potentially accumulate in the air during weather period of consecutive windless days. This concentration is unlikely to be attained frequently. Information on consecutive windless days in Australian cities is not readily available as this is not a parameter normally monitored. As such, a conservative estimate of 3 consecutive windless days has been used in this assessment.

Present use scenario

RME Concentration for Mn

It is estimated that the LRP market for 2001 was 2500 ML (see Section 7). Assuming MMT has 100% market share and is dosed at a rate of 72.6 mg/L, this equates to an importation of 180 tonnes per annum of MMT. If 20% of this were to be used in Sydney, this is equivalent to approximately 500 ML of MMT-treated LRP containing approximately 36 tonnes of MMT (9.1 tonnes of Mn). Combustion of the MMT will lead to formation of Mn sulphate, phosphate and oxide containing this Mn. Although most of these Mn compounds are expected to remain in the vehicle exhaust systems, it is likely that up to 20% would be released (see section on emission rates in 8.1.4.1), which corresponds to an annual release of approximately 1.8 tonnes of Mn into the Sydney atmosphere. As indicated in Section 8.1.4, this released Mn is expected to be in the form of inorganic Mn compounds contained as components of fine particles, which are not expected to immediately precipitate, and may remain suspended in the atmosphere for prolonged periods.

It is readily shown that the effective height of the air column over a particular area is 6.15 km (see for example Connell and Hawker, 1986), and so this 1.8 tonnes of Mn would be released into an atmospheric volume of 1550 km^2 x 6.15 cubic kilometres, or approximately 10^{13} m^3. However, the assumption that the Mn particles would be homogeneously distributed throughout a 6.15 km air column is unrealistic. A more realistic assumption is to assume that the particles are only distributed in the lowest 615 metres (ie. 10^{12} m^3).

In order to go any further it is now necessary to make some simplifying assumptions, and while these are not entirely realistic they nevertheless allow for a first approximation to the atmospheric Mn level. If it is assumed that the air column is perfectly static, that the particulate matter is homogeneously distributed through the air column volume and that none is precipitated with rain or through other mechanisms, then after one year the atmospheric Mn level is estimated as 1.8 x 10^{15} nanograms/10^{12} m^3 = 1800 ng/m^3.

The assumptions made above are considered unrealistic in that no dispersion through wind or by rain is considered. If it is assumed the particles remained suspended for an average of 3 days without removal, as may potentially occur, albeit rarely following 3 consecutive windless days, then the atmospheric RME concentration could be as high as 15 ng/m^3 (see Table 7).

AVE Concentration for Mn

An AVE Mn concentration in air at ground-level may be estimated taking into account losses due to wind dispersion out of the urban area. The average concentration at any one time within the atmospheric box may be estimated as the influx rate minus the emission rate from the atmosphere box.

An influx of 1.8 x 10^{15} nanograms Mn/year (4.9 x 10^{12} ng Mn/day) has been estimated above. Emitted into an air volume of 10^{12} m^3 each day, an average daily air concentration of 4.9 ng/m^3 has been estimated using this model (see Table 7).

2004 Scenario

This scenario assumes bulk sales of LRP have declined to 1000 ML as outlined in the Use Section. With a treat rate of 72.6 mg/L this results in 72.6 tonnes of MMT (18.3 tonnes Mn). Assuming 20% (14.5 tonnes MMT/3.7 tonnes Mn) are released to the Sydney atmosphere, the calculations and assumptions for this scenario are identical to the above. Therefore, with a 20% release rate, 0.74 tonnes of Mn can be expected to be released into the air column. The results of these estimations are summarised in Table 7.

Due to the complexities implied by uncertainties as to the use rate of MMT and the prevailing atmospheric conditions in particular areas, these estimates of the atmospheric Mn associated with particulate matter originating from exhaust emissions should be treated as indicative only. The level of particulate matter in the atmosphere would be very dependent on factors such as rain and wind, and it is likely that ambient and prior weather conditions would impact on any particular daily measurement.

Table 7. Estimated average and reasonable maximum atmospheric Mn levels in Sydney – various MMT use scenarios and conditions

	Atmospheric Dispersion [a]		
	Nil [b]	AVE [c]	RME [d]
Present Use			
36 tonnes of MMT used as AVSR in Sydney fuel.	1800 ng/m^3	4.9 ng/m^3	15 ng/m^3
2004			
14.5 tonnes of MMT used as AVSR in Sydney fuel	725 ng/m^3	2.0 ng/m^3	6.0 ng/m^3

a. Air column volume of 10^{12} m^3 (ie. 615 m high x 1550x10^6 m^2).
b. No dispersion assumed throughout year (unrealistic).
c. AVE (Long-term Average), assumes wind dispersion with daily clearance of atmospheric box.
d. RME (Reasonable Maximum Exposure), assumes quiescent conditions for 3 days.

8.3.4 Release of Mn to the water compartment

If, as in the Present Use scenario above, the use of MMT were restricted to its addition to LRP at a concentration of 72.6 mg/L (corresponding to 18 mg/L of Mn), then annually approximately 1.8 tonnes of Mn would be released into the Sydney atmosphere.

The majority of the released Mn will be in the +2 valence state in the form of either Mn sulphate or Mn phosphate. Eventually, the particulate material will precipitate to the surface where the soluble nature of both $MnSO_4$ and $Mn_3(PO_4)_2$ means that the Mn would be leached from the particles and enter the water compartment. If it is assumed that Sydney with a land area of approximately 1550 km^2 receives an average annual rain fall of 1 metre, then it is possible to estimate the worst case concentration of Mn in

storm water, assuming static atmospheric conditions as 1.8 x 10^6 (grams)/ 1550 x 10^6 x 1 (cubic metres) = 0.0012 mg/L. This is a small concentration and comparable with the concentration of Mn in seawater, which is stated as 0.001-0.01 mg/L (CRC, 1977). This estimate does not take into account wind dispersion of Mn from the atmosphere above the urban area, which would reduce the estimated concentration.

8.4 Occupational exposure to MMT

Occupational exposure to MMT is possible during import, transport and handling of imported MMT solutions and also during transport and handling of petrol and petrol additives containing MMT.

MMT is imported in bulk as a 62% solution in a mixed hydrocarbon solvent (HiTEC 3062) in isotanks of 10,000L capacity and transported by road or rail to several fuel refineries for addition to fuel. MMT is also imported in 205L steel drums and less commonly in 450 L CYL-type steel cylinders as 60% or 62% solutions and transported by road or rail to a small number of third party formulators for blending and packaging into aftermarket fuel additives. Most of the blending and packaging is conducted by two formulators. MMT is also imported in preformulated, prepackaged fuel additives and with locally formulated fuel additives and bulk LRP are distributed to numerous petrol stations and retail outlets.

8.4.1 Bulk fuel and fuel additive blending at refineries and formulators

Isotanks, steel drums and cylinders transported to fuel refineries or third party formulators by road or rail will remain unopened prior to blending operations. Consequently, in the absence of accidental puncture of import containers, exposure of import and transport workers to MMT is not expected.

At refineries, isotainers are positioned by crane in a bunded area. A flexible hose is then connected manually to the lower delivery flange of the isotank through which the MMT solution is metered directly to the blending manifold at the designated LRP finished product tank or firstly pumped to a storage tank prior to metering to the LRP finished product tank. To facilitate emptying, the isotank is pressurised with nitrogen. All pumping and metering of the MMT solution in the fuel blending operation are conducted under automatic control in enclosed transfer systems. Bulk LRP containing MMT is then pumped from the finished product tank via enclosed lines to terminals or directly to road tankers.

At the refinery or terminals, blended LRP containing MMT at < 0.01% is pumped to road tankers for transport to petrol retailers. Transfer involves a manual connection and disconnection of a flexible transfer line between the LRP finished product tank or terminal manifold and lower fill port of the road tanker.

A total of 10-20 personnel are involved in the import, storage and blending of the MMT solution. At each site, fewer than 5 personnel are involved directly in the unloading of the MMT solution from isotanks and these are engaged in these operations typically for 10 -15 minutes, 4 times per year.

At third party formulators, drums or cylinders of MMT concentrate are typically opened in bunded areas and emptied by manually connecting a flexible hose to the dip leg located at the top of the cylinder or manually inserting a spear through a bung at the

top of the 205 L drum. Cylinders may be pressurised with nitrogen to facilitate emptying. MMT is then pumped to a closed mixing vessel or to storage. After emptying drums and cylinders, residual MMT is captured typically by adding petroleum diluent by pump, manually swirling the containers and pumping the residue to the mixing vessel. After mixing, the formulated fuel additive containing MMT at < 10% w/w is gravity fed to and packed in sealed plastic bottles of up to 500 mL capacity.

Typically at each formulator, up to 3 warehouse personnel and up to 3 blending and 3 filling personnel handle imported MMT solutions in imported drums, cylinders or filled end-use plastic bottles. Blending activities typically occur for 2 - 8 hours/day for 2 –12 days/year. Filling/packing activities may occur for up 15 hours/day for 2 days/year.

Quality analysis personnel test blended LRP and aftermarket additives and handle samples during laboratory analysis. Sampling is conducted manually on a per batch basis from several stopcocks located at various depths on the outside of the LRP finished product tank and also from the additive blending tank. Quality analysis personnel conduct sampling and laboratory analysis once per week for LRP blending and approximately 4 days per year for additive blending.

The main routes of exposure of workers to MMT are dermal and ocular from slops and spills during manipulation of transfer lines and spears and also sampling and laboratory analysis. Despite the possibility of gas leakage if pressurised transfer is used, the low vapour pressure of MMT (0.01 kPa at 20°C) renders inhalation exposure of workers unlikely. Once in storage or blending tanks, exposure of refinery or formulation workers during addition to bulk fuel or formulation of aftermarket additives would not be envisaged given the enclosed, automatic nature of the blending/filling processes.

8.4.2 Petrol stations and maintenance workshops

At petrol stations, LRP will be transferred from road tankers to underground storage tanks. In a similar fashion to unloading of imported MMT solution, transfer requires that tanker drivers manually connect and disconnect flexible tansfer lines between the tanker and storage tank. During this process, dermal and ocular exposure to diluted MMT is possible from slops and spills. Notwithstanding the possible fitment of vapour recovery systems, although contact with fuel vapours is also possible during transfer, the low vapour pressure of MMT renders inhalation exposure of tanker drivers to MMT unlikely. Potential exposure of drivers may occur frequently during the day in metropolitan areas with numerous offloads and less frequently during tanker deliveries to regional areas.

Similar exposure, mainly dermal, may be envisaged for petrol station workers during dip measurement of underground tanks. Typically, dipping occurs for up to 10 minutes, once per week. Automechanics at petrol stations and maintenance workshops may be exposed also to diluted MMT in LRP and in aftermarket additives during maintenance of automotive fuel systems. The extent of exposure during these activities is likely to be highly variable.

8.5 Occupational exposure to manganese from MMT use

The combustion of MMT produces particulates containing Mn, with a majority of particulates in the respirable size range. Several classes of workers are exposed

potentially to Mn in occupational settings not via exposure to MMT but to particulates from automotive exhaust.

In addition to exposure to MMT, petrol station and maintenance workers may experience occupational inhalation exposure to Mn particulates in exhaust emissions. The exposure of petrol station attendants is likely to be highly variable depending on the required duties – purely retail versus petrol pumping, the level of customer traffic, the separation of retail from service areas and the vehicle fleet i.e. cars using LRP versus unleaded fuel.

Automechanics may be particularly exposed to Mn particulates when servicing operating automotive engines in poorly ventilated workshops.

Attendants, security and other personnel who work in enclosed car parks such as underground parking stations also have a potential for inhalation exposure to particulates containing Mn during routine duties. Exposure to MMT for these workers is unlikely given the enclosed nature of automotive petrol systems, low vapour pressure of MMT and expected very low levels of MMT emissions in exhaust. Like service station workers, exposure during the working day is likely to be highly variable and dependent on the level of and proximity to customer traffic and the effectiveness of ventilation of the enclosed parking station.

Professional drivers such as taxi and truck operators and road maintenance workers may also be exposed to Mn from inhalation of particulates from automotive exhaust. Again, exposure is likely to be highly variable and dependent on traffic, particulate filtering within automotive airconditioning systems and, in the case of road workers, whether work is on new, uncommissioned or light duty roads or on heavily trafficked arterial roads repaired whilst in service.

8.5.1 Exposure data and estimates

Few data are available regarding personal exposure levels to MMT or to Mn as a result of the use of MMT in fuels. The following limited data for personal 8-hour Time-Weighted-Average occupational exposures (TWA8) to MMT (as Mn) have been submitted for Ethyl facilities in USA, Canada and England for the period 1987 to 1991 (Albemarle Corporation 1994):

Manufacturing	16-1600 (arithmetic mean 200) $\mu g/m^3$ (n = 12)
Laboratory Analysis	< 40 - < 200 $\mu g/m^3$ (n = 3)
Shipping	< 100 $\mu g/m^3$ (n = 2)

Anecdotal exposure data for refinery handling have also been supplied by Ethyl Corporation. These are based on data provided by Ethyl Corporation customers:

Refinery Handling	< 10 $\mu g/m^3$ (TWA8)

References, location and details of the extent and type of sampling for these refinery handling data are not available.

No information is available regarding Australian refinery exposures or occupational exposure during formulation of aftermarket fuel additives. No MMT manufacture occurs presently in Australia and so these manufacturing, laboratory analysis and

shipping data are not directly comparable to those of local occupational environments. However, it is likely that local exposures to MMT would be much lower than those associated with overseas manufacturing because Australian occupational use scenarios involve handling MMT in diluted forms on a much more intermittent basis. Similarly, exposures associated with local refinery handling are expected to be less than those overseas due to the more limited use of MMT.

No quantitative data are available regarding personal exposures to or environmental levels of MMT in workplaces in Australia. However, some limited overseas non-manufacturing data are available. Zayed et al. (1999a) measured airborne MMT (measured as Mn) and total and respirable (< 5 μm) Mn levels in selected occupational microenvironments in Montreal. Stationary sampling was conducted over 36 hours and six samples were collected at each site (outlined in Environmental Concentrations Section 8.3.2). The highest levels of both MMT and total Mn were found at petrol stations (MMT, total and respirable Mn were 12, 141 and 35 ng/m^3 respectively) whilst the highest levels of respirable Mn were found in the vicinity of an expressway (MMT, total and respirable Mn were 6, 127 and 53 ng/m^3 respectively). Lower levels of MMT, total and respirable Mn were found in the underground car park (0.4, 78 and 30 ng/m^3 respectively).

It should be emphasised that these are environmental monitoring data and their relevance to personal occupational exposures is unclear.

In a limited personal occupational exposure study, Zayed et al. (1994) monitored the exposure of garage mechanics and taxi drivers to airborne Mn (> 0.8 μm) using personal breathing zone air samplers. Ten garage mechanics from the same garage and ten taxi drivers were assessed for 5 consecutive working days and for 2 days off work. For both worker groups, exposure levels were significantly higher at work compared to off-work (Table 8).

Table 8. Personal total manganese exposure of Montreal taxi drivers and garage mechanics (Zayed et al., 1994)

	Off-Work		At Work	
	Mean Exposure (ng/m^3)	Number of Samples	Mean Exposure (ng/m^3)	Number of Samples
Taxi drivers (total)	7	19	24	48
Garage Mechanics (total)	11	8	250	49
Open Workshops	-		152	nr
Closed Workshops	-		314	nr

nr – not revealed

Garage mechanics showed very high levels of exposure compared to taxi drivers (mean Mn exposures of 250 ng/m^3 versus 24 ng/m^3 respectively). Moreover, garage exposures varied significantly depending upon whether garage doors were open or closed. Highest levels were measured in closed garages (mean Mn exposure of 314 ng/m^3), supporting the notion that automobiles, whether as a result of the inhalation of exhaust or generation of airborne particulates from servicing Mn-contaminated components, are the source of Mn.

A further similar study of personal occupational exposures to Mn from automotive use of MMT was conducted by Sierra et al. (1995) where personal exposures of 35 garage mechanics to airborne Mn (> 0.8 μm) were compared to those of 30 nonautomotive workers. In this study, garage doors were reported "mostly" closed and exhaust gases were not always vented to the outside. The average Mn exposure for garage mechanics at work was even higher than the previous study with Mn exposures at 448 ng/m^3 versus 250 ng/m^3 respectively (Table 9).

Table 9. Personal total manganese exposure of Montreal garage mechanics and non-automotive workers (Sierra et al., 1995)

	Off-Work		At Work	
	Mean Exposure (ng/m^3)	Number of Samples	Mean Exposure (ng/m^3)	Number of Samples
Non-automotive workers	8	60	44	143
Garage Mechanics	12	59	448	160

Occupational exposure of mechanics was 10 times higher than that of non-automotive workers at 44 ng/m^3. Levels of other metallic particulates were also elevated within the garage environment and the exact contribution to Mn exposures from the use of MMT could not be determined. However, approximately 60 % of Mn particulates were < 1.5

μm and approximately 37 % were < 0.93μm. Given that the majority of particulates from MMT combustion are < 1 μm (Ardeleanu et al., 1999; Roos et al., 2000), this suggests that only up to one third of Mn particulates in the workshop resulted from MMT combustion.

Occupational exposures to total (> 0.8μm) and respirable (< 5 μm) Mn particulates in Canada were also studied by Zayed et al. (1996) for 9 taxi drivers and 20 office workers in Toronto. For office workers, the average total and respirable Mn levels measured over 7 days, 24 hours per day were 12 ng/m^3 and 10 ng/m^3 respectively. Levels were significantly higher for taxi drivers at 28 ng/m^3 and 15 ng/m^3 respectively. The average fraction of respirable to total Mn was 76-90%.

Personal exposures to airborne Mn were studied in London taxi drivers and office workers in 1995 and 1996 by Pfeifer, Harrison and Lynam (1999) prior to and following the introduction of MMT as a diesel fuel additive. Personal exposures to Mn in total suspended particulates did not increase as a result of MMT introduction. For $PM_{2.5}$ Mn particulates, there were no significant differences between exposures of taxi drivers and non-underground railway commuting office workers. Interestingly, underground railway commuting office workers showed significantly higher Mn exposures.

The extrapolation of these data to Australian occupational settings should be conducted with extreme caution. As indicated in Section 8.3, background atmospheric levels of Mn are an order of magnitude lower in Australia compared to Canada and this is attributable at least in part to the more widespread, multifunctional use of MMT in Canada. Also, no data are available to compare overseas and local work practices and these may be subject significantly to local conditions. For example, autorepair, which is identified in the above studies as a critical occupation with respect to exposure to atmospheric Mn, is likely to occur more frequently within closed workshops with greater contact with cars using MMT-supplemented fuels in Canada compared to Australia. Finally, these Canadian studies are only of small duration (1-2 weeks) with small sample sizes and the representativeness of the sampled populations cannot be assessed.

Notwithstanding study uncertainties, these overseas microenvironmental and personal exposure data suggest that automotive maintenance workshops are potential sites of high airborne particulate Mn levels and that garage mechanics may experience relatively high exposures to Mn from MMT use. However, given the potential differences in occupational conditions and extent of use of MMT, it is likely that local occupational exposures to Mn would be significantly less than those of Canada.

8.6 Public exposure

8.6.1 Consumer exposure

Exposure to MMT is likely to occur as a result of contact during refuelling vehicles or adding aftermarket product to petrol tanks, contact during the use of LRP as a solvent or cleaner or as a result of substance abuse (petrol sniffing). In the cases of deliberate exposure to LRP petrol, the low concentrations of MMT in petrol and low vapour pressure will probably limit the extent of exposure to MMT and exposure to the petroleum solvent is likely to be of greater potential concern. Since they contain higher

concentrations of MMT, exposure to aftermarket products is likely to be of greater potential concern.

Accidental dermal and possibly ocular exposure to MMT (and Mn) in petrol is possible when refuelling vehicles and when adding aftermarket products to fuel tanks. The concentration of MMT in LRP is about 72.6 mg/L (18 mg/L Mn). Assuming, as a worst case, a person spills 200 mL of LRP onto the skin then they would be exposed to a dermal dose of approximately 208 µg/kg bw of MMT (51 µg/kg bw Mn). Assuming that 100 mL of an aftermarket product containing, for example, 7% v/v (approximately 10% w/w) MMT was spilt onto the skin, then a person would be exposed to a dermal dose of approximately 130 mg/kg bw MMT (32.5 mg/kg bw Mn). The amounts to which people will be dermally exposed will be highly variable and lower than the above worstcase estimates.

Accidental ocular exposure as a result of splashes of LRP and/or aftermarket products is also likely to occur only infrequently and involve very small amounts of MMT (Mn).

Ingestion exposure is generally unlikely, but, if aftermarket products are stored in or around the home, accidental ingestion might occur in young children. Children between one and a quarter and three and a half years of age can swallow approximately 4.5 mL of liquid (Gosselin et al., 1976). A child (10kg) ingesting one mL of a product containing 7% v/v (10% w/w) would receive an oral dose of 11.8 mg/kg bw MMT (2.9 mg/kg bw Mn). However, aftermarket products are likely to be stored in garages and the information supplied indicates that such products are packaged in containers fitted with child resistant closures.

Accidental ingestion of MMT in LRP could occur when syphoning petrol. Accidental ingestion by a child could occur also if MMT containing LRP is stored in inappropriate containers in or around the home environment. Australian National Hospital Morbidity Data show approximately 133 hospital discharges/year between 1998 and 2000 were associated with the toxic effects of petroleum products (AIHW, 2002). Victorian data show that there were 75 hospital admissions between 1987 to 1994 involving children below five years of age that were poisoned by petroleum fuels and cleaners including kerosene. Data from a selection of Victorian hospitals showed that there were 16 emergency department presentations between 1989 and 1995 involving children below 5 years of age ingesting petrol. Three of the 16 had siphoned petrol from a car or lawn mower and two had drunk petrol from drink bottles (Ashby and Routely, 1996).

Although no data was available on the amounts of petrol ingested, it is likely that only small amounts of LRP would be accidentally ingested. Data collected by Watson et. al (1983) show that the average volume of a swallow (of tap water) for a child up to 5 years of age is between approximately 1 and 7 mL and for a person between 5 and 18 years of age is between 2 and about 30mL. Given these low amounts of LRP and the low concentrations of MMT in LRP, ingestion would involve potentially only very small amounts of MMT and with the solvent nature of petroleum products, repeated ingestion or ingestion of larger amounts e.g. 100mL or more is unlikely.

8.6.2 Indirect exposure via environment

Exposure to MMT

As outlined in Section 8.3.1, the atmospheric concentration of MMT is likely to be very low due to the diffuse nature of releases and the rapid photochemical decomposition of

the compound. Since there appears to be no Australian data on atmospheric concentrations of MMT, no estimate of inhalation exposure can be made that is directly relevant to Australian conditions. However, the mean atmospheric concentration of MMT of 5 ng/m^3 measured in Montreal (Zayed, 1999a) can be used as an example to demonstrate that the lifetime average daily inhalation dose of MMT is likely to be low (1.4 ng/kg bw/day for a 70 kg adult).

Inhalation exposure to MMT might be higher in microenvironments where the air concentration is likely to be higher. e.g. in a service station. Although MMT has a low vapour pressure (0.01 kPa at 20^{o}C), some inhalation exposure to MMT is possible when refuelling vehicles. No Australian data are available for the air concentration of MMT in service stations. Zayed et al. (1999) measured the air concentration of MMT in Canadian service stations as 12 ng/m^3. Assuming that the time spent refuelling is 6 minutes/day (USEPA, 1997), an adult inhalation rate of 0.8 m^3/hour, body weight of 70 kg, average lifespan of 75 years, all vapour inhaled is absorbed and refuelling occurs once/week, then the lifetime average daily inhalation exposure to MMT during refuelling is very low, as estimated below:

Lifetime average daily dose of MMT

= (12 ng/m^3 x 0.8 m^3/hr x 0.1hr/day x 3900 days)/(27375 days x 70kg)

= 0.002 ng/kg bw/day.

Section 8.3.1 states that very little release of MMT is expected in the soil compartment of the environment, unless there is a gross spill of HiTEC 3062. Therefore it is likely that public exposure to MMT as a result of soil contamination is likely to be very low.

Similarly, public exposure to MMT as a result of water contamination is also likely to be very low, since, as outlined in Section 8.2.2, any MMT that does enter the water compartment of the environment would be subject to photolysis and evaporation.

No information is available on the possible contamination of food with MMT, however, public exposure via MMT contaminated food is likely to be very low, since the expected low environmental concentrations of MMT should not result in significant contamination of foodstuff with MMT.

Exposure to manganese via air

Although most MMT will be destroyed during combustion in the engine, a proportion of exhaust emissions will contain MMT combustion products in the form of inorganic Mn compounds. These combustion products have the potential to increase public exposure to airborne Mn. Using atmospheric $PM_{2.5}$ Mn concentrations from the most realistic atmospheric dispersion model (Section 8.3.3), an estimate can be made for the potential public inhalation exposure to Mn according to the two use scenarios, firstly where LRP market share is maintained at present levels and use patterns (Present Use scenario) and then when it is reduced to aftermarket use only (2004 scenario).

The mean air concentration estimated for Sydney will be used as a basis for estimating lifetime exposure of the Australian public. Since most of the Mn-containing combustion products of MMT are associated with particles of 2.5 μm or smaller and the $PM_{2.5}$ fraction of air particulate matter is of most toxicological significance, the $PM_{2.5}$ Mn concentration for Sydney of 3 ng/m^3 (Table 6) is used as a "baseline" level of exposure. The estimated atmospheric Mn levels given under the Present Use scenario

and 2004 scenario (Section 8.3.3) represent the estimated increase in air Mn concentrations and exposures attributable to MMT combustion when MMT is used as an AVSR. As a worst-case, it could be assumed that indoor and outdoor air concentrations of respirable Mn are the same and therefore people will be exposed to ambient air Mn for 24 hours/day. The following exposure estimates also assume an average respiration rate of 20 m^3/day for a 70 kg adult and assume a 60% pulmonary deposition for inhaled particles in the size range expected from MMT combustion (McClellan and Henderson, 1989; USEPA 1994d). The calculation of dose assumes 100% absorption.

Table 10. Lifetime average estimated human exposure to Mn in ambient air

Scenario	Average Ambient Air Concentration ($PM_{2.5}$ Mn ng/m^3)	Human Exposure (ng/day)	Human Dose (ng/kg bw/day)
Baseline ($PM_{2.5}$ Sydney)	3	36	0.51
Increase due to MMT – Present Use: Maintained LRP Market Share	4.9	58.8	0.84
Increase due to MMT - 2004: Decreased LRP Market Share	2	24	0.34

These estimated potential exposures to respirable Mn are lower than those reported for other countries where MMT is used widely. Based on the mean ambient air concentration of respirable Mn particulates (36 ng/m^3) reported by Zayed et al. (1999a), average intakes of respirable Mn for Montreal can be calculated at 720 ng/day. A similar calculation can be made based on mean outdoors $PM_{2.5}$ Mn levels of up to 17.1 ng/m^3 measured in Toronto by Pellizzari et al (1999). In this case, average intakes of respirable Mn total 352 ng/day. This study also reported Mn levels from personal air monitoring. Across 925 subjects, a mean $PM_{2.5}$ Mn level of 14 ng/m^3 (median 8.5 ng/m^3) was derived giving a daily exposure derived from personal exposure data of 280 ng/day.

Loranger and Zayed (1997) estimated the average air concentration of respirable Mn in a low traffic urban site (botanical gardens, approx 15 ng/m^3) in Montreal and from this data a daily exposure of approximately 300 ng/day can be calculated. Ambient air $PM_{2.5}$ concentrations of approximately 5-50 ng/m^3 were reported by Wood and Egyed (1994) in a range of Canadian cities with most having ambient air $PM_{2.5}$ concentrations in the range of 10-20 ng/m^3. From these data, mean inhalation intakes can be estimated at 200-400 ng/day for Canadian urban centres without Mn emitting industries.

Data from ambient air $PM_{2.5}$ Mn monitoring in Riverside California in 1990 (Pellizzari et al., 1992 as cited in USEPA 1994) showed a 24 h median concentration of approximately 10 ng/m^3 from which exposures of about 200 ng/day can be calculated.

It should be noted that the ambient air values reported overseas include Mn due to MMT combustion as well as other airborne sources such as windblown dusts. It is very difficult to determine the proportion of ambient air Mn that is directly attributable to MMT combustion. Based on the data of Lyons et al. (1993) the USEPA (1994c) concluded that approximately 75% of the $PM_{2.5}$ Mn collected in the Los Angeles basin

was from automotive sources. Using dispersion modelling estimates, Loranger and Zayed (1997) predicted the contribution of automotive sources to background Mn concentrations as 50% at 25m from a Canadian highway and only 8% at 250m from the road. However, based on a comparison of respirable Mn concentrations and MMT use in Canadian urban centres, Wood and Egyed (1994) concluded that MMT use did not contribute significantly to ambient air respirable Mn concentrations.

Crump (2000) in analysing Mn exposures in Toronto also concluded that most of personal Mn exposure in this city was from non-MMT sources. Evidence cited for this was a negative correlation between MMT usage and $PM_{2.5}$ Mn levels and a reduction of average exposures by 40% by eliminating study participants with Mn exposures from known non-MMT sources together with the existence of multiple non-MMT sources for the remaining Mn exposure of study participants.

Ambient air concentrations of Mn, and hence exposures, are also expected to vary significantly dependant upon the environment in which people live. People living in rural areas would be expected to have lower exposure than people living in cities and those living in areas affected by large Mn emitting industries could be expected to have the highest levels of exposure. For example, people living in Canberra would be expected to have exposures much lower than those living in any other major Australian city (Table 6). Although the contribution of regional Mn emitting industries to Mn levels in Launceston is unknown, based on the data of Ayers et al (1999), those living in this city would have had Mn exposures of up to approximately 500 ng/day ($PM_{2.5}$) during 1997. People living in rural/remote areas would be expected to have very low exposures to respirable Mn. In the USA, $PM_{2.5}$ Mn concentrations in national parks were measured at 1 ng/m^3 from which exposures of approximately 20 ng/day can be calculated (Wallace and Slonecker, 1997). Given that the estimated respirable Mn concentration measured in Canberra in 1997 was below 1 ng/m^3, exposures of Australians living in rural and remote regions is expected to be even lower. Overseas data also reflect the relatively high exposures expected in areas with Mn emitting industries. Based on ambient air data reported by Wood and Egyed (1994), exposures of up to 3160 ng/day can be calculated for people living in Canadian cities with large Mn emitting industries. Similarly, WHO (1981) estimated exposures of up to 10 000 ng/day in areas associated with ferro- or silicomanganese industries with 24-hour peak values over 200 000 ng/day.

It should also be noted that ambient air concentrations might not always reflect the actual exposure of individuals living in a given area, because typical human activity patterns result in time spent in microenvironments with higher or lower concentrations of a pollutant and for which there is generally no monitoring data. Hence, a measure of personal exposure to a compound is preferable to ambient air data, and that estimate should be representative of the population of interest throughout the time period of interest.

Canadian personal and ambient air monitoring studies demonstrate outdoor microenvironments of importance e.g. in a vehicle, at a petrol station, an underground car park, the subway and areas of high traffic density (Loranger et al., 1997; Zayed et al. 1999; Pellizzari et al., 1999; Crump 2000). Also, the amount of time spent indoors or outdoors can also be a significant determinant of personal exposure to respirable Mn. From the Toronto study of Pellizzari et al. (1999), Crump (2000) observed that the mean indoor residential air concentration of respirable Mn of 5.5 ng/m^3 ($PM_{2.5}$) was approximately 60% of that of the average air concentration measured at several outdoor

residential sites. Also, the earlier data of Pellizzari et al. (1992) as reported by the USEPA (1994c) showed that the median ambient indoor air concentration of $PM_{2.5}$ was about 80% of the outdoors concentration measured outside the homes of participants.

No Australian ambient air Mn concentration data are available for particular outdoor microenvironments or indoor air and no personal monitoring studies have been completed in Australia. Therefore, the above worst-case estimate of exposure cannot be refined without assuming that overseas data are applicable to Australian conditions.

An environmental and epidemiological study of Mn from MMT use is currently being conducted in Australia. The objectives of the project are to determine the contribution of MMT use to Mn levels in air, dust, soil and water and also blood and urine Mn levels in children aged 1-5 years. At the time of writing, 78 exposed children ranging in age from 6 to 18 months have been recruited to the study. All environmental and biological sampling has been completed for this whole cohort with repeated samplings conducted in approximately half. Analytical results for all samples have been obtained. No results are yet available. The project has been delayed by difficulties with funding and further delays are likely to result in termination of the project.

Exposure to manganese via food

Food is the most significant source of exposure to Mn. Fardy et al. (1992) as reported by Wood and Egyed (1994) estimated the average Australian dietary intake of Mn to be 5 530 μg/day for males and 2 960 μg/day for females (an average of 4 245 μg/day for both sexes). According to New Zealand Ministry of Health (1999), median adult Mn intake is 4 327 μg/day in New Zealand. Assuming 3% of this dietary intake is absorbed from the gastrointestinal tract (WHO, 1981), the systemic dose of Mn from the diet can be estimated as approximately 127 μg/day or 1.82 μg/kg bw/day (for a 70 kg adult). The WHO (1981) estimated the average daily Mn intake from the diet to be in the range of 2 000 – 9 000 μg/day and estimates of dietary intake of Mn from the USEPA (1984) give a typical intake at 3 800 μg/day.

It is conceivable that Mn levels in foodstuff may be increased as a result of environmental contamination with the combustion products of MMT. There are no Australian studies on the possible contribution of MMT combustion product to food Mn. Given the expected low soil, water and atmospheric levels of MMT combustion products (especially in rural areas), it is considered that the contribution of MMT combustion products to Mn intake from foodstuff is likely to be very low.

Exposure to manganese via water

In Australian reticulated water supplies, the Mn concentration can be up to 0.25 mg/L with typical concentrations usually less than 10 μg/L (NHMRC, 1996). Assuming that a person drinks up to 2L/day, intake from drinking water can be up to 500 μg/day, but is probably usually about 20 μg/day or less. Assuming 3% of this intake is absorbed from the gastrointestinal tract, the systemic dose of Mn from the diet can be estimated as approximately 8.6 ng/kg bw/day for a 70 kg adult. The USEPA (1984) estimates the typical concentration of Mn in the water to be 4 μg/L and intake to be 8 μg/day. Manganese concentrations in Canadian drinking water were generally below 50 μg/L, but a conservative value of 100 μg/L was used for a Canadian exposure assessment (Wood and Egyed, 1994) giving intakes at approximately 200 μg/day.

The concentration of Mn in Sydney's stormwater as a result of MMT combustion is estimated at 1.2 μg/L (Section 8.3.4). Given the expected low water concentrations of MMT combustion products (especially in water catchment areas), it is considered that the contribution of MMT combustion products to Mn intake from water is also likely to be very low.

Other possible sources of exposure

Other possible sources of Mn exposure include smoking and soil ingestion. Manganese exposures as a result of smoking are likely to contribute significantly to the total inhalation exposure to Mn in some individuals. The personal exposure data analysed by Crump (2000) show that the median $PM_{2.5}$ Mn exposure was higher for smokers (9.2 ng/m^3) than non-smokers (8.3 ng/m^3). People exposed passively to environmental tobacco smoke (9.0 ng/m^3) had exposure levels similar to smokers, whereas those not exposed to tobacco smoke from any sources had the lowest levels of personal exposure (7.7 ng/m^3). Manganese exposures as a result of smoking are outside the scope of this report and will not be considered further.

It is conceivable that Mn produced as a result of MMT combustion could increase soil levels of Mn and hence increase Mn exposures as a result of soil ingestion. However, given that soil Mn concentrations in Australia are not expected to be significantly increased by MMT use, then Mn exposure as a result of soil ingestion is not expected to increase.

Table 11. Summary of main sources of human exposure to Mn*

Source of Exposure	Estimated Absorbed Dose – No Exposure to MMT (ng/kg bw/day)	Estimated Absorbed Dose - With Exposure to MMT (ng/kg bw/day)
Air	0.5	0.85-1.35
Food	1820	1820**
Water	8.6	8.6**
Total	1829.46	1828.9-1829.4

* - for a 70 kg adult

**- no increase expected due to MMT use

9. Kinetics and Metabolism of MMT

9.1 Absorption

Although no studies were located describing the absorption of MMT, acute and repeated dose studies indicate that absorption does occur via dermal, oral and respiratory routes, as demonstrated by the toxic effects observed following MMT administration.

9.2 Distribution

The distribution of MMT was examined 1.5-96 hours after subcutaneously administering a single dose of MMT (4 mg/kg bw) to male Sprague-Dawley rats. The level of Mn in the blood, lungs, liver and kidney was increased throughout the study and peaked at 3-6 hours post injection. Levels of brain Mn were not significantly increased in treated animals. The level of Mn in the lung, liver, kidney, and blood at 3 hours post injection was 9 mg/kg, 2.75 mg/kg, 3.9 mg/kg, and 0.75 mg/kg respectively. The number of animals per treatment group was not stated (McGinley et al., 1987).

A single subcutaneous injection of MMT (4 and 10 mg/kg bw) to male Sprague-Dawley rats resulted in a significant increase in lung Mn content. After 24 hours rats that had not received MMT had 0.7 μg Mn per lung. By comparison rats that received 1 mg/kg bw MMT had 6.5 μg Mn per lung, and those that received 2.5 mg/kg bw MMT had 20.1 μg Mn per lung. An additional study was performed assessing Mn lung burden resulting from MMT administration in the presence of piperonyl butoxide, a cytochrome P450 monooxygenase inhibitor. A 1 hour pre-treatment with piperonyl butoxide (400 mg/kg bw) was found to protect against lung Mn accumulation resulting from a single subcutaneous injection of 4 mg/kg bw MMT (approximately 5 μg Mn/lung compared with 10 μg Mn/lung). Heptane extraction of lung homogenates from MMT-treated rats indicated less than 2% of the pulmonary Mn was extractable, suggesting the presence of metabolites as opposed to MMT. Furthermore the decrease in Mn lung content in the presence of piperonyl butoxide suggests the presence of cytochrome P450 dependent monoxygenase metabolites. Each treatment group contained between 4 and 9 rats (Clay and Morris 1989).

The level of Mn in the brain of CD-1 mice was significantly increased by subcutaneous injection of MMT. In an acute study mice received a single MMT injection and were sacrificed after 24 hours. Mice in the control group were found to have 0.61 μg Mn/g brain. By comparison mice that received 11 mg Mn/kg bw MMT injection had 0.93 μg Mn/g brain, and those that received 22 mg Mn/kg bw MMT injection had 1.35 μg Mn/g brain. In a separate chronic study mice received 10 injections (given on alternate days) and were sacrificed 24 hours after the tenth injection. At the end of the study mice in the control group had 0.64 μg Mn/g brain, while mice receiving 11 mg Mn/kg bw MMT had 1.37 μg Mn/g brain, and those receiving 22 mg Mn/kg bw MMT had 3.33 μg Mn/g brain. On a temporal basis the concentration of brain Mn reached a level approximately twice that of controls within 4-8 hours post treatment and remained elevated for the length of the study. The number of animals per treatment group was not stated (Gianutsos et al., 1985).

The disposition of MMT was assessed in male ddY mice after chronic oral administration of MMT in food (0.5 g Mn/kg food) for 12 months. Daily food intake per mouse was reported as 3.6 g for controls and 3.1 g in the MMT-treated group. At the end of the exposure period there was significantly more Mn in the liver, kidney, pancreas, sublingual gland, lung and muscle in the MMT-treated group than in the control group. The highest level of Mn in MMT-treated mice was observed in the kidney (approximately 12.5 μg Mn/g ww), followed by the thyroid gland (12 μg Mn/g ww), then the liver (10.5 μg Mn/g ww), prostate (7.5 μg Mn/g ww) and sublingual gland (7 μg Mn/g ww). The level of Mn in blood was significantly elevated in MMT-treated mice when compared to controls. The blood Mn concentration was 1.12 ± 0.19 μg/mL creatinine in the MMT group and 0.14 ± 0.05 μg/mL creatinine for the control. The weight gain of MMT-treated mice was significantly reduced after 9 months of the treatment and remained depressed until the study was concluded. Each treatment group contained between 4 and 6 animals (Komura and Sakamoto 1992).

An increase in the concentration of Mn in the brain of mice was reported following either a 12 months treatment with MMT at 0.5 g Mn/kg in food or a single IP MMT injection (100-2000 mg/kg bw in propylene glycol or corn oil) (Komura and Sakamoto 1994; Fishman et al., 1987) (See Section 11.11).

The disposition of MMT was investigated in male Charles River rats following oral and intravenous (IV) administration of [^{54}Mn]MMT. One day following oral administration of 2.5 mg [^{54}Mn]MMT in 0.2 mL Wesson oil, the highest ^{54}Mn concentrations were observed in the liver, lungs, kidneys, urinary bladder, pancreas, and abdominal fat. Nine days following oral administration, the highest ^{54}Mn concentrations were observed in the kidneys, liver, pancreas, and lungs. Each treatment group contained 12 animals. The concentration of ^{54}Mn in individual tissues was not reported (Moore et al., 1974).

The concentration of tissue Mn was investigated in COBS rats following a single oral dose of MMT at 15-150 mg/kg bw in Wesson oil. A number of animals that received 45-150 mg/kg bw of MMT died within 6 days post treatment. The concentration of Mn in selected tissues (duodenum, kidney, liver, lung, heart and brain) of rats that died was significantly increased and generally in a dose dependant manner. At 14 days post treatment, with the exception of the lung, the levels of tissue Mn had fallen to approximately normal levels. Each treatment group contained 10 animals. No statistical analysis was performed (Hysell et al., 1974).

Repeated dermal contact of MMT (0.4-16 g/L) in gasoline solutions (with or without tetraethyl lead) in rabbits (5 days/week, for 14 weeks), did not result in increased organ Mn concentrations that could be directly attributed to MMT exposure. In contrast, there was an increase in lung Mn levels in rats dermally exposed to MMT for 5 days/week, for 6 months rats. The level of Mn in the brain, kidney and liver was normal. Each treatment group contained 3 rabbits and an unknown number of rats. The distribution of Mn was also examined following inhalation exposure in several species. When guinea pigs, rats, and cats were exposed to airborne MMT for 7 hours per day on each of 45 or 150 days, an increase in liver, kidney, and lung Mn levels were observed. The highest values were observed in the cat, then the rabbit, rat and guinea pig. The highest Mn levels were observed in the liver, followed by the kidney, lung, heart and urine. Results of 1 rabbit, post exposure, indicated rapidly decreasing levels of Mn in tissues, which were within normal range by day 21. Two dogs, 1-2 rabbits, and an unknown number

of cats, rats and guinea pigs were used in each treatment group (Witherup et al Unknown date d).

The distribution of Mn in male golden hamsters and male outbred albino rats was investigated following exposure to MMT combustion products generated using a 1972 Chevrolet 350 CID (cubic inch displacement) engine dynamometer system. Emissions were derived by passing exhaust generated from the combustion of fuel consisting of indolene "clear" containing MMT at 0.25 g Mn/gallon through a muffler, followed by dilution (25:1) with clean conditioned air. The final diluted emissions were split in two with one half being irradiated prior to exposure to animals. Irradiated emissions typically contained 855 $\mu g/m^3$ particles (0.29 μm) consisting of 117 mg/m^3 Mn (13.7%). Nonirradiated emissions typically contained 635 $\mu g/m^3$ particles (0.26 μm) consisting of 131 mg/m^3 Mn (20.7%). Animals were fed a low Mn diet and exposed for 8 hours per day for 56 consecutive days. At the end of the exposure period, the concentration of Mn in the brain, liver and lung was significantly increased in the irradiated emission group when compared to controls. In the nonirradiated emission group, heart Mn levels were reduced while brain and liver Mn concentration were significantly increased. Kidney Mn levels were unaffected. Similar results were obtained with animals fed a regular (higher) Mn diet. No difference in Mn concentration was observed in the hamster in all tissues examined. The number of animals per treatment group was not stated (Moore et al., 1975b).

The distribution of Mn in various tissues has also been investigated in rats and monkeys following inhalation of the combustion products of MMT according to a procedure described by Rinehart, (1975) and Ulrich et al. (1979a). Briefly, the experimental procedure involves generating MMT combustion products by burning MMT vapours in a propane flame, which reportedly produces a solid product consisting of Mn oxide (Mn_3O_4) with an aerodynamic diameter of approximately 0.11μ (Ulrich et al., 1979a). The animals were exposed for 24 hours per day for nine months to 11.6-1152 μg Mn/m^3 as Mn oxide (Mn_3O_4) aerosol. After nine months the level of Mn in the kidney, lung, and blood were significantly increased when compared to controls. A significant increase in spleen Mn levels was also observed in the monkey. The level of Mn in the liver was unaffected in both species. Six months post exposure the level of Mn in the spleen of rats was slightly elevated at low dose and reduced in the blood at high dose in rats. The Mn content in all other tissues examined in both species was normal. Each treatment group contained 15 male and 15 female rats and 4 male and 4 female monkeys (Rinehart, 1975; Ulrich et al., 1979b,c).

9.3 Metabolism

The biotransformation of [^{54}Mn]MMT was assessed in vitro using brain, liver, lung and kidney homogenates from male Charles River rats. Liver homogenates were found to metabolise 64.2% of [^{54}Mn]MMT to inorganic ^{54}Mn within 20 minutes, at a rate of 8.02 ng/min/mg tissue. Lung homogenates metabolised 26.9% of the administered [^{54}Mn]MMT at 0.07 ng/min/mg tissue, kidney homogenates 2.59% at 0.11 ng/min/mg tissue, and brain homogenates 1.64% at 0.07 ng/min/mg tissue (Moore et al., 1974).

Hanzlik et al. (1980a) investigated the metabolism of MMT in male Sprague-Dawley rats. Intraperitoneal pre-treatment with phenobarbital (60 mg/kg bw), an inducer of the cytochrome P450 system, significantly reduced the incidence of death in rats after oral administration of MMT (125 mg/kg bw in corn oil). Each treatment group contained

between 5 and 7 animals (Hanzlik et al., 1980a). This result suggests that MMT is metabolised by the cytochrome P450 system.

In a separate study investigating the metabolism of MMT in male Sprague-Dawley rats, Hanzlik et al. (1980b) demonstrated that a single oral dose of [H^3]MMT (125 mg/kg bw) resulted in two major urinary metabolites, carboxycyclopentadienyl manganese tricarbonyl (CMT) ((CO_3)$MnC_5H_4CO_2H$), and hydroxymethylcyclopentadienyl manganese tricarbonyl (HMT) ((CO_3)$MnC_5H_4CH_2OH$). Each treatment group contained between 3 and 6 animals. In vitro the metabolism of MMT by liver and lung microsomes was demonstrated to be cytochrome P450 dependant, in that it requires NADPH (an essential cofactor for cytochrome P450 activity) and is inhibited by carbon monoxide and N-decylimidazole (inhibitors of cytochrome P450 activity). Rat liver microsomes were found to metabolise MMT in vitro with a K_m of 78 μM and a V_{max} of 3.12 nmol/mg protein/min. The K_m for MMT metabolism was unchanged while the V_{max} doubled when liver microsomes from phenobarbital (60 mg/kg bw) treated rats were used. In fact 90% of MMT was metabolised within 15 minutes by liver microsomes from phenobarbital treated rats. Lung microsomes were also found to metabolise MMT, but this effect was not enhanced by phenobarbital.

The metabolism of MMT in male rats was also investigated after a single subcutaneous injection of MMT at 2 μg Mn/g bw in propylene glycol. Urine collected from MMT-treated rats 25 minutes after administration was found to contain a single Mn peak when analysed by high-performance liquid chromatography with a laser-excited atomic fluorescence detector. The single metabolite was identified as CMT. The urine from the control group contained no detectable Mn species. The number of animals per treatment group was not stated (Walton et al., 1991).

The metabolism of MMT in female LAC-P Wistar rats was investigated after a single IP injection (4 and 6 mg/kg bw in oil). Inhibitors of the cytochrome P-450 2B isoenzyme (O,O,S-trimethylphosphorodithioate, bromophos, 2,4-dichloro(6-phenylphenoxy)ethylamine and p-xylene) reduced the pulmonary toxicity of MMT by approximately 10-fold as determined by LD50 values and lung weight. Inhibitors of cytochrome P-450 1A, 2E and 4B isoenzymes had no effect on the pulmonary toxicity of MMT. Each treatment group contained 5 animals. These findings suggest that the cytochrome P-450 2B isoenzyme is responsible for the metabolism of MMT in rats (Verschoyle et al., 1993).

9.4 Elimination and excretion

The toxicokinetics of Mn resulting from a single oral dose of MMT was examined in Sprague-Dawley rats. MMT was administered orally by gavage at 20 mg MMT/kg bw and blood samples were taken 0-456 hours post treatment. Plasma Mn levels reached a maximum concentration (C_{max}) of 0.93 μg/mL between 2-12 hours following MMT administration (T_{max} = 7.75 hr). From these values the plasma half-life ($T_{1/2}$) of Mn following MMT administration was determined as 55.2 hours. The clearance of MMT-derived plasma Mn was extremely slow at 0.09 L/h kg. The authors noted that the plasma Mn $T_{1/2}$ was longer in female (68.4 hrs) than male (42 hrs) rats. Furthermore the clearance rate of plasma Mn was slower in female (0.07 L/h kg) than male (0.11 L/h kg) rats. Each treatment group contained 4 male and female animals (Zheng et al 2000).

The toxicokinetics of MMT in Sprague-Dawley rats has also been examined by Hanzlik et al. (1980a). A single IP injection of [H^3]MMT (30 mg/kg bw in corn oil) to

phenobarbital (60 mg/kg bw) pre-treated rats resulted in a linear increase in Mn and H^3 concentrations in bile. During the first 6 hours following [H^3]MMT injection approximately 13% of the administered H^3 was excreted in the bile. The concentration of Mn in the bile 6 hours post injection of MMT was 25-40 ppm. The Mn concentration was 50-130 times higher in MMT-treated than in control rats. The toxicokinetics of MMT was also assessed following a single IV injection of MMT (10 mg/kg bw) to phenobarbital (60 mg/kg bw) pre-treated rats and control animals. This resulted in an increase in the biliary excretion of MMT from 3 mg/kg bw/hr (MMT alone) to 5.7 mg/kg bw/hr (MMT + Phenobarbital). Each treatment group contained between 4 and 6 animals.

In a separate study investigating the toxicokinetics of MMT in male Sprague-Dawley rats, Hanzlik et al. (1980b) demonstrated that 48 hours after a single oral dose of [H^3]MMT (125 mg/kg bw), urinary and faecal excretion of H^3 accounted for 81% and 2-4% respectively of administered MMT. It was also shown that 67% of the H^3 in the urine was CMT and 14% was in the form of HMT. In a separate study it was shown that a single IV injection of [H^3]MMT (10 mg/kg bw) resulted in 12% of the H^3 being present in the bile within 30 minutes. This was increased to 24% in phenobarbital (60 mg/kg bw) pre-treated rats. CMT and HMT accounted for 49% and 18% respectively of the total biliary H^3. Each treatment group contained between 3 and 6 animals.

The toxicokinetics of MMT in male rats was also investigated after a single subcutaneous injection of MMT at 2 μg Mn/g bw in propylene glycol. Urine collected from MMT-treated rats 25 minutes after administration was found to contain a single metabolite, CMT, which accounted for 1-4% of the total Mn administered as MMT. The urine from the control group contained no detectable Mn species. The number of animals per treatment group was not stated (Walton et al., 1991).

The elimination and excretion of MMT was investigated in male Charles River rats following oral and IV administration of [^{54}Mn]MMT. Rapid clearance of ^{54}Mn was observed in the first several days following oral administration of 0.5 or 2.5 mg [^{54}Mn]MMT in 0.2 mL Wesson oil. Clearance was due to excretion in urine and faeces. During the first 24 hours following oral administration of 2.5 mg [^{54}Mn]MMT, rats excreted 73% of the administered ^{54}Mn. Urine was determined to contain 36% of the excreted ^{54}Mn. In a similar manner to that observed for oral dosing, IV administration of [^{54}Mn]MMT (0.34 mg Mn/rat) in ethanol resulted in rapid clearance of ^{54}Mn within a few days. Again clearance was due to excretion via urine and faeces, with more in the faeces. Each treatment group contained 12 animals (Moore et al., 1974).

The excretion of MMT was assessed in male ddY mice after chronic oral administration of MMT in food (0.5 g Mn/kg food) for 12 months. Daily food intake per mouse was slightly lower in the MMT-treated group. The level of Mn in urine was significantly elevated in MMT-treated mice when compared to controls. The mean urinary Mn concentration was 112 mg/g creatinine in the MMT group and approximately 2 mg/g creatinine for the control. The excretion of Mn in the urine of MMT-treated rats constituted 5.4% of the daily oral intake. Each treatment group contained between 4 and 6 animals (Komura and Sakamoto 1992).

The level of Mn in the urine of dogs exposed to 12 mg/m^3 MMT for 7 hrs/day, 5 days/week, for nine weeks, was elevated at all time points above controls. In rabbits exposed to 17.9 mg/m^3 MMT (12 x 7 hr exposures) the level of Mn in urine was found to increase during days of exposure, then rapidly declined on days when no exposure occurred. The level of urine Mn returned to normal within 5 days of the last exposure.

A similar pattern of urine Mn content was observed in a rabbit exposed to 150 seven-hour exposures (Witherup et al Unknown date d).

9.5 Summary

Acute and repeated dose toxicity studies indicate that MMT is absorbed via dermal, oral and respiratory routes. Disposition studies in animals indicate that the liver, kidney, brain, and lung are the primary sites of Mn accumulation following oral or dermal exposure to MMT. Manganese also accumulated in the pancreas, sublingual gland, thyroid, prostate, muscle, duodenum, urinary bladder, heart, abdominal fat and blood, but to a lesser extent. Inhalation exposure of rats and monkeys to MMT combustion products resulted in the accumulation of Mn in the brain, liver and lung. The finding in rats that less than 2% of pulmonary Mn resulting from subcutaneous exposure to MMT was extractable with heptane, suggests the presence of metabolites as opposed to MMT.

Studies investigating the biotransformation of MMT in vitro indicate the liver is the predominant site of MMT metabolism, followed by the lung, kidney and brain. As the metabolism of MMT in lung and liver microsomes in vitro is inhibited by carbon monoxide and N-decylimidazole, it is likely the cytochrome P-450 monoxygenase enzyme is responsible for the metabolism of MMT in rats. MMT and its metabolites are predominantly excreted in the urine and faeces of rats. The most abundant MMT metabolite was determined to be CMT followed by HMT.

10. Toxicity of MMT

10.1 Acute toxicity

Acute lethality studies are summarised in Table 12.

The major acute toxic effects of MMT include damage to the lungs by all routes, kidney, liver and spleen effects, tremors, convulsions, dyspnea and weakness.

Table 12. Summary of MMT acute lethality studies

Route	Species	Result	Reference
Inhalation	Rat	LC50 (4hr) > 2 mg/m^3	Moore et al., 1975a
	Rat	LC50 (1hr) = 247 mg/m^3	Ethyl Corporation, 1976h; Hinderer, 1979
	Rat	LC50 (4hr) = 76 mg/m^3	Ethyl Corporation, 1976h; Hinderer, 1979
	Rat	LC50 (1hr) > 19.8 g/m^3 (approx.)*	Ethyl Corporation, 1976a
	Rat	LC50 (1hr) = 220 mg/m^3	Witherup et al, Unknown date b
Oral	Rat (f)[a]	LD50 = 22.9 mg/kg bw	Witherup and Larson, 1965
	Rat (f)[b]	LD50 = 16.8 mg/kg bw	Witherup and Larson, 1965
	Rat (m)[a]	LD50 = 38.5 mg/kg bw	Witherup and Larson, 1965
	Rat (m)[b]	LD50 = 23.7 mg/kg bw	Witherup and Larson, 1965
	Rat (m)	LD50 = 175 mg/kg bw**	Witherup and Roell, 1965
	Rat (f)	LD50 = 89 mg/kg bw**	Witherup and Roell, 1965
	Rat	LD50 = 58 mg/kg bw	Hysell et al., 1974; Moore et al., 1975a
	Rat	LD50 = 58 mg/kg bw	Ethyl Corporation, 1975a; Hinderer, 1979
	Rat	LD50 = 175 mg/kg bw*	Ethyl Corporation, 1976b
	Rat	LD50 = 50 mg/kg bw	Hanzlik et al., 1980a
	Rat[a]	LD50 = 23-176 mg/kg bw	Witherup et al., Unknown date b
	Rat[b]	LD50 = 9->80 mg/kg bw	Witherup et al., Unknown date b
	Mouse	LD50 = 230 mg/kg bw	Ethyl Corporation, 1977c; Hinderer, 1979
	Mouse (f)	LD50 = 60 mg/kg bw	Majima, 1985

Table 12. Summary of MMT acute lethality studies (cont.)

Route	Species	Result	Reference
	Mouse (m)	LD50 = 34 mg/kg bw	Majima, 1985
	Mouse	LD50 = 352 mg/kg bw	Witherup et al., Unknown date b
	Guinea pig (f)	LD50 = 905 mg/kg bw	Witherup et al., Unknown date b
	Rabbit (f)	LD50 = 95 mg/kg bw	Witherup et al., Unknown date b
Dermal	Rabbit	LD50 (24 hrs) = 1350 mg/kg bw**	Witherup and Roell, 1965
	Rabbit	LD50 (24 hrs) = 140 mg/kg bw	Ethyl Corporation, 1975b; Hinderer, 1979
	Rabbit	LD50 (24 hrs) > 2000 mg/kg bw*	Ethyl Corporation, 1976c
	Rabbit	LD50 (24 hrs) = 196.7 mg/kg bw	Ethyl Corporation, 1976e; Hinderer, 1979
	Rabbit	LD50 (24 hrs) = 420 mg/kg bw	Ethyl Corporation, 1976f; Hinderer, 1979
	Rabbit	LD50 (24 hrs) = 795 mg/kg bw	Ethyl Corporation, 1976g; Hinderer, 1979
	Rabbit[a]	LD50 (6 hrs) = 665 mg/kg bw	Witherup et al., Unknown date b
	Rabbit[b]	LD50 (24 hrs) = 135 mg/kg bw	Witherup et al., Unknown date b
Intraperitoneal	Rat	LD50 = 23 mg/kg bw	Hanzlik et al., 1980a
	Rat	LD50 = 6 mg/kg bw	Hakkinen & Haschek, 1982
	Rat	LD50 = 12.1 mg/kg bw	Cox et al., 1987
	Rat	LD50 = 4 mg/kg bw	Verschoyle et al., 1993
	Mouse	LD50 = 138 mg/kg bw	Hakkinen & Haschek, 1982
	Mouse[c]	LD50 = 152 mg/kg bw	Fishman et al., 1987
	Mouse[d]	LD50 = 999 mg/kg bw	Fishman et al., 1987
	Hamster	LD50 = 270 mg/kg bw	Hakkinen & Haschek, 1982
Subcutaneous	Rat	LD50 > 10 mg/kg bw	Clay & Morris, 1989
Intravenous	Rabbit	LD50 = 6.6 mg/kg bw	Witherup et al., Unknown date b

a = peanut oil vehicle
b = kerosene vehicle
c = propylene glycol vehicle
d = corn oil vehicle
m = male only
e = Wesson oil vehicle
f = female only
* = product tested is 62% MMT in petroleum distillate
** = product tested is 10% MMT in kerosene

Oral LD50 values in rats range from 9 to 176 mg/kg bw MMT. The oral LD50 in rats for 62% MMT in petroleum distillate is 175 mg/kg bw and for 10% MMT in kerosene is 89-175 mg/kg bw.

The LC50 for the rat ranges from 220 to 247 mg/m^3 for a 1 hour exposure and >2 to 76 mg/m^3 for a 4 hour exposure. The LC50 for 62% MMT in petroleum distillate (1 hour exposure) is >19.8 g/m^3.

Dermal (24 h) LD50 values for undiluted MMT in the rabbit range from 140 to 795 mg/kg bw. The dermal (24 h) LD50 for 10% MMT in kerosene is 1350 mg/kg bw and for 62% MMT in petroleum distillate is > 2000 mg/kg bw.

10.2 Irritation and corrosivity

10.2.1 Skin

Ethyl Corporation (1976d) assessed the ability of a MMT solution to act as a skin irritant on six female New Zealand rabbits. In this study, 0.5 mL of 62% MMT in petroleum distillate was applied as an occlusive application for 24 hours to intact or abraded dorsal skin that had been shaved. Effects were graded when patches were removed (24 hrs) and 24 hrs later (48 hrs) in accordance with OECD guideline 404. MMT in petroleum distillate was found to induce skin irritation at 24 and 48 hours in both intact and abraded skin. Erythema was scored as 1.2 and 1.0 for intact skin and 1.5 and 1.0 for abraded skin, at 24 and 48 hours respectively. Oedema was scored as 1.7 and 0.8 for intact skin and 2.3 and 1.0 for abraded skin, at 24 and 48 hours respectively.

Campbell et al. (1975) examined the skin irritancy potential of MMT in groups of six male albino rabbits. MMT was applied under occlusion, as a neat solution (0.1 mL) to intact or abraded dorsal skin. The covering and test solution were removed after 24 hours. Skin reactions were assessed when the patch was removed (24 hrs) and 48 hours later (72 hrs) and were scored using an approach described by Campbell et al. (1975). Signs of erythema and oedema were confined to the test area and no eschar formation was observed (no further details provided). Campbell et al. concluded that MMT is not an irritant in intact skin and is a mild irritant in abraded skin.

The ability of MMT to induce skin irritation was assessed in intact and abraded skin of female New Zealand albino rabbits according to the method of Draize et al. (1944). In this study MMT (0.5 mL) was applied to groups of six rabbits under occlusion for 24 hours. MMT was found to cause well-defined erythema and slight oedema in both abraded and intact skin. Slight irritation was still present 72 hours post application. Mean irritation scores for erythema/eschar formation and oedema were 1.29 and 1.5 respectively, averaged over 24 and 72 hours (Ethyl Corporation 1976i; Hinderer 1979).

In acute lethality dermal studies, skin reactions were also noted. MMT (112-2000 mg/kg bw) was applied to intact and abraded rabbit skin under occlusion for 24 hours. At 24 hours post dosing, a slight to well-defined erythema and moderate oedema were noted in most animals. Skin irritation had generally cleared by day 3 in surviving rabbits. Each treatment group contained 4 rabbits (Ethyl Corporation 1975b, 1976f, 1976g).

Two poorly reported studies examining skin irritation were also identified. The first reported that undiluted MMT applied to the skin of rabbits for 24 hours caused no remarkable signs and a 6 hour exposure of 10% MMT in peanut oil to rat skin resulted in a mild transient irritation (Witherup et al Unknown date b). The second study found that a 24-hour exposure to Combustion Improver No. 2 Product (10% MMT in kerosene) caused erythema and oedema at 24 and 72 hours in rabbits (Witherup and Roell 1965).

10.2.2 Eye

Ethyl Corporation (unknown date) assessed the ability of MMT to act as an eye irritant on six Albino New Zealand rabbits. In this study, 0.1 mL of 62% MMT in petroleum distillate was applied to the conjunctival sac of the right eye. Ocular reactions were graded 24, 48 and 72 hours post application in accordance with OECD guideline 405. Conjunctival redness was scored as 1.0, 0.167 and 0 at 24, 48 and 72 hours respectively (mean values). Conjunctival chemosis was scored as 1.167, 0.167 and 0 at 24, 48 and 72 hours respectively. Corneal opacity and iridal lesions were not observed. Two rabbits reportedly vocalised at instillation.

The ability of MMT to cause eye irritation was assessed also according to the grading method of Draize et al. (1944). In this study, MMT (0.1 ml) was applied to the conjunctival sac of the right eye of six Albino New Zealand rabbits. MMT resulted in mild conjunctival redness but no corneal effects. Mean Draize scores on day 1 of 0.83 and 0.17 for conjunctival redness and chemosis respectively were reported. A conjunctival discharge was observed in one animal on day 2 and one animal still showed minor conjunctival redness (score 1) on day 3. No effects were observed from day 4 onwards (no further details provided) (Ethyl Corporation 1976j; Hinderer 1979).

In an acute inhalation lethality study, rats receiving whole body exposure to MMT vapours (0.108-0.309 mg/L for 1 hr or 0.047-0.1 mg/L for 4 hrs) experienced eye irritation that lasted for a maximum of one day. Each treatment group contained 10 animals (Ethyl Corporation 1976h). Lacrimation and mild eye inflammation were observed also for up to 30 minutes post exposure in a similar on1 hour inhalation toxicity study of a product consisting of 62% MMT in petroleum distillate (Ethyl Corporation 1976a).

Two poorly reported studies examining eye irritation were also identified. In the first study, occasional mild injection of the vessels of the bulbar conjunctivae was observed in rabbit eyes that had been exposed to 10% MMT in kerosene (Witherup et al Unknown date b). In the second study, a 24-hour exposure to Combustion Improver No. 2 Product (10% MMT in kerosene) resulted in a mild hyperemia in the palpebrae in two of six New Zealand albino rabbits. Eyes were considered normal on days 2 and 3 (Witherup and Roell 1965).

10.3 Sensitisation

There are no animal studies or human case reports of skin or respiratory sensitisation to MMT.

10.4 Repeated dose toxicity

In a 30-week inhalation study, mice and rats (up to 30 animals/group, sex not specified) were exposed to between 0.0062-0.413 mg/L MMT for 7 hours per day, 5 days per week, for up to 30 weeks. Weight loss and death were observed in animals as a result of MMT exposure. In mice at 0.014 mg/L, the percentage weight loss reported was 26.2% and mortality occurred in 1/10 animals. At 0.017 mg/L, weight loss increased to 35.9% and mortality occurred in 27 of 28 mice prior to 77 exposures and in one mouse after 127 exposures. Rats exposed to 0.017 mg/L showed 10.7% weight loss with mortality in 9 of 20 animals.

At the lower dose of 0.0062 mg/L animals gained weight and none died. Many of the animals, including controls, died as a result of a chronic infectious disease (pneumonitis) and were not included in the analysis.

The viscera were examined for gross pathological changes and several tissues were examined for microscopic changes. The only findings noted in the report were that pathological changes resulting at high MMT concentrations were observed primarily in the liver and kidneys and at lower concentrations degenerative changes in the liver and kidneys occurred less consistently. The NOAEL for rats and mice was 0.0062 mg/L (6.2 mg/m^3). Using the data of Gold et al (1984) as reference values for dose calculations, assuming a respiratory volume of 6 L/hour and a (male) body weight of 0.2 kg, this NOAEL corresponds to an intermittent dose of 1.3 mg/kg bw/day in rats.

Small groups of cats (1/dose), rabbits (1-4/dose), and guinea pigs (6-9/dose) were exposed to similar doses of MMT for 4 to 150 weeks. Very few animals died and none died at exposures at and below 0.017 mg/L MMT for 150 weeks. Two dogs were exposed to 0.012 mg/L MMT for 100 weeks and neither died. No MMT-dependent toxic effects were observed in cats, rabbits, guinea pigs or dogs. This is an unpublished study and no individual animal data or statistical analyses were reported (Witherup et al unknown date a).

Toxicity resulting from repeated dermal exposure to 0, 0.4, 2.4 or 16 g/L MMT (equivalent to 0, 0.8, 4.8 and 32 mg MMT/kg bw/day) in gasoline with and without tetraethyl lead (TEL) (~ 2 g/L) was assessed in Weanling CFW rats and male New Zealand White rabbits. Rats were exposed 5 days per week, for 25 weeks while rabbits were exposed 5 days per week, for 14 weeks. Repeated dermal contact with the gasoline solutions (2 mL/kg), regardless of whether they contained MMT with or without lead, resulted in severe and extensive skin injury in rabbits. Initial gasoline exposure caused a mild transient erythema, which developed into a mild oedema with continued exposure. The skin eventually became dry, hard, wrinkled with numerous fissures and ulcerations. At 4.8 and 32 mg MMT/kg bw/day, vacuolar degeneration of the liver and kidney was observed in some rabbits. Mild skin damage was seen in rats exposed to the gasoline solutions, regardless of whether they contained MMT with or without lead. No neurological irritation or significant effects on mortality, body weight, blood content (haemoglobin and leukocyte number), organ weight (heart, liver, lungs, kidneys, brain), or the viscera could be attributed to MMT. Five male and 5 female rats and 5 male rabbits were used per treatment. This is an unpublished report and individual animal data and scores and statistical analysis were not reported (Witherup et al unknown date c).

10.5 Reproductive toxicity

The developmental toxicity of MMT was examined in COBS CD rats. Male and female rats were mated at a 1:1 ratio. Copulation was determined by the identification of a copulation plug, marking day 0 of gestation. Pregnant females were dosed orally with MMT (2-9 mg/kg bw) in corn oil daily, on days 6-15 of gestation. Pregnant females were examined daily on days 0-20 of gestation for body weight gain, toxicological effects and mortality. Upon completion of the study (day 20 of gestation), mated females were sacrificed; the uterus was excised and weighed. The location of viable and nonviable foetuses, early and late resorptions, the number of total implantations and corpora lutea, and maternal liver weights were recorded. The abdominal and thoracic cavities, palate, and eyes of the foetuses were examined. Foetal weight, length, and sex were recorded. Approximately one-third of foetuses were subjected to visceral examination and the remaining foetuses for skeletal examinations.

MMT-treated females suffered from a slight increase in matting and staining of the anogenital haircoat at 9 mg/kg bw/day. Differences in the number of maternal deaths and pregnant dams between MMT-treated and control groups were not statistically significant. Mean maternal body weights were slightly lower than controls at all dose levels during gestation. Compared to controls, weight loss in animals receiving the highest dose of 9 mg/kg bw/day reached statistical significance ($p<0.01$) at day 9 after gestation. Mean maternal liver weights for MMT-treated pregnant female rats were not significantly different from controls.

No statistically significant differences were observed between MMT-treated and control groups in the ratio of male to female foetuses, mean number of early resorptions, mean number of viable foetuses, or mean foetal crown-rump lengths. A slight but significant decrease in mean foetal body weight ($p<0.05$) was observed only in the 6.5 mg/kg bw/day MMT group. A statistically significant increase ($p<0.05$) in the number of foetuses and litters with malformations was detected at a dosage of 9 mg/kg bw/day MMT. At this dose, 14 foetuses (7 litters) showed malformations out of 163 foetuses (21 litters) examined skeletally. This compares with 5 foetuses (1 litter) showing malformations out of 196 control foetuses (23 litters) examined skeletally.

The significant increase in malformations in the high dose MMT-treated group was due to the presence of bent ribs in this group and not in controls. With the exception of a single foetus showing microphthalmia, all other malformation endpoints were normal. Across doses, the prevalence of bent ribs showed a dose related increase in incidence although a dose relationship was not evident for other malformation endpoints. The authors argue that bent ribs are not regarded as a usual malformation and that the exclusion of other malformation endpoints suggests a lack of a teratogenic response.

Maternal weight losses at the highest MMT dose are evidence of minor maternal toxicity. Historical control data provided in this study show both microphthalmia and rib anomalies as spontaneous events in this species. Given this history of spontaneous rib anomalies, an association between maternal toxicity and delayed ossification and the uncertainty over whether delayed foetal growth in possible association with maternal toxicity constitutes embryofoetotoxicity (Guittin, Eléfant and Saint-Salvi, 2000), data are insufficient to consider the prevalence of bent ribs alone as indicating abnormal enbryogenesis.

The NOAEL for maternal and developmental toxicity was 9 mg/kg bw/day. Twenty-five mated female rats were used in each treatment group (Ethyl Corporation 1979a).

The developmental toxicity of MMT was also examined in Long-Evans rats. Males and female rats were mated nightly at a 1:1 ratio. Vaginal smears were taken each morning and examined for the presence of sperm or a vaginal plug. The day mating was observed was considered day 0 of gestation. Pregnant females (9-59 animals per dose level) were dosed daily by gastric intubation with MMT (0, 5, 10, 20 and 40 mg/kg bw) in corn oil on days 6-15 of gestation.

Maternal body weight gain was significantly reduced during treatment on gestation days 6-15 in all MMT treatment groups. Weight gain was similar for the MMT-treated groups and controls by day 21 of gestation. MMT-treated females suffered from epistaxis, irregular or rapid breathing, and urinary incontinence during the treatment period. In addition to these symptoms, females exposed to 20 or 40 mg/kg bw/day were cachectic, dehydrated, lethargic with some alopecia and pilo-erection. Maternal death rates were comparable to controls at doses of 5 and 10 mg/kg bw/day but were increased significantly at the two highest dose levels, with mortality observed in 41 of 59 rats receiving 20 mg/kg bw/day and mortality after initiation of dosing in rats receiving 40 mg/kg bw/day leading to termination of this dose group. All deaths at 40 mg/kg bw/day occurred within 1-5 days of the treatment (days 7-11 of gestation). Examination of the animals in the high dose group revealed that lungs were mottled (5/9), dark red (6/9) and firm (5/9), the trachea contained a foamy liquid (3/9), and livers were dark red (3/9).

At 20 mg/kg bw/day, a significant decrease in maternal pregnancy rate was observed accompanied by significant decreases in fetal viability. At this dose, fetuses showed significant increases in soft tissue malformations, skeletal malformations and ossification variations.

At 5 mg/kg bw/day, in addition to significantly decreased maternal body weight gains, a significant increase in fetuses with skeletal malformations (total 7.4%, $p<0.05$) and ossification variations (total 47%, $p<0.05$) was recorded. This incidence of skeletal malformations at this dose was attributable predominantly to increased observations of curly tail. However, these findings were not supported by external fetal examination at term sacrifice, were not seen at the higher dose of 10 mg/kg bw/day and so were considered of uncertain toxicological significance.

Skeletal malformations observed in MMT-treated fetuses especially at the highest dose of 40 mg/kg bw/day included derangement of ocular pigmentation, curly tail and vertebral defects (missing or fused ribs).

The incidence of soft tissue malformations in MMT-treated fetuses was comparable between controls and 5 and 10 mg/kg bw/day dose groups. Soft tissue malformations observed especially in the 40 mg/kg bw/day dose group included microphthalmia, anophthalmia and distended ureter.

The NOAEL for developmental toxicity was determined as 10 mg/kg bw/day with effects seen at the maternally toxic dose of 20 mg/kg bw/day (Ethyl Corporation 1978a).

In a separate study by Ethyl Corporation (1979b), pregnant female Sprague-Dawley rats (5 per dose group) were treated daily with a single oral dose of MMT (1-30 mg/kg bw/day) on days 6-15 of gestation. Several females treated with 10 or 30 mg/kg bw/day and most treated with 20 mg/kg bw/day showed ocular discharge and matting and staining of the anogenital region. One female receiving 10 mg/kg bw/day died on

gestation day 11, four rats treated with 20 mg/kg bw/day and all treated with 30 mg/kg bw/day died between days 7-10 of gestation. Most of the rats that died during the study had congestion of the lungs and liver. A moderate reduction in body weight was observed in females treated with 10 mg/kg bw/day. The reduction in weight gain at 20 mg/kg bw/day was described as severe. Between 1-10 mg/kg bw/day a small increase in the mean number of early resorptions was observed. At 1 and 10 mg/kg bw/day a slight decrease in the mean number of implantations and live fetuses was noted. The one surviving female from the 20 mg/kg bw/day was gravid at day 20 of gestation. No individual animal data or statistics were provided. Insufficient data were provided to establish NOAELs and LOAELs.

10.6 Genotoxicity

The genotoxicity of MMT was investigated in vitro on *Salmonella typhimurium* strains TA98, TA100, TA1535, TA1537, TA1538 and *Saccharomyces cerevisiae* strain D3. MMT was tested at 1, 10, 50, 100, 500, 1000, 5000 μg/plate for the *S. typhimurium* strains and 0.1-5% for *S. cerevisiae* in the presence and absence of a metabolic activator (Aroclor 1254-stimulated rat liver homogenate). Cytotoxic effects were observed in all *S. typhimurium* strains tested at MMT concentrations between 500-5 000 μg/plate. In the presence of the metabolic activator, MMT when tested at 0.1-1% was found to reduce the survival of *S. cerevisiae* by approximately 50%. The survival of *S. cerevisiae* was doubled in the presence of 5% MMT and reduced at lower doses, in the presence of metabolic activator. MMT did not result in a significant increase in the average number of *S. typhimurium* histidine revertants per plate or *S. cerevisiae* mitotic recombinants (Ethyl Corporation 1977b).

MMT was also investigated in vitro in a chromosome aberration study using Chinese hamster ovary (CHO) cells and in vivo in a micronucleus assay using C57B1 mice. MMT induced chromosomal aberrations in vitro but did not induce effects in vivo (Blakey, 1996, personal communication).

A dominant lethal study was conducted on CD-1 mice. Sexually competent males were dosed via gastric intubation with MMT (80 and 160 mg/kg bw) in corn oil daily, for 5 consecutive days. On the last day of the treatment period, at least two hours after the last dosing, three untreated virgin females were placed with each male. Male and females remained together for seven days and then the females were removed and replaced with three new untreated virgins. This procedure continued for eight weeks. Males were observed daily for evidence of pharmacologic and toxicologic effects and mortality during both the exposure period and during mating. Females were sacrificed 8 days after removal from the male and the number of uterine implantations were recorded. Implantations were distinguished as early resorption sites (early fetal death), late resorption sites (late fetal deaths) and viable fetal swellings. During days 1 to 3 of the exposure period, male mice showed signs of hypoactivity, dehydration, and lacrimination. The male mortality rate at 80 mg/kg bw/day was 17% (2/12) and 23% (3/13) at 160 mg/kg bw/day. All males that died during the exposure period did so on day 3 or 4 of the treatment. Mottled liver (2/5), bright red lungs (1/5), bladder (1/5) and thoracic cavity abnormalities (1/5) were observed in the deceased males.

The pregnancy rate of the MMT groups was similar to controls. There was no statistically significant difference in the mean number of early fetal deaths or viable fetal swellings per pregnant female between the negative control and MMT-treated groups. An exception occurred in week three where 80 mg/kg bw/day MMT treatment

resulted in an increase in the mean number of viable fetal swellings per pregnant female. Expressed as a percentage of total implantation sites, early fetal death data were comparable between negative controls and MMT-treated groups. Exceptions were a significant decrease at week three for the 80 mg/kg bw/day MMT treatment and a significant increase at week seven for 160 mg/kg bw/day MMT treatment. These deviations from negative controls were not considered biologically significant. Ten male and 240 female mice were used per treatment. Negative and positive controls (corn oil alone and triethylenemelamine respectively) behaved accordingly. Under the conditions of the study, MMT did not cause dominant lethal effects in mice (Ethyl Corporation 1977a).

10.7 Carcinogenicity

The effect of MMT on lung tumour development was assessed by Witschi et al. (1981) in female A/J mice. Sixty mice were injected IP with 500 mg/kg bw urethan and sixty with 0.9% sodium chloride. One week later 30 mice from each group were given IP injections of MMT (80 mg/kg bw) in oil once a week for six weeks. The remaining 60 mice received corn oil alone. All mice were sacrificed 4 months after the first urethan injection. MMT alone or when administered repeatedly after urethan or sodium chloride treatment did not enhance lung tumour formation (Table 13).

Table 13. Tumour Incidence in MMT Treated Mice

Initial treatment	Weekly injections	Percentage of mice with tumours (%)	Number of tumours per mouse	Number of mice with tumours
Urethan	MMT + corn oil	100	7.6 ± 0.6	23
Urethan	Corn oil	100	8.3 ± 0.5	27
NaCl	MMT + corn oil	11	0.1 ± 0.1	24
NaCl	Corn oil	13	0.2 ± 0.1	27

The report states that lung cell proliferation, as measured by thymidine incorporation into DNA, was reduced on day one after MMT treatment, increased by 200% above controls on day 2, was 50% higher on day 4 and normal after day 6 (no further details were provided).

10.8 Pulmonary toxicity

As a result of evidence of lung damage in early reports of MMT toxicity, studies specifically examining pulmonary effects resulting from MMT exposure in animals have been conducted. These confirm the lungs as a target organ for MMT toxicity with common features of parenchymal inflammation, haemorrhaging and damage to nonciliated bronchiolar epithelial (Clara) cells.

Hanzlik et al. (1980a) investigated the pulmonary toxicity of MMT in male Sprague-Dawley rats. Single oral dosing with 125 mg/kg bw MMT (in corn oil) resulted in haemorrhage and alveolar and perivascular oedema of the lung after 24 hours. An accumulation of proteinaceous material in the alveoli characterised the alveolar

oedema. Lung weight, a measure of pulmonary toxicity, was significantly elevated 24 and 72 hours after oral dosing of MMT (125 mg/kg bw) and 8/14 rats died within 24 hours. The lungs of the deceased rats showed extensive haemorrhaging and congestion. There were minor lesions in the liver and kidneys. Lung weight was also significantly elevated 24, 48, and 72 hours after IP injection of MMT (20 mg/kg bw) in corn oil. Pre-treatment with phenobarbital (60 mg/kg bw for 3 days) protected against the pulmonary toxicity of MMT but induced mildly increased plasma GPT and decreased liver G6P indicating liver damage. The authors postulate that the protective effect of phenobarbital may be due to a first-pass effect where an enlarged, metabolically-induced liver limits the amount of MMT entering the systemic circulation. Between 3 and 14 animals were used per treatment.

The effect of MMT on Clara cells was examined after a single IP injection to female BALB/C mice (120 mg/kg bw), female S/A albino rats (5 mg/kg bw) and female LV_6/LAK Syrian hamsters (180 mg/kg bw). The incorporation of radiolabelled thymidine into pulmonary DNA, as a measure of cellular proliferation, was found to decrease slightly one day post MMT administration in mice and hamsters. All species showed a significant increase in thymidine incorporation by day 2, with peak incorporation at day 2 in rats and hamsters and day 4 in mice. Labelling indices in rats and mice, as determined by cell kinetic studies, demonstrated a significant increase in bronchiolar and parenchymal indices at day 2. Interstitial pneumonitis characterised by interstitial thickening and infiltration by neutrophils and macrophages, was observed in all animals two days post MMT injection but all were found to clear by day 21. With respect to interstitial pneumonitis, rats were the most sensitive species to MMT treatment, followed by mice, and then hamsters. Clara cell necrosis was evident in all species one day post MMT administration. This effect was greatest in distal airways and was most severe in mice, which had failed to return to normal by day 21. Bronchiolar morphology had returned to normal by day 7 in the hamster and day 21 in the rat. In addition, necrosis of the tubular epithelium in the renal cortex was observed in mice and minimally in the other species on days 1 and 2 post MMT administration. The number of animals per treatment totalled 36 for mice and 18 for rats and hamsters (Hakkinen and Haschek 1982).

The effect of MMT on Clara cells was also examined after a single IP injection to female BALB/C mice (120 mg/kg bw) and male Fischer-derived rats (8.4 mg/kg bw). Histopathological analysis 24 hours post MMT injection revealed a selective necrosis of Clara cells, particularly at terminal bronchioles. Mice were found to be more sensitive than rats. The pulmonary toxicity of MMT (90 mg/kg bw) was also assessed in female mice after a 1 hour pre-treatment with piperonyl butoxide, an inhibitor of the mixed-function oxidase system. The pre-treatment was found to significantly enhance the toxicity of MMT. Clara cell damage extended into the larger bronchioles and moderate oedema, inflammation and localised haemorrhaging became apparent within the parenchyma. In addition, the incidence of mortality was increased. The number of animals used per treatment was not stated (Haschek et al., 1982).

The ability of oxygen to enhance the pneumotoxic effects of MMT was investigated by Hakkinen et al. (1983) in female BALB/C mice and female CD/CR rats. Animals were injected IP with MMT in corn oil (5 mg/kg bw for rats and 120 mg/kg bw for mice) and immediately dosed with either 80% oxygen or air for 6 days. Total lung hydroxyproline levels were unaffected by MMT in mice 3 weeks after MMT dosing. A significant increase in total lung hydroxyproline was observed in treated mice when MMT was combined with oxygen treatment. The lungs of these mice were found to contain

scattered areas of interstitial thickening characterised by a mild hypercellularity and fibrosis, located mainly at terminal bronchioles and alveolar ducts. Although MMT was found to significantly increase total lung hydroxyproline levels in rats 3 weeks post MMT dosing, this effect was not enhanced by oxygen. Fibrosis noted in the lungs of rats exposed to both MMT and oxygen was similar in rats treated with only MMT. Between 8-10 mice and 4-6 rats were used per treatment (Hakkinen et al., 1983).

The toxicity of MMT was examined in male CD rats 1.5-96 hours after subcutaneous administration of a single dose of MMT (4 mg/kg bw in propylene glycol). Pulmonary lavage protein levels were used as an indicator of pulmonary toxicity. Pulmonary lavage protein levels were significantly elevated at all time points examined with levels peaking (5-fold increase) indicating maximal pulmonary toxicity at 24-48 hours after MMT administration. Pulmonary Mn levels peaked 3-6 hours post injection. Plasma urea and sorbitol dehydrogenase levels were not significantly altered by MMT, indicating little or no hepatic or renal injury. The number of animals used per treatment was not stated (McGinley et al., 1987).

Cox et al. (1987) examined the pulmonary toxicity of MMT in male Sprague-Dawley rats. A single IP injection of MMT (6-37.4 mg/kg bw) resulted in extensive mottling, haemorrhage and distension of the lungs and the presence of a pink, frothy, serosanguineous liquid in the trachea. Four animals were used per treatment.

A single subcutaneous injection of MMT (4 or 10 mg/kg bw) in corn oil vehicle to male Sprague-Dawley rats resulted in significant pneumotoxic responses. No deaths were observed at the lower dose. At the highest dose, 1/6 of the rats died within 24 hours. Laboured breathing prior to death and the presence of a frothy fluid in the trachea at necropsy were observed. Hepatic and renal markers (plasma lactate dehydrogenase, sorbitol dehydrogenase, and blood urea nitrogen) were considered normal. The lavage fluid of rats surviving for 24 hours after MMT administration (10 mg/kg bw) contained increased lactate dehydrogenase, albumin and total protein. These results correlate well with increased lung Mn content resulting from MMT administration (See Section 9). An additional experiment was performed assessing pneumotoxic responses resulting from MMT (4 mg/kg bw) administration in the presence of piperonyl butoxide, a cytochrome P450 monooxygenase inhibitor. A 1-hour pre-treatment with piperonyl butoxide (400 mg/kg bw) was found to protect against increases in lavage albumin and reduce the levels of Mn in the lungs. Pulmonary nonprotein sulfhydryl levels were significantly increased 24 hours after administration of MMT at 4 mg/kg bw, but this effect was reduced by piperonyl butoxide. The level of pulmonary thiobarbituric acid reactive materials was not altered by MMT. Heptane extraction of lung homogenates from MMT-treated rats indicated less than 2% of the pulmonary Mn was extractable, suggesting the presence of metabolites as opposed to MMT. Furthermore, the decrease in pneumotoxicity in the presence of piperonyl butoxide suggests that cytochrome P450 dependent monoxygenase metabolites are responsible for toxicity. Each treatment group contained 4-9 animals (Clay and Morris 1989).

The pneumotoxicity of MMT in female LAC-P Wistar rats was investigated after a single IP injection (6 mg/kg bw in oil). Lung weight and the activity of γ-glutamyltranspeptidase and alkaline phosphatase in bronchoalveolar lavage fluid were quantified as measures of pulmonary toxicity. The lung wet weight of MMT-treated rats was approximately twice that of the controls at 3-5 days post administration. MMT also resulted in a significant increase in the activity of the bronchoalveolar lavage fluid enzyme alkaline phosphatase 24 hours post administration. Pneumotoxic effects

consisted of a loss of type I pneumocytes, proliferation of type II cells and macrophage infiltration. Inhibitors of the cytochrome P-450 2B isoenzyme (O,O,S-trimethylphosphorodithioate, bromophos, 2,4-dichloro(6-phenylphenoxy)ethylamine and p-xylene) protected against the pulmonary toxicity of MMT. Five animals were used per treatment (Verschoyle et al., 1993).

The effect of MMT on Clara cells of the small airways was investigated in Sprague-Dawley rats. Each experimental group consisted of six rats. In this study rats were sacrificed 24 hours after a single IP injection of MMT (5 mg/kg bw). The lungs were lavaged and bronchoalveolar lavage fluid (BALF) was isolated and analysed for biochemical markers. MMT was found to cause a significant decrease in 16-17 kDa Clara cell protein (CC16) in BALF and a significant increase in albumin content. MMT did not alter the serum concentration of CC16 or renal function parameters (serum creatinine and albuminuria). However, the concentration of CC16 in urine was significantly increased. Histopathological analysis of the lung parenchyma revealed a slight interstital thickening and mild oedema in the alveolar walls and perivascular connective tissue. An increase in the numbers of enlarged type II pneumocytes and alveolar macrophages were observed in the alveolar lining and alveolar spaces respectively. The number and activity of neutrophils and lymphocytes appeared normal. Although ciliated cells of the epithelial lining of bronchioles appeared normal, Clara cell necrosis was evident, especially in distal airways (Halatek et al., 1998).

10.9 Neurotoxicity

Studies specifically examining the neurotoxicity of MMT in animals have been conducted. These indicate the ability of MMT to induce seizure activity and brain neurotransmitter and enzyme imbalances.

The ability of MMT to induce neurotoxic effects was investigated in male CD-1 mice injected subcutaneously with MMT (10, 20 or 80 mg/kg bw in propylene glycol). The concentration of dopamine in the striatum of mice that received MMT at 20 and 80 mg/kg bw on alternate days for 3 weeks (total of 11 injections) was reduced by 10% and 23% respectively. The level of dopamine in the olfactory tubercle was also significantly reduced in mice receiving 80 mg/kg bw. MMT at 80 mg/kg bw increased 4-aminobutyric acid (GABA) levels in both the striatum and olfactory tubercle but not the cerebellum. MMT did not significantly alter the activity of choline acetyltransferase in the striatum, substantia nigra, hippocampus or cerebral cortex. There was no significant change in dopamine or GABA levels in mice that received a single 80 mg/kg bw MMT injection when examined 1 and 21 days post injection. Between 6 and 16 animals were used per treatment (Gianutsos and Murray 1982).

Yong et al. (1986) investigated the neurotoxic effects in female Wistar rats resulting from repeated subcutaneous injections of MMT in propylene glycol. Rats received either 24 injections over a 48-day period and were sacrificed 24 hours after the last injection or 75 injections over a 5-month period and sacrificed one month after the last injection. The first MMT injection was given at 5 mg/kg bw, the second at 10 mg/kg bw, the third 15 mg/kg bw, the fourth 25 mg/kg bw, and the remainder at 50 mg/kg bw. The concentration of Mn in the cerebellum of rats surviving to 24 hours after the last of 24 injections was approximately twice that of controls (4.59 verses 1.71 μg/g dry weight). One month after the last of 75 MMT injections the level of Mn in rat cerebellum was only slightly increased above controls. Although 3,4-dihydroxyphenylacetic acid (DOPAC) levels in the striatum were slightly depressed in

rats that received 24 MMT injections, tyrosine hydroxylase activity and dopamine and homovanillic acid (HVA) levels were considered normal. All neurological markers examined in rats that received 75 injections were similar to controls. Histological analysis of the zona compacta of the substantia nigra indicated that the numbers of perikarya per unit area in rats that received 75 MMT injections were similar to controls. Between 8 and 13 rats were used per treatment.

The neurotoxicity of MMT was assessed in male CD-1 mice after a single IP injection of MMT (100-2000 mg/kg bw in propylene glycol or corn oil). Each treatment group contained between 4 and 6 animals. In animals that died, death was seizure-related and occurred within 2 hours of MMT administration. Seizure activity was observed within 0.5-1.5 min post MMT administration. MMT-induced seizure activity was accompanied by a 2.5-fold increase in brain Mn concentrations. The Mn brain content of control mice was 0.9 μg/g. The brain Mn content of mice demonstrating seizure was 2.45 μg/g when MMT was administered in propylene glycol and 3.25 μg/g when MMT was administered in corn oil. Only a small increase in brain Mn concentrations was observed in MMT-treated mice that did not show seizure activity (1.14 μg/g for propylene glycol and 1.63 μg/g in corn oil). The synthesis and release of GABA was unaffected 30 min after animals were injected with MMT (25-50 mg/kg bw) and aminooxyacetic acid (AOAA) (20 mg/kg bw, ip) to inhibit GABA transaminase. MMT was found to inhibit the binding of t-butylbicycloorthobenzoate (TBOB), a ligand for the GABA-A receptor linked chloride channel, to mouse brain membranes (median inhibitory concentration (IC50) = 22.8 μM) suggesting that seizure activity of MMT may be linked to inhibitory action at this site (Fishman et al., 1987).

The neurotoxicity of MMT was assessed in male ddY mice after chronic oral administration of MMT in food (0.5 g Mn/kg food) for 12 months. Between 4 and 6 animals were used per treatment. Daily food intake per mouse was reported as 3.6 ± 0.9 g for controls and 3.1 ± 0.7 g in the MMT-treated group. The dosage was therefore equivalent to approximately 51.7 mg Mn/kg bw/day (208.5 mg MMT/kg bw/day). MMT-treated mice showed significant weight loss compared to controls during the 12-month treatment period. Spontaneous motor activity was measured over a 30 minute period at intervals during the 12-month exposure period. The level of spontaneous motor activity was similar for the control and MMT-treated groups throughout the study, except on day 80, when the MMT-treated group showed significantly more motor activity compared to controls (Komura and Sakamoto 1992).

Although the MMT dose in this study are of similar magnitude to oral LD50 values for MMT in mice (Section 10.1), no deaths were reported in this study. This suggests a likely greater tolerance of a gradual MMT and Mn intake in food compared to a similar amount as a bolus dose.

In what appears to be a further study of the above animals, effects of MMT on various brain biogenic amines were reported by Komura and Sakamoto (1994). At the end of the exposure period the concentration of normetanephrine in the cerebellum of MMT-treated mice was significantly increased (46 ± 8 ng/g wet wt) when compared to the control group (6 ± 1 ng/g wet wt). This effect correlated with a significant increase in Mn levels in the cerebellum (0.29 μg Mn/g ww versus 0.13 μg Mn/g ww). Additional alterations were observed in brain biogenic amine levels but these effects did not correlate significantly with an increase in Mn. For example, the concentration of norepinephrine was significantly decreased and homovanillic acid was significantly increased in the corpus stratum; 3-methoxytyramine was significantly increased in the

midbrain; 3,4-dihydroxyphenylacetic acid was significantly decreased in the cerebellum; 3,4-dihydroxyphenylacetic acid, homovanillic acid, and serotonin were significantly decreased in the medulla oblongata and metanephrine was significantly increased in the medulla oblongata. The concentration of Mn in the corpus striatum, hypothalamus, midbrain, cerebral cortex, hippocampus and medulla oblongata was similar in MMT-treated and control groups (Komura and Sakamoto, 1994).

Evidence of neurotoxicity has been reported in ICR mice treated with MMT. Mice were injected IP daily with 0.05 or 0.1 mg/g bw MMT in corn oil for 3 days. Between four and six animals were used per treatment. Each treatment group contained between 4 and 6 animals. Both doses of MMT were found to significantly decrease motor nerve conduction velocity and reduce ouabain-sensitive Na^+K^+-ATPase activity in the sciatic nerve in vivo. MMT (0.03-3 mM) did not affect the activity of sciatic nerve Na^+, K^+-ATPase in vitro. The reduced ATPase activity correlated with a 58% decrease in the amount of catalytic $\alpha 1$ subunit polypeptide. These effects were associated with significantly increased Mn concentrations in blood and sciatic nerve of MMT-treated mice. These results suggest that MMT-induced neuropathy is associated with reduced nerve Na^+, K^+-ATPase activity and motor nerve conduction velocity (Liu et al 2000).

The mechanisms of MMT neurotoxicity have also been studied in vitro. In a recent study of cultured dopamine-producing PC-12 cells and nondopaminergic striatal γ-aminobutyric acidergic M213-20 cells, MMT was shown to be acutely cytotoxic particularly to dopamine-producing cells and decreased intracellular dopamine levels. Generation of intracellular reactive oxygen species (ROS), an early effect in toxicant-induced apoptosis, was observed within 15 minutes of exposure. A hallmark of apoptosis, genomic DNA fragmentation, was induced in a concentration dependent fashion. Lastly, PC-12 cells overexpressing the apoptosis inhibitory molecule Bcl-2 were shown to be significantly refractory to MMT-induced ROS. These in vitro data indicate that oxidative stress plays an important role in mitochondrial-mediated apoptotic neuronal death after exposure to MMT (Kitazawa et al., 2002).

10.10 MMT combustion products

Several studies exist examining the toxicity of combustion products of MMT generated either via a propane flame or from the operation of an automotive engine.

The chronic inhalation toxicity of Mn oxide (Mn_3O_4) as a combustion product of MMT was the subject of a report (Rinehart, 1975) published subsequently by Ulrich et al. (1979 a,b,c).

Ulrich et al. (1979a) documented the experimental procedure to examine the chronic inhalation toxicity of MMT combustion products. MMT combustion products, 'similar to that produced by an internal combustion engine', were generated by burning MMT vapours in a propane flame. This method was reported to produce a particulate matter consisting of Mn oxide (Mn_3O_4) with an aerodynamic diameter of approximately 0.11μm.

Using the experimental procedure published by Ulrich et al. (1979a), monkeys and rats were exposed to Mn oxide (Mn_3O_4) aerosol produced by the combustion of MMT. The animals were exposed for 24 hours per day for nine months to 0, 11.6, 112.5 or 1152 μg Mn/m^3 as Mn oxide (Mn_3O_4) aerosol. Each treatment group contained 15 male and 15 female rats and 4 male and 4 female monkeys. No clinical signs of toxicity were

observed at the end of the exposure period. Weight gain was normal in all monkeys, while rats exposed to 1152 μg Mn/m^3 as Mn oxide exhibited an accelerated weight gain. Monkeys in the highest dose group had increased levels of haemoglobin, mean corpuscular haemoglobin, and mean corpuscular haemoglobin concentration. The mean corpuscular haemoglobin level was also increased at 112.5 μg Mn/m^3 as Mn oxide. At the highest dose, rats exhibited increased haemoglobin, erythrocytes, mean corpuscular haemoglobin concentration and a decrease in mean corpuscular volume. At the same dosage male rats also showed increased mean corpuscular haemoglobin. At 112.5 μg Mn/m^3 as Mn oxide, male rats showed decreased reticulocytes and leukocytosis, while females exhibited decreases in hematocrit, haemoglobin, mean corpuscular haemoglobin and mean corpuscular volume. The authors state that while the effects were statistically significant, they may be within an acceptable normal range. All effects were reversible, as demonstrated by normal values at 6-months post exposure. Clinical chemistry evaluations revealed that at 1152 μg Mn/m^3 as Mn oxide male rats were found to have a depressed serum phosphate level. Microscopic evaluations revealed that brain, sternal bone marrow, and lung tissue were free of any changes. A small increase in liver weight was observed in female rats at 1152 μg Mn/m^3 as Mn oxide. The weight of other major organs was considered normal (Ulrich et al., 1979b).

In a follow-up publication by Ulrich et al. (1979c), the effect of MMT combustion products on pulmonary function was reported in each treatment group containing 15 male and female rats and 4 male and female monkeys. With regard to pulmonary function, there was a significant but small increase in tidal volume in male monkeys that received 112.5 μg Mn/m^3 as Mn oxide. Apart from this effect pulmonary function was considered normal. Although 14/112 electromyographic and limb tremor oscillograph records demonstrated possible abnormalities, the abnormal findings were evenly distributed between the dosage groups suggesting there were no exposure related effects (Ulrich et al., 1979c).

The toxicity of MMT combustion products was also tested via exposure of 180 male golden hamsters and 370 male outbred albino rats to automotive emissions generated using a 1972 Chevrolet 350 CID engine dynamometer system. Emissions were derived by passing exhaust generated from the combustion of fuel consisting of indolene "clear" containing MMT at 0.25 g Mn/gallon through a muffler, followed by dilution (25:1) with clean conditioned air. The final diluted emissions were split in two with one half being irradiated prior to exposure to animals. Irradiated emission typically contained 855 $\mu g/m^3$ particles (0.29 μm) consisting of 117 mg/m^3 Mn (13.7%). Nonirradiated emission typically contained 635 $\mu g/m^3$ particles (0.26 μm) consisting of 131 mg/m^3 Mn (20.7%). Animals were exposed for 8 hours per day for 56 consecutive days. Animals were sacrificed and tissues were collected for histological evaluation and Mn analysis. Alterations in general condition, appearance and weight gain were not observed. Hamsters were deemed to be free of abnormalities at necropsy while chronic respiratory disease lesions were observed in rats. Lesions observed in the lung consisted of a thickened, cuboidal epithelium at the terminal bronchiole that extended partly down the respiratory tree. These changes were noted in 21%, 14%, and 6% of irradiated, nonirradiated and control animals respectively. The degree of severity of the lesions did not appear to increase with exposure duration. A chronic hepatitis around portal triads was also observed. Manganese levels in the tissues (brain, liver and lung) of exposed animals were generally higher than controls (Moore et al., 1975b).

10.11 Human exposure

No epidemiological data are available. The following few overseas incidents of human exposure are described briefly in the Ethyl Corporation *Medical Guide for Use by Companies Handling HiTEC 3062 Octane Booster* (Ethyl Corporation, 2000).

Ethyl Corporation reported an incident of acute exposure to MMT. Three workers were reportedly exposed to an unknown concentration of airborne MMT for a short period and two workers were sprayed with the material. Symptoms reported included burning of the skin, a metallic taste in the mouth, headache, nausea and chest tightness. These effects abated within 24-48 hours.

Four workers were reportedly exposed to MMT in an 18 x 20 foot room when approximately 25 gallons (half a drum) of neat MMT was poured into a large open steam-heated pot. The MMT was heated long enough to form vapours as the workers detected an unusual odour within 5 minutes, when they shut off the heat and left the building. The four workers were examined immediately and no adverse effects or symptoms were noted. No symptoms were also reported 24 hours post exposure. Three hours post exposure the urine of the four workers contained 23, 87, 20, and 10 μg Mn/L. Twenty three hours post exposure urine levels had dropped to 8, 22, 5, and 10 μg Mn/L and workers were still free of symptoms.

Six individuals who reportedly experienced a 30 min skin exposure to MMT all reported a burning sensation of the skin and metallic taste in the mouth. Other symptoms included headache (4/6), nausea (4/6), gastrointestinal upset (3/6), dyspnea (3/6), chest tightness (1/6) and paresthesia (1/6). All symptoms appeared within 5-60 min post exposure and had abated in four individuals within 2-4 hours. The remaining two individuals reported that abdominal distress lasted for 2 days.

In 1959, two men wearing rubber gloves and air masks were exposed to a fine spray of neat MMT caused by a leak during a pumping operation. Although the hands and face of the two workers were covered, the spray moistened the remainder of both workers bodies for approximately 1.5 hours. The socks and shoes of both workers were saturated. On examination, the two men complained of a slight burning of the skin. Blood parameters and muscular co-ordination were unaffected. On the day of the exposure, urine Mn levels of the two workers were 137 and 46 μg/L. Several weeks later urine Mn levels were 3.4 and 2.9 μg/L.

A small volume of MMT, reportedly 5-15 mL when spilt on the wrist of a worker caused “thick tongue”, giddiness, nausea and headache within five minutes (U.S. Navy, 1968).

11. Pharmacokinetics and Toxicity of Manganese

Normally, MMT in fuel is destroyed during combustion resulting in the formation of inorganic Mn compounds. In early studies, MMT was reported to combust predominantly to Mn tetraoxide. More recent tests indicate combustion also to Mn phosphate and Mn sulphate with lesser oxides at higher oxidation states. Given particulate inorganic Mn emissions resulting from MMT use and that Mn is likely to reach target organs, it is prudent that a review of MMT as an AVSR should include a toxicological review of Mn.

Manganese is found in rock, soil, water and air and constitutes 0.1% of the Earths crust (NAS 1973). Manganese is generally not found as a base metal but is present as a variety of compounds such as oxides, sulphides, chlorides, carbonates, silicates, sulphates, nitrates and borates (NAS 1973). Different salts of Mn have a wide range of solubilities and are absorbed through biological membranes at different rates. Elemental Mn can exist in seven oxidation states depending on the compound, the majority of environmental Mn exposures being to Mn (II) and Mn (IV).

Atmospheric Mn is produced primarily from industrial emissions as particulate matter, with a mass median equivalent diameter of less than 5 μm, 50% of which is smaller than 2 μm (USEPA 1984; WHO 2000). Average airborne concentrations of Mn range from ~0.5-14 ng/m^3 in remote locations, to ~40 ng/m^3 in rural areas, and ~65-166 ng/m^3 in urban locations. Airborne Mn concentrations can rise to ~8000 ng/m^3 in source-dominated areas such as foundries (USEPA 1984; Stokes et al., 1988). WHO (1981) has estimated the mean daily intake of Mn from air in the general US population is less than 2 μg/day. This rises to 10 μg/day (24 h peak values exceed 100 μg/day) for individuals living near industrial areas that utilise Mn.

Exhaustive reviews of Mn and Mn compounds have been conducted in "Toxicological Profile for Manganese (Update)" (ATSDR 2000) and the Concise International Chemical Assessment Document 12 – "Manganese and Its Compounds" (WHO 1999). The following toxicological information is based primarily on this latter document.

11.1 Kinetics and metabolism

Manganese is an essential element and part of a normal diet of humans and animals. It plays a role in protein and energy metabolism, metabolic regulation, bone mineralisation, nervous system function and free radical neutralisation. Manganese is absorbed in the gastrointestinal tract after ingestion and also across the alveoli of the lungs after inhalation of Mn-containing dust or fumes. Manganese is transported in the plasma by transferrin, can cross the blood-brain barrier and placenta and tends to concentrate in the brain as well as tissues rich in mitochondria, such as the liver and kidney (WHO 1981). Dermal uptake of Mn or inorganic Mn compounds is considered extremely limited in the absence of an absorbable solvent. Dietary Mn intake is an important exposure route. In humans, the fraction of Mn absorbed in the gastrointestinal tract is variable but is in the order of 3-5%. The extent of absorption via

inhalation is determined by particle size and the location of pulmonary deposition. Particles of sufficiently small size to deposit in the lower airways are likely to be absorbed whilst larger particles confined to the upper airways may be transported vertically to the throat via the mucociliary elevator then swallowed and absorbed in the gastrointestinal tract.

Absorption of inorganic Mn compounds is dependent on the route of exposure as well as the chemical species. For example, in rodents, absorption of Mn chloride as measured by Mn levels in blood and brain occurs readily via oral, intraperitoneal or intratracheal routes. In contrast, while Mn dioxide is also absorbed significantly via intraperitoneal or intratracheal routes, poor absorption occurs via the oral route. Also, highly elevated Mn levels in the brain follow intratracheal but not oral administration of either Mn species. Single dose kinetic studies also show that Mn chloride is absorbed rapidly particularly via the intratracheal route compared to the oral route whereas Mn dioxide is absorbed relatively slowly. Also, although pulmonary clearance rates following intratracheal instillation in rats appear to be similar for the sulphate, phosphate and tetraoxide forms of Mn (half-time less than 0.5 days), the mechanisms of clearance i.e. absorptive (dissolution) versus nonabsorptive (mechanical transport) for each may be different (Vitarella et al., 2000a). These data underline differences in absorption of different inorganic Mn species via different routes and in particular the importance of inhalation exposure when considering neurological impacts of excessive Mn.

Separate rodent studies show that absorption of Mn may occur also in the intranasal airways and the uptake by olfactory neurons may serve as a pathway for Mn uptake bypassing the blood-brain barrier. Recently, with neutron activation analysis, Vitarella et al. (2000b) showed particular accumulation of Mn in the olfactory bulb in rats following inhalation of Mn phosphate over 14 days. Brenneman et al (2000) also confirmed transport of Mn to the brain via the olfactory pathway in a unilateral nasal occlusion model in rats subject to a single 90 minute nose-only exposure to a Mn chloride isotope. Other inhalation studies in the rat indicate that aqueous solubility is predictive of Mn absorption in the lung and transport to the brain with exposure to more soluble forms of Mn such as Mn sulphate resulting in higher brain Mn compared to insoluble forms such as Mn tetraoxide (Dorman et al., 2001).

Absorption is also affected by diet. In humans, low dietary iron is associated with increased Mn absorption, probably because iron and Mn share the same transport mechanism in the gut. Similar results are observed in animals where Mn uptake is increased by iron deficiency and decreased by pre-exposure to high dietary Mn levels. In chicks, high dietary intakes of phosphorus and calcium also have been shown to depress Mn uptake. Additionally, absorption is age-dependent. Human infants, especially premature infants, retain a higher proportion of Mn than adults (Dorner et al., 1989, cited in ATSDR, 2000).

Once absorbed, adult humans normally maintain stable tissue levels of Mn through regulation of Mn excretion. Manganese is removed from the blood by the liver where it is conjugated with bile and excreted into the small intestine. The majority is then removed in faeces. Some of the Mn in the intestine is also reabsorbed via the hepatic portal circulation. Excretion of Mn also occurs via urine, milk and sweat. In humans, the whole-body clearance half-life of Mn is 37.5 days, while that for the head is 54 days (Cotzias et al., 1968, cited in WHO 1981).

11.2 Human health effects

In humans, exposure to high levels of Mn is associated with adverse effects in pulmonary, reproductive and nervous systems. However, the hallmark of excessive Mn exposure is a progressive neurological syndrome featuring altered gait, tremor and occasional psychiatric disturbances referred to as "manganism".

The neurological dysfunction of manganism appears to be related to both dose and duration of Mn exposure. Initial signs may be vague and non-specific with complaints of general weakness, muscle pain, irritability, apathy and headache. Loss of libido, impotence, compulsive, aggressive or destructive behaviour may also occur. Dysfunction of basal ganglia may occur next as indicated by altered gait, clumsy limb movements, fine tremor, slow and halting speech and dull and expressionless facial expressions. A characteristic staggering gait with erect spine may develop further accompanied occasionally by psychological disturbances.

Isolated case reports describe manganism following occupational exposure to dusts or fumes containing inorganic Mn in mining, alloy machining or battery manufacture workers and also in individuals consuming water containing elevated Mn. However, long-term match-controlled epidemiological studies are able to confirm subtle neurological abnormalities in the absence of overt signs of manganism. Neurobehavioural tests such as the WHO Neurobehavioural Core Test Battery, Swedish Performance Evaluation System as well as supplementary manual dexterity and questionnaire evaluations uncover subclinical alterations in neurological performance and behavioural indicators associated with inhalation of Mn dusts or fumes. Subclinical nervous system toxicity through to overt manganism have been observed after inhalational exposure to total Mn dust levels ranging from 0.14-1.0 mg/m^3 for the former and from 2-22 mg/m^3 for the latter with exposure durations of 1-35 years.

In response to difficulties in detecting the subtle neurobehavioural alterations of manganism, magnetic resonance imaging (MRI) has been used in an attempt to detect early signs of Mn exposure. In male workers exposed occupationally (mean exposure > 10 years) to Mn dioxide dust (personal monitoring mean total atmospheric Mn 387 $\mu g/m^3$; blood Mn 14.8 µg/L; n = 11), Dietz et al. (2001) reported that despite the inability to detect changes in electrophysiology, MRI scans revealed increases in the ratio of globus pallidus to subcortical frontal white matter signal intensity (pallidal index) in Mn exposed workers compared to matched control subjects (personal monitoring mean total atmospheric Mn 10 $\mu g/m^3$; blood Mn 11 µg/L; n = 11). These changes are similar to those described by Kim et al. (1999) who reported increases in pallidal index during MRI scans of asymptomatic Mn workers (blood Mn 14.2 µg/L; n = 89) but not unexposed manual workers (blood Mn 11.7 µg/L; n = 16). Such changes in imaging are noteworthy as they reflect recent exposure to Mn and deposition of Mn in a brain area noted for association with Parkinsonian-like symptoms.

Few data are available regarding reversibility of neurological effects. The progression of clinical symptoms of manganism in five surviving workers 9-10 years removed from chronic 3-13 year exposure to Mn in a ferroalloy plant was documented by Huang et al. (1998) (cited in ATSDR, 2000). Despite dramatic decreases in blood and tissue Mn concentrations, neurologic examinations revealed a continuing deterioration of health indicated by abnormalities in gait, rigidity and writing, suggesting progression and permanence of neurological effects from frank Mn exposure.

In a prospective study of a cohort of affected Mn dioxide exposed workers at a battery plant, Roels et al. (1999) reported that a decrease in levels of Mn in total dust over 8 years was associated with normalisation of hand-forearm movement ability in a low exposure subgroup (personal monitoring mean total atmospheric Mn approximately 400 $\mu g/m^3$). However, medium (mean total Mn approximately 600 $\mu g/m^3$) and high (mean total Mn approximately 2000 $\mu g/m^3$) exposure subgroups showed no or only partial improvement in neurophysiological tests over this period.

In addition to neurological effects, acute and long-term inhalation of particulate Mn is associated with inflammatory responses in lungs. Symptoms and signs include reductions in lung function parameters, cough, bronchitis and pneumonia. Pneumonia is reported from acute and long-term inhalation exposure mostly in occupational settings but also in residential populations in proximity to Mn sources. A threshold level for respiratory effects has not been established. It is possible that pulmonary irritation, inflammation and increased susceptibility to infection may not be caused by Mn itself but may be a secondary effect of the inhalation of matter in particulate form.

Reproductive effects are also associated with excessive Mn exposure. Impotence and loss of libido are common symptoms in male workers showing clinical manganism following chronic occupational exposure. Chronic occupational exposure of males has been linked with impaired fertility as measured by decreases in numbers of children per married couple. However, dose-response data are unavailable and so a threshold level for reproductive effects in humans is not definable. Also, few data are available regarding reproductive effects in women.

Several recent reports suggest a possible link between Mn exposure and the development of the human prion disease known as Creutzfeldt-Jakob disease (CJD) (Brown 2001). It has been established that prion protein when isolated from brain tissue is bound to copper and that this interaction is necessary for the normal functioning of the protein as an antioxidant (Brown et al. 2001). A central characteristic of prion disease is the conversion of the normal prion protein to a corrupted form (Prusiner 1998). Experimental evidence suggests that the corrupted prion protein lacks antioxidant activity, is resistant to proteinases, and aggregates to form fibrils (Prusiner 1982; Brown et al. 1997). It was subsequently demonstrated in vitro that the prion protein can bind Mn and this interaction promotes the conversion to the corrupted form (Brown et al 2000). Other evidence for a possible link between Mn and CJD is provided from epidemiological studies. For example, Purdy (2000) reports that areas in the UK that have unusually high incidence of prion disease also have high Mn and low copper content in soil and plants. The reverse was noted for low prion disease areas. A second example comes from Slovakia, where people living in areas that have a high degree of industrial Mn contamination also have elevated body Mn levels. These same areas are known to experience an unusually high incidence of sporadic CJD (Mitrova 1991; Purdy 2000). Overall, although a link is suggested, data are not sufficient to define a causal relationship between Mn exposure and CJD.

The critical effect of chronic exposure to Mn is neurotoxicity although the pathogenic mechanisms are not fully understood. Manganese-related neurobehavioural effects are reported at lower doses in humans compared to animals suggesting that humans are more sensitive to Mn. However, such differences may also be related to differences in the sensitivity of test methods used to detect neurobehavioural effects in humans compared to animals.

The most reliable and robust epidemiological study for Mn exposure is Roels et al. (1992). In this study, neurofunctional endpoints were examined in 92 male workers exposed to Mn dioxide dust at an alkaline battery factory. Manganese workers were compared to a group of 104 age-matched control workers not exposed to neurotoxic chemicals or lung irritants recruited from a polymer processing plant. The prevalence of neuropsychological and respiratory symptoms and changes in lung ventilatory parameters, neurofunctional performances (visual reaction time, eye-hand coordination, hand steadiness, audioverbal short term memory) and several biological parameters including luteinising hormone, follicle stimulating hormone and prolactin concentrations in serum, blood counts and Mn concentrations in blood and urine were examined. For each worker, current exposure and lifetime integrated exposure to respirable and total airborne Mn dust were also determined. This allowed grouping of exposed workers according to lifetime integrated exposures to respirable Mn dust (<600, 600-1 200, >1 200 μg Mn/m^3 x year) and total Mn dust (<2 500, 2 500-6 000, >6 000 μg Mn/m^3 x year).

Manganese concentrations in blood and urine were significantly higher in the battery workers compared to control workers. In individual workers, however, Mn levels in blood or urine were not related to external exposure parameters. In comparison to control workers, Mn workers showed significantly poorer performance for visual reaction time, eye-hand coordination and hand steadiness. Underperformance was related to lifetime integrated exposures to total and respirable Mn dust, being most significant in the highest dose group.

From these data, a dose-response relationship was derived. A lower 95% confidence limit was estimated around the level of Mn exposure expected to result in a 5% response rate and this value (30 $\mu g/m^3$) was considered a surrogate for a NOAEL for neurological effects (WHO 1999; 2000).

Other dose-response estimates based on Roels et al. (1992) have derived a NOAEL of 32 $\mu g/m^3$ and LOAEL of 50 $\mu g/m^3$ (WHO 1999).

11.3 Effects in animals

Studies in animals identify the lungs and nervous system as target organs following acute exposure to Mn. In rodents, lung inflammation is reported following acute particulate inhalation exposures to 2.8-43 mg Mn/m^3 as Mn dioxide or Mn tetraoxide. It is notable again that inhalation of particulates in general are reported to cause pulmonary inflammatory responses and thus lung inflammation seen with Mn may, at least in part, be a generalised response to the physicochemical nature of the Mn load.

In different strains of rats, single oral exposures to Mn chloride by gavage have resulted in LD50 values of 275-804 mg/kg bw/day. Similar single exposures to Mn sulphate and Mn acetate have resulted in LD50 values of 782 and 1082 mg/kg bw/day respectively.

In non-lethal doses, decreased activity, alertness, muscle tone, touch response and respiration have been recorded in mice dosed with 58 mg Mn chloride/kg bw by oral gavage.

Little information is available regarding dermal toxicity, irritation and sensitisation properties of inorganic Mn compounds, possibly due to low dermal absorption. A single murine local lymph node assay study reported no cell proliferation with Mn salts inferring little sensitisation potential.

As in acute studies, neurological and pulmonary effects appear also to be a consequence of repeated Mn exposure. In contrast to acute bolus gavage administration, inorganic Mn appears to be more tolerated when administered over a longer term in feeding studies. The apparent differences in survival for bolus gavage versus feeding could be explained by species differences and/or the inability of clearance mechanisms to adequately handle high acute loads versus similar loads spread over time (ATSDR 2000).

Mice showed increased susceptibility to infection when exposed to Mn dioxide via inhalation for up to 4 days. Mild lung inflammation is reported in rhesus monkeys exposed to atmospheric Mn dioxide for 10 months.

A spectrum of neurological effects has been recorded in animals following short-term or chronic Mn exposure. Decreased motor activity or increased activity and aggression have been observed in rodents in food or drinking water studies. Although no evidence of neurological effects was observed in repeat dose studies in monkeys exposed to 20-40 mg Mn chloride/m^3, movement tremors with increased Mn in the globus pallidus and substantia nigra have been reported in monkeys following IV administration of 5-40 mg Mn/kg bw (as Mn chloride). In rodents, significant alterations in pup retrieval and open field behaviour are also reported with short-term exposure to inorganic Mn compounds.

In addition to activity and behavioural signs, repeat dose studies also report changes in brain histochemistry, brain enzyme function and neurotransmitter levels in rats and mice following Mn at oral doses ranging from 1 to 2270 mg Mn/kg bw over 14-364 days. Decreased levels of dopamine in the caudate and globus pallidus regions of the brain are reported in rhesus monkeys exposed via inhalation for up to 2 years to 30 mg Mn/m^3 (as Mn dioxide). Neurochemical changes are also reported in neonate rats at Mn levels similar to or slightly higher than dietary levels suggesting a particular susceptibility of the young to Mn.

To further investigate the impact of Mn for susceptible subpopulations, bioaccumulation and neurotoxicity of Mn have been investigated also in animal models of chronic liver disease (Salehi et al., 2001). Male rats with portacaval anastomosis were exposed via inhalation to 3050 µg/m^3 Mn phosphate for 4 weeks. Mn levels in blood, lung, cerebellum, frontal cortex and globus pallidus were significantly elevated compared to unexposed portacaval shunted rats. Neuronal cell losses from the frontal cortex, caudate putamen and globus pallidus was also significantly higher in Mn exposed rats. These results show Mn bioaccumulation and neurotoxicity following intranasal and respiratory tract (inhalation) exposure in animals with compromised Mn clearance.

The exacerbating effects of Mn exposure on neurological dysfunction have also been investigated in animal models of pre-parkinsonism (Witholt, Gwiazda and Smith 2000). Female rats in which a pre-parkinsonism state was induced by intrastriatal injections of 6-hydroxydopamine received IP injections of 4.8 mg Mn/kg bw (as $MnCl_2$) thrice weekly for 5 weeks. In contrast to control pre-parkinsonism rats in which no abnormalities were detected in neurobehavioural tests, rats also receiving Mn showed significant impairment of neurobehaviour in 8 of 10 neurofunctional tests. These results suggest that chronic Mn exposure may increase the risk of neurobehavioural impairment in pre-parkinsonism subpopulations.

Animal studies also show effects of Mn exposure on reproduction and development. Studies in rabbits, rats and mice report degenerative changes in the testes. In rabbits, a single dose of 160 mg Mn/kg bw (as Mn dioxide) resulted in slow degeneration of seminiferous tubules over 1-8 months with a loss of spermatogenesis leading to infertility.

In female rats, slight decreases in pregnancy rates were observed with Mn exposure via diet. In mice, exposure to 85 mg Mn/m^3 via inhalation for 16 weeks prior to and 17 days after conception was reported to decrease pup weight and activity. In a similar fashion to studies showing more efficient absorption of Mn following parental compared to oral administration, other developmental studies suggest that parenteral administration may cause greater toxicity when compared to administration via gavage. In rats, IV injection of 1.1 mg Mn chloride/kg bw on gestation days 6-17 induced mild skeletal malformations in foetuses. No effects were observed at 0.28 mg Mn/kg bw.

A recent fertility study was conducted by Elbetieha et al. (2001) in mice given Mn chloride in drinking water at 1-8 g/L for 12 weeks. Males showed decreased fertility at the highest dose but not at lower doses. Females showed no reductions in fertility at any dose but numbers of implantations and viable foetuses were significantly reduced at the highest dose. Females also showed significantly increased ovarian weights at 4 and 8 g/L and increased uterine weights at all doses. Although results are mixed, data indicate that Mn has the capacity to induce reproductive and developmental effects in animals.

The carcinogenic potential of Mn has also been examined in rodent studies but only limited oral exposure data are available and results are equivocal. Tumours of the lungs (following IP injection), pancreatic, pituitary and thyroid gland follicular cell adenomas are reported in separate studies in rats and mice but incidences are often not dose responsive, only marginally increased compared to internal controls and often within the bounds of historical controls. These data based on rodent studies do not provide sufficient evidence for carcinogenic properties of Mn.

In reverse mutation assays in bacteria and fungi, at least some forms of inorganic Mn are reported to have mutagenic potential. Mixed findings are also reported in in vitro clastogenicity studies using mammalian and plant cell cultures. Similar inconsistencies are also reported in in vivo mammalian studies. From these data, no firm conclusions can be drawn regarding the genotoxic properties of Mn.

12. Hazard Classification

This section discusses the classification of the health effects of MMT according to the NOHSC *Approved Criteria for Classifying Hazardous Substances* (the Approved Criteria) (NOHSC, 1999a) or, in the case of physicochemical hazards, the *Australian Code for the Transport of Dangerous Goods by Road and Rail* (ADG Code) (FORS, 1998). The Approved Criteria are cited in the NOHSC *National Model Regulations for the Control of Workplace Hazardous Substances* (NOHSC, 1994c) and provide the mandatory criteria for determining whether a workplace chemical is hazardous or not.

Where adequate human data were unavailable, the classification for health hazards has been based on experimental studies (animal and *in vitro* tests). In extrapolating results from experimental studies to humans, consideration was given to relevant issues such as quality of data, weight of evidence, metabolic and mode of action/mechanistic profiles, inter- and intra-species variability and relevance of exposure levels.

Classification of MMT in accordance with the OECD *Globally Harmonized System of Classification and Labelling of Chemicals* (GHS) (OECD 2002) can be found in Appendix 4.

MMT (as Mn) is currently listed in the NOHSC *List of Designated Hazardous Substances* (NOHSC, 1999b) with no classification. This is a result of several chemicals being included on the Designated List because they had an exposure standard already assigned by NOHSC.

12.1 Physicochemical hazards

MMT is a dark orange or yellow volatile liquid (vapour pressure 0.01 kPa at 20^{o}C) with a boiling point of 231.67^{o}C and a flash point (closed cup) of 96^{o}C. The ignition temperature is 257°C.

With respect to the ADG Code (FORS 1998), MMT does not meet the criteria for classification as a dangerous good on the basis of physicochemical hazards.

12.2 Health hazards

12.2.1 Acute toxicity

Animal studies with rats, rabbits and mice have shown MMT to induce damage to the lungs by all routes, kidney, liver and spleen effects, tremors, convulsions, dyspnea and weakness.

The LD50 for a single oral exposure to MMT for the rat ranges from 9 to 176 mg/kg bw, with several values < 25 mg/kg bw. The LC50 for the rat ranges from 0.22 to 0.25 mg/L for a 1 hour exposure and > 0.002 to 0.076 mg/L for a 4 hour exposure.

The dermal LD50 values for undiluted MMT range from 140 to 795 mg/kg bw.

In humans, the acute effects of MMT by dermal or inhalation exposure are reported to be burning of the skin, a metallic taste in the mouth, "thick tongue", giddiness, headache, nausea, chest tightness, gastrointestinal upset, dyspnea, and paresthesia. Symptoms appeared within 5-60 min post exposure and had abated by 2 days.

Classification:

Based on animal experiments, MMT meets the criteria of the ADG Code (FORS, 1998) for classification as a toxic substance Class 6.1, Packing Group I.

MMT meets the Approved Criteria (NOHSC, 1999a) for *acute lethal effects* by the inhalation route (R26 - Very Toxic by Inhalation), the oral route (R28 – Very Toxic if Swallowed) and dermal route (R24 – Toxic in Contact with Skin).

12.2.2 Irritation and corrosive effects

Accidental exposure of human skin to MMT vapours for 30 minutes and 1.5 hours is reported to result in a burning sensation of the skin. Symptoms appeared within 5-60 min post exposure and had abated by 2 days. Unfortunately, these reports lack detail regarding the extent of dermal inflammation. In several adequately reported studies in rabbits, MMT when applied for 24 hours was found to cause slight skin irritation.

Inadequate data exist to characterise the human ocular response to MMT. Rabbits exhibited slight conjunctival redness and chemosis after direct exposure of the eye to liquid MMT. The inflammatory response was resolved within 1-3 days.

In humans, accidental respiratory exposure to MMT vapours resulted in chest tightness. Symptoms had abated by 2 days post exposure. There are no animal studies of respiratory irritation from MMT.

Classification:

MMT does not meet the Approved Criteria (NOHSC, 1999a) for skin or eye irritation and data are insufficient to classify for respiratory irritation.

12.2.3 Sensitising effects

There are no animal studies or human case reports of skin or respiratory sensitisation to MMT.

12.2.4 Effects from repeated or prolonged exposure

There are no human case reports or studies detailing symptoms resulting from prolonged exposure to MMT.

One limited study is available detailing the effects of repeated (30 week) inhalation exposure to MMT in rats and mice. These animals showed weight loss and death at 0.014 mg/L MMT exposures and above. In mice at 0.014 mg/L, the percentage weight loss reported was 26.2% and mortality occurred in 1/10 animals. At 0.017 mg/L, weight loss increased to 35.9% and mortality occurred in 28 of 28 mice. Rats exposed to 0.017 mg/L showed 10.7% weight loss with mortality in 9 of 20 animals. Degenerative changes resulting from MMT exposure were seen in the liver and kidney. The NOAEL for rats and mice was 0.0062 mg/L.

Reports of the effects of repeated dermal exposure to MMT in animals are limited to one inadequate study where MMT in gasoline was applied to rats and rabbits at doses up to approximately 32 mg MMT/kg bw/day for between 14 and 25 weeks respectively. Repeated dermal contact with gasoline in the presence or absence of MMT resulted in mild skin injury in rats and extensive injury in rabbits. At 4.8 and 32 mg/kg bw/day in gasoline, vacuolar degeneration of the liver and kidney was observed in some rabbits.

The effects of repeated oral exposure to MMT are presented in several animal studies examining neurological and developmental effects. In a neurological study, mice were exposed to MMT in food (0.5 g Mn/kg food) for 12 months. MMT-treated mice showed significant weight loss during exposure and neurotransmitter imbalances following the 12 months exposure.

Three developmental studies document effects from oral exposure to MMT during days 6-15 of gestation. Slight weight loss in pregnant dams was observed with MMT at 2-9 mg/kg bw/day. In a second study, significantly reduced body weight gain was observed at doses down to 5 mg/kg bw/day. At this lowest dose, rats showed epistaxis, irregular or rapid breathing and urinary incontinence. Mortality was observed in 41 of 59 rats receiving 20 mg/kg bw/day. A third study showed moderate weight reductions in rats receiving 10 mg/kg bw/day and significant mortality at 20 mg/kg bw/day and above.

A repeat dose neurotoxicity study was conducted where female rats received up to 50 mg MMT/kg bw in propylene glycol via subcutaneous injections (24 injections over 48 days or 75 injections over 5 months). In animals receiving MMT over 5 months, enzyme and neurotransmitter markers showed no changes compared to controls and numbers of perikarya per unit area in the substantia nigra were also similar to controls. Slight depressions of 3,4-dihydrophenylacetic acid in the striatum were observed in animals receiving MMT over 48 days.

The neurotoxicity of MMT was assessed in male ddY mice after chronic oral administration of MMT in food (0.5 g Mn/kg food) for 12 months. Between 4 and 6 animals were used per treatment with dosages equivalent to approximately 51.7 mg Mn/kg bw/day (208.5 mg MMT/kg bw/day). MMT-treated mice showed significant weight loss compared to controls during the 12-month treatment period. Spontaneous motor activity was measured over a 30 minute period at intervals during the 12-month exposure period. The level of spontaneous motor activity was similar for the control and MMT-treated groups throughout the study, except on day 80, when the MMT-treated group showed significantly more motor activity compared to controls.

Classification:

There are insufficient data for the classification of MMT against the Approved Criteria (NOHSC, 1999a) with respect to severe effects after repeated/prolonged exposure via oral or dermal routes. However, data are sufficient from the 30 week repeat dose inhalation toxicity study for MMT to meet the Approved Criteria (NOHSC, 1999a) for *severe effects after repeated or prolonged exposure* by the inhalation route (R48/23 – Toxic: Danger of Serious Damage to Health by Prolonged Exposure Through Inhalation).

12.2.5 Reproductive effects

There have been no reports of adverse reproductive effects in humans attributed to MMT in the literature. Also, no fertility studies have been conducted in animals.

Three developmental studies of MMT in rats have been conducted with two studies establishing NOAELs of 9 and 10 mg/kg bw/day respectively for developmental effects. Data were insufficient to establish a NOAEL in the third study. These studies do not indicate that exposure levels below those associated with maternal toxicity significantly affect embryonic or foetal development.

Classification:

There are insufficient data for the classification of MMT against the Approved Criteria (NOHSC, 1999a) with respect to *fertility effects* (R60). MMT does *not* meet the Approved Criteria (NOHSC, 1999a) for *developmental effects* (R61).

12.2.6 Genotoxicity

The results of Ames testing (with or without metabolic activation), using several strains of *S. typhimurium* were negative for MMT. A mutation assay with *S. cerevisiae* (with or without metabolic activation) was also negative.

One unpublished study investigated the ability of MMT to promote chromosomal aberrations in a mammalian cell line (CHO). MMT was found to induce chromosomal aberrations when cultured in the presence of a metabolic activator in vitro.

In another unpublished study investigating the ability of MMT to induce chromosomal effects in vivo, MMT was found not to increase the number of micronucleated polychromatic erythrocytes in mice.

MMT was found not to cause dominant lethal effects when male mice were dosed by gastric intubation at up to 160 mg/kg bw/day for five consecutive days.

Classification:

MMT does *not* meet the Approved Criteria (NOHSC, 1999a) for *mutagenic effects* (R40, R46).

12.2.7 Carcinogenicity

One limited study is available examining the ability of MMT to affect lung tumour development in mice. Intraperitoneal injections of MMT (80 mg/kg bw) in oil once a week for six weeks did not enhance lung tumour formation in NaCl or urethan pre-treated mice.

Classification:

There are insufficient data for the classification of MMT against the Approved Criteria (NOHSC, 1999a) with respect to *carcinogenic effects* (R40, R45, R49).

13. Effects on Organisms in the Environment

This section provides information on the effects of MMT and Mn, the predominant combustion by-product, on animals and plants. Based on MMT use patterns, the review of effects has included the potential effects to organisms typically inhabiting terrestrial and aquatic environments.

The following information on MMT has been obtained from Kem-Tech Laboratories (1977) and Analytical Bio-chemistry Laboratories, Inc. (1990). Information on Mn, a component of MMT, has been obtained from various sources but principally the United States Environmental Protection Agency (USEPA) Ecotox Database (USEPA, May 2000) and the Australian and New Zealand Water Quality Guidelines (ANZECC and ARMCANZ, 2000). As these reference sources on Mn have been peer-reviewed, all of the publications referenced from these sources have not been peer reviewed for this present report (see citation for specific reference sources). Table 14 provides a summary of toxicity test data for aquatic organisms.

Table 14. Summary of aquatic toxicity data for MMT and Manganese

Taxa	Habitat	Compound	NOEC (mg/L)	LC(EC)50 (mg/L)
Plants/Algae	Freshwater	MMT	---	---
		Mn	≤4.5 [a]	≥4.98 [b]
	Marine	MMT	---	---
		Mn	---	≥25.7 [c]
Invertebrates	Freshwater	MMT	≤0.29 [d]	≥0.83 [e]
		Mn	≤3.9 [f]	≥4.7 [g]
	Marine	MMT	---	---
		Mn	---	1-10 [h]*
Fish	Freshwater	MMT	<0.14 [i]	≥0.20 [j]
		Mn	≤0.96 [k] (as LC10)	≥33.8 [m]
	Marine	MMT	---	---
		Mn	---	---
Amphibians	Freshwater	MMT	---	---
		Mn	---	≥14.3 [n]

Sources:

a. Den Dooren and de Jong, 1965 as cited by USEPA, 2000
b. Fargasova et al., 1999.
c. Rosko and Rachlin, 1975 as cited by USEPA 2000.
d & e. Analytical Bio-chemistry Laboratories, Inc., 1990.
f. Kimball, 1978 as cited by USEPA, 2000
g. Baird et al., 1991.
h. MacDonald et al., 1988.
i & j. Kem-Tech Laboratories, 1977.
k. Birge et al., 1981 as cited by USEPA, 2000.
m. Kimball, 1978.
n. Rao et al., 1987, as cited by USEPA, 2000.
* Range derived from MacDonald et al., 1988.
---No data available.

13.2 Terrestrial animals

13.2.1 MMT

Kinetics/metabolism and toxicity of MMT to mammals (e.g. rats, mice, monkeys, rabbits) have been presented in Sections 9 and 10, respectively. No information was available on the potential effects of excessive MMT exposure to birds or other terrestrial organisms.

13.2.2 Manganese

Mammalian toxicity data for inorganic Mn compounds resulting from MMT combustion have been presented in Section 11. No information was available on the potential effects of excessive Mn exposure to birds or other terrestrial organisms.

13.3 Terrestrial plants

13.3.1 MMT

No information was available on the toxicity of MMT to terrestrial plants.

13.3.2 Manganese

Manganese is an essential trace element for micro-organisms, plants and animals (CCREM, 1987, as cited by ANZECC and ARMCANZ, 2000). It is involved in nitrogen assimilation, as a catalyst in plant metabolism and functions with iron in the synthesis of chlorophyll (Labanauskas, 1966, as cited by Efroymson et al., 1997). Toxicity symptoms include marginal chlorosis and necrosis of leaves and root browning. Excess Mn interferes with enzymes, decreases respiration and is involved in the destruction of auxin (Foy et al., 1995, as cited in Efroymson et al., 1997).

Plant uptake of soil Mn occurs mainly via the roots of plants. However, intake through leaves may also contribute a fraction of the total uptake, and leaf uptake is slower (May, 1998). Fertilizer application of Mn to crops and other plants is undertaken to correct Mn deficiency by either soil or foliage application.

Most Mn in soils is precipitated as Mn oxide or hydroxide; however, the Mn^{2+} ion is the form available to plants. Soil Mn recommendations are based on the soil pH and crop being grown.

Excessive soil Mn may be problematic in acid soils (approximately pH <4.8; Rosen and Eliason, 2002). A toxic Mn situation may also develop in plants if excessive soil and/or foliar applications are used. Foliar-applied Mn fertilizer in excess of recommended amounts for Mn deficiency adjustment, or in small volumes of water, may burn leaves of plants (e.g. wheat, oats and sugar beets; Ohio State University, 1996).

In the early stages of plant growth, Mn toxicity symptoms may be similar to deficiency symptoms (e.g. interveinal chlorosis). Spotting, scorching on leaf margins and cupping of leaves are also typical toxicity symptoms. In potatoes, the symptoms are chlorosis and black specks on the stems and undersides of the leaves, followed by death of the lower leaves. Crops, including alfalfa, cabbage, cauliflower, clover, dry edible beans, potatoes, small grains, sugar beets and tomatoes, are sensitive to excess Mn.

Plant tissue analysis is used to diagnose Mn status in plants. Values below 20 mg/kg are usually considered deficient. Readings of 30 to 200 mg/kg are normal, and those over 300 mg/kg may lead to adverse effects.

Liming soils to the desired pH range for the crop will usually prevent soil Mn toxicity.

Soil Mn may be classified by concentrations as follows: Very High >400 mg/kg, High 201 to 400 mg/kg, Medium 51 to 200, Low 25 to 50 mg/kg and Very Low <25 mg/kg (Stanley and Baker, 2002).

Efroymson et al. (1997) has established soil (bulk) and soil solution toxicity benchmarks for Mn of 500 mg/kg in soil and 4 mg/L in soil solution. Wallace et al. (1977) evaluated the effects of Mn, added as $MnSO_4$ to a loam soil, on leaf and stem weights of bush beans grown from seed for 17 days. Stem weight was reduced 29% by 500 mg Mn/kg. This was the lowest concentration tested. As the 500 mg/kg benchmark for Mn is based on this one study, confidence in the benchmark is low; however, confidence in the soil solution benchmark is higher as more data are available (Efroymson et al., 1997). As indicated above, soil Mn toxicity is a function of soil pH as well as Mn concentration.

No published phytotoxicity data were available on the acceptable concentration of Mn in air for terrestrial plants. Recommended rates for foliar Mn fertilizers vary but range between approximately 0.008 and 2 kg Mn/ha, and frequent applications may be required (Vitosh, 1990; Barmac, 2002). Recommended foliar concentrations also vary but approximate 0.7 to 1.1 mg Mn/L (Barmac, 2002).

The information available indicates that Mn is an essential nutrient for plants and of low toxicity but exposure to high to very high soil Mn concentrations, combined with low pH soil conditions, or excessive foliar Mn may lead to adverse effects in plants. Adverse effects arise mainly due to excessive soil Mn bioavailability and toxicity from foliar application is unlikely.

13.4 Aquatic plants

13.4.1 MMT

No information was available on the toxicity of MMT to aquatic plants.

13.4.2 Manganese

Manganese is widely distributed in the earth's crust, most commonly as MnO_2. It is present in natural waters in suspended form (similar to iron) although soluble forms may persist at low pH or low dissolved oxygen (ANZECC and ARMCANZ, 2000).

The information presented below indicate that Mn is slightly to moderately toxic to freshwater and marine aquatic plants with acute LC(EC)50 values in the range of 4.98 mg/L or greater (Mensink et al., 1995).

Freshwater aquatic toxicity data for Mn were available for 7 aquatic plant species including 2 macrophytes and 5 species of algae. The data are summarised in Table 15.

Table 15. Summary of aquatic phytotoxicity data for manganese

Species	Endpoint	Result (mg/L)	Reference
Duckweed *Lemna minor*	96-hour EC50 (growth)	31	Wang ,1986, as cited by USEPA, 2000
Rice *Oryza sativa*	144-day IC50 (growth)	100	Wang ,1994, as cited by USEPA, 2000
Green algae *Scenedesmus quadricauda*	12-day EC50 (growth)	4.98	Fargasova et al., 1999
	12-day EC50 values (chlorophyll content)	1.91 - 2.28	Fargasova et al., 1999
Algae *Chlorella vulgaris*	NOEC (population growth)	4.5	Den Dooren & de Jong, 1965, as cited by USEPA, 2000
	LOEC (population growth)	11	Den Dooren & de Jong, 1965, as cited by USEPA, 2000
Algae *Chlorella pyrenoidosa, C. salina* & *S. quadricauda*	84-hour	100	Wong et al., 1980, as cited by USEPA, 2000
	144-hour LT50	50	Wong et al., 1980, as cited by USEPA, 2000

Two studies have investigated the effects of Mn to marine diatoms (Fisher and Jones, 1981, as cited by USEPA, 2000; Rosko and Rachlin, 1975, as cited by USEPA, 2000). The 96-hour EC50 (growth) values for diatoms (*Asterionella japonica* and *Nitzschia closterium*) range from 25.7 to 53.8 mg/L.

13.5 Aquatic invertebrates

13.5.1 MMT

The acute (48 hour) toxicity of MMT (95% purity) was studied in cultured neonates (<24 hours old) of the freshwater crustacean *Daphnia magna* (waterfleas) under static test conditions (Analytical Bio-chemistry Laboratories, Inc., 1990). The study was undertaken with measured MMT concentrations (means) of 0, 0.29, 0.65, 1.0, 2.0, and 3.5 mg/L. Measured concentrations were less than estimated nominal concentrations, presumably due to photodegradation of MMT. Test dilution water had hardness 172 mg/L (as $CaCO_3$), alkalinity 192 mg/L (as $CaCO_3$), pH 7.9, and conductivity 325 µMhos/cm. The 48-hour EC50 was 0.83 mg/L (95% C.I. 0.70 to 0.99 mg/L). The 4-hour and 24-hour EC50 were 0.87 and 0.94 mg/L, respectively. The 48-hour NOEL, based on the absence of immobility and abnormal effects, was 0.29 mg/L. Abnormal effects including immobility and surfacing were observed with the mean measured MMT concentrations of 0.65 mg/L and greater under test concentrations.

Acknowledging data limitations, these results for *Daphnia magna* suggest that MMT may be considered highly toxic to aquatic invertebrates, with acute LC(EC)50 values in the range of <1 mg/L (Mensink et al., 1995).

13.5.2 Manganese

The information presented below indicates that Mn is slightly to moderately toxic to freshwater and marine invertebrates with acute and chronic LC(EC)50 values in the range of 1 to 10 mg/L (Mensink et al., 1995).

Manganese is a neurotoxin and can block the release of neurotransmitters such as acetylcholine, while inhibiting acetylcholine esterase activity (Skukla and Singhal, 1984, as cited by MacDonald et al., 1988).

Acute and chronic toxicity data for Mn are available for several species of freshwater invertebrates with acute and chronic LC50 values ranging from 12.6 and 9 mg/L, respectively. Sublethal effects including intoxication and aberrant reproduction have been recorded above 4.7 mg/L. The data are summarised in Table 16.

Table 16. Summary of freshwater invertebrate toxicity data for manganese

Species	Endpoint	Result (mg/L)	Reference
Crayfish *Austropotamobius pallipes* & *Orconectes limosus*	4-day LC50	28 - 51	Boutet and Chaisemartin, 1973, as cited by USEPA, 2000
	30-day LC50	17 - 34	Boutet and Chaisemartin, 1973, as cited by USEPA
Rotifer *Brachionus calyciflorus*	24-hour LC50	38.7	Couillard et al., 1989, as cited by USEPA, 2000.
Waterfleas *Daphnia magna*	Acute LC50	≥12.6	Sorvari and Sillanpaa, 1996, as cited by USEPA, 2000; Kimball, 1978, as cited by USEPA, 2000; Cabejszek and Stasiak, 1960, as cited by USEPA, 2000
	21-day LC50	9	Kimball , 1978, as cited by USEPA, 2000
	EC50 (intoxication)	≥4.7	Baird et al., 1991; Anderson, 1948 as cited by USEPA, 2000; Biesinger and Christensen, 1972 as cited by USEPA, 2000; Khangarot and Ray, 1989 as cited by USEPA, 2000; Rossini and Ronco, 1996 as cited by USEPA, 2000
	48-hour NOEC (intoxication)	28	Bowmer et al., 1998 as cited by ANZECC and ARMCANZ, 2000
	48-hour EC50 (intoxication)	40	Bowmer et al., 1998, as cited by ANZECC and ARMCANZ, 2000
	21-day EC50 (intoxication)	5.7	Biesinger and Christensen, 1972 as cited by USEPA, 2000

Table 16. Summary of freshwater invertebrate toxicity data for manganese (cont.)

Species	Endpoint	Result (mg/L)	Reference
	21-day EC50 (reproduction)	5.2	Biesinger and Christensen, 1972 as cited by USEPA, 2000
	28-day NOEC	1.1	Kimball, 1978 as cited by USEPA, 2000
	7-day NOEC	3.9	Kimball , 1978 as cited by USEPA, 2000
	28-day MATC [a]	1.1	Kimball, 1978 as cited by USEPA, 2000
	7-day MATC	5.5	Kimball, 1978 as cited by USEPA, 2000
Tubificid worm *Tubifex tubifex*	24- and 96-hour EC50 (intoxication)	301 & 270	Khangarot, 1991 as cited by USEPA, 2000 Khangarot, 1991 as cited by USEPA, 2000
Sowbugs *Asellus aquaticus*: Crustacea	48-hour EC50 (intoxication)	771	Martin and Holdich, 1986 as cited by USEPA, 2000
	96-hour EC50 (intoxication)	333	Martin and Holdich, 1986 as cited by USEPA, 2000
Aamphipods *Cragonyx pseudogracilis*	48-hour EC50 (intoxication)	1389	Martin and Holdich, 1986 as cited by USEPA, 2000
	96-hour EC50 (intoxication)	694	Martin and Holdich, 1986 as cited by USEPA, 2000
Protozoa *Spirostomum ambiguum*	24-hour LC50	92.8	Nalecz-Jawecki and Sawicki, 1998 as cited by USEPA, 2000
	48-hour LC50	109	Nalecz-Jawecki and Sawicki, 1998 as cited by USEPA, 2000
	24-hour EC50 (development)	148	Nalecz-Jawecki and Sawicki, 1998 as cited by USEPA, 2000
	48-hour EC50 (development)	146	Nalecz-Jawecki and Sawicki, 1998 as cited by USEPA, 2000
Ciliates *Tetrahymena pyriformis*	3-hour IC50	152	Sauvant et al., 1995 as cited by USEPA, 2000
	6-hour IC50	117	Sauvant et al., 1995 as cited by USEPA, 2000
	9-hour IC50	106	Sauvant et al., 1995 as cited by USEPA, 2000

a. Maximum acceptable threshold concentration (MATC) is a hypothetical threshold concentration that is the geometric mean between the NOEC and LOEC concentration.

Manganese toxicity data are available for several species of marine invertebrates with acute toxicity (mortality) in the range of between 16 to 75 mg/L and chronic EC50 values in the range of 1 to 10 mg/L (refer Table 17).

Table 17. Summary of saltwater/marine invertebrate toxicity data for Manganese

Species	Endpoint	Result (mg/L)	Reference
American oyster *Crassostrea virginica*	48-hour LC50	16	Calabrese et al., 1973 as cited by USEPA, 2000
Blue mussel *Mytilus edulis*	48-hour EC50	30	Morgan et al., 1986 as cited by USEPA, 2000
Harpacticoid copepod *Nitocra spinipes*	96-hour LC50	70	Bengtsson, 1978 as cited by ANZECC and ARMCANZ, 2000
Brine shrimps *Artemia* spp.	24-hour LC50	75	Gajbhiye and Hirota, 1990 as cited by USEPA, 2000
	48-hour LC50	51.8	Gajbhiye and Hirota , 1990 as cited by USEPA, 2000
Starfish *Asterias rubens*	72-hour LT50	50	Hansen and Bjerregaard, 1995 as cited by USEPA, 2000
Yellow Crabs *Cancer anthonyi*	96-hour LD50 (embryo mortality)	10 - 100	MacDonald et al., 1988
	96-hour EC50 (hatching success)*	1 to 10	MacDonald et al., 1988
Oyster *Crassostrea gigas*	NOEC (larval settlement & behaviour)	0.02	Watling (1983)

* ANZECC and ARMCANZ (2000) noted the apparent spurious data generated in this study for lower tested concentrations of manganese.

MacDonald et al. (1988) noted that embryos of the crab species *Cancer anthonyi* live on the outside of the adult crab and may receive a higher exposure than many other aquatic organisms, explaining the higher sensitivity compared to other aquatic organisms. MacDonald et al. (1988) suggest that adverse effects of metals such as Mn may not be expressed within the typical time frame of standard toxicity tests (e.g. 96 hours), and that effects of Mn may not be fully expressed until at least 120 hours. However as they indicated, the increased rate of effects they noted at 120 hours in the toxicity test coincided with a peak in metamorphosis and hatching of viable embryos, which may be a more sensitive life stage. Other confounding factors in the tests, such as disease, cannot be excluded.

Eggs of the marine crab *Carcius maenas* can accumulate Mn during ovogenesis (Martin, 1976a, as cited in MacDonald et al., 1988). Further, eggs of the marine crab *Cancer irroratus* can accumulate Mn following exclusion, due to their selective adsorption to the chitinous vitelline membrane (Martin, 1976b, as cited in MacDonald et al., 1988). Bioconcentration of Mn by these crab species, may explain the high sensitivity of these species to Mn relative to other marine organisms (e.g. Rao and Saxema, 1981, as cited in MacDonald et al., 1988; Morgan et al., 1986, as cited in USEPA, 2000).

Watling (1983) investigated the effects of Mn on settlement of the oyster *Crassostrea gigas*, finding no effects on larval settlement or larval behaviour (as evidenced by foot

extension and crawling movement) when exposed to 0.02 mg/L. This was the highest concentration tested. The author suggested that minor effects in growth of 51-day old young (spats) may have been evident following 14-days exposure to Mn at the lowest concentration tested (i.e. 0.01 mg/L). However, further testing would be required to verify this hypothesis, and spat growth recovered following removal to clean seawater for 14 days.

13.6 Fish

13.6.1 MMT

The acute (96-hour) toxicity of MMT was studied in two species of freshwater fish - Bluegill sunfish (*Lepomis macrochirus*) and Fathead Minnow (*Pimphales promelas*) under static test conditions (Kem-Tech Laboratories, 1977). Bioassays were conducted with three applied concentrations of MMT with 10 fish in 12 litres (in 20 litre glass cylinders). Test dilution water had a hardness of approximately 125 ppm (as $CaCO_3$), pH 7.0 and dissolved oxygen (saturated). Light was limited as much as practical during the tests with MMT. The fish were conditioned to semi-dark conditions at 20°C. MMT was added to the medium with acetone as solvent.

The Kem-Tech Laboratories (1977) study was undertaken in duplicate with measured MMT concentrations (means) of <0.04 (control), 0.14, 0.25 to 0.36, and 0.45 to 0.47 mg/L. Measured concentrations were less than estimated nominal concentrations, presumably due to both spontaneous degradation of MMT and MMT degradation associated with contact with fish. MMT concentrations in each test solution declined significantly throughout the test duration.

Median Threshold Limit (TLm or TL50) is the concentration of a chemical estimated to kill 50% of exposed organisms in a given time period. It is often used interchangeably with aquatic LC50 (USEPA, 1977). TLm concentrations (measured, mg/L) over 12, 24, 48, 72 and 96 hours for L. macrochirus and P. promelas are summarised in Table 18.

Table 18. Summary of freshwater fish toxicity data (TLm mg/L) for MMT

Fish Species	12 Hours	24 Hours	48 Hours	72 Hours	96 Hours
P. promelas	0.23 - 0.36	0.23 - 0.36	0.21 - 0.34	0.21 - 0.34	0.21 - 0.34
L. macrochirus	0.20	0.20	0.20	0.20	0.20

As indicated above, most lethality occurred within the first 12 hours. Mortality was rare in the initial hour in tests under 3 ppm (measured). However, stress was evident in the first few minutes (Kem-Tech Laboratories, 1977). The constancy of effects through time probably reflects the rapid degradation of MMT from the test solutions. Monitoring of MMT in test solution indicated 80 to 88% reduction in MMT within a 96-hour period. TLm results beyond 12 hours are probably not reliable. The lowest 12-hour TLm derived for MMT was 0.20 mg/L. Sensitivity to MMT was similar between the species, with mortality evident in the concentration of 0.18 to 0.34 mg/L or greater.

Survival was evident below an exposure concentration of 0.18 mg/L. However, stress (irritation) was evident in fish at the lowest test concentration (0.14 mg/L). The threshold for stress was not determined. Recovery from stress was evident following cessation of exposure.

The mode of toxicity in both fish species tested was similar with symptoms including fitful activity, gradual loss of equilibrium (horizontally usually first, then vertically), excess mucous production except in the lowest test concentrations, and finally gulping at the surface with fitful swimming.

Acknowledging data limitations, these results suggest that MMT may be considered highly toxic to fish, with acute LC(EC)50 values in the range of <1 mg/L (Mensink et al., 1995).

13.6.2 Manganese

The data presented below indicate that Mn is slightly to moderately toxic to freshwater fish with acute and chronic LC(EC)50 values in the range of 10 to 100 and 1 to 10 mg/L, respectively (Mensink et al., 1995). Several studies have investigated the effects of Mn on freshwater fish. ANZECC and ARMCANZ (2000) reported acute (48 to 96-hour) LC50 values of 33.8 to 4540 mg/L. Several data are available on the effects of chronic exposure of freshwater fish to Mn, and chronic NOEC values in the range of 1.27 to 9.99 mg/L (growth and mortality). The toxicity data have been summarised in Table 19.

Table 19. Summary of freshwater fish toxicity data for manganese

Species	Endpoint	Result (mg/L)	Reference
Fathead minnows *Pimphales promelas*	96-hour LC50	33.8	Kimball (1978), as cited by USEPA, 2000
Longfin dace *Agosia chrysogaster*	96-hour LC50	130	Lewis (1978), as cited by USEPA, 2000
Silverside *Basilichthys australis*	96-hour LC50	>50	Trucco et al. (1991), as cited by USEPA, 2000
Giant gourami *Colisa fasciata*	24-hour LC50	478	Nath and Kumar (1987), as cited by USEPA, 2000
	48-hour LC50	345	
	72-hour LC50	324	
	96-hour LC50	295	Nath and Kumar (1987), as cited by USEPA, 2000
			Nath and Kumar (1987), as cited by USEPA, 2000
			Nath and Kumar (1987), as cited by USEPA, 2000
	96-hour LC50	1040	Agrawal and Srivastava (1980), as cited in USEPA, 2000

Table 19. Summary of freshwater fish toxicity data for manganese (cont.)

Species	Endpoint	Result (mg/L)	Reference
Medaka *Oryzias latipes*	24-hour LC50	>1000	Tsuji et al. (1986), as cited by USEPA, 2000
	48-hour LC50	>1000	Tsuji et al., 1986, as cited by USEPA, 2000
Rainbow trout *Oncorhynchus mykiss*	4-hour LC01	0.39	Birge et al., 1981 as cited by USEPA, 2000
	4-hour LC10	0.96	Birge et al., 1981 as cited by USEPA, 2000
	28-day LC50	2.91	Birge et al., 1980 as cited by USEPA, 2000
	100-day MATC [a]	0.77 -1.53 [b]	Goettl and Davies, 1978 as cited by USEPA, 2000
Goldfish *Carssius auratus*	7-day LC50	8.22	Birge, 1978 as cited by USEPA, 2000
Fathead Minnow *Pimphales promelas*	8-day LC50	34.6	Kimball, 1978 as cited by USEPA, 2000
	28-day LOEC (mortality)	19.7	Kimball, 1978 as cited by USEPA, 2000
	28-day MATC (mortality)	14.0	Kimball, 1978 as cited by USEPA, 2000
	28-day NOEC (mortality)	9.99	Kimball, 1978 as cited by USEPA, 2000
	LOEC (growth)	2.48	Kimball , 1978 as cited by USEPA, 2000
	MATC (growth) [a]	1.77	Kimball, 1978 as cited by USEPA, 2000
	NOEC (growth)	1.27	Kimball, 1978 as cited by USEPA, 2000
Brown trout *Salmo trutta*	62-day IC25	4.67 - 8.68 [c]	Stubblefield et al., 1997 as cited by USEPA, 2000
	62-day NOEC (mortality	4.41	Stubblefield et al., 1997 as cited by USEPA, 2000
	62-day NOEC (growth)	4.55	Stubblefield et al., 1997 as cited by USEPA, 2000

a - Maximum acceptable threshold concentration (MATC) is a hypothetical threshold concentration that is the geometric mean between the NOEC and LOEC concentration. b - Range not refined. c. Water hardness dependent (refer below).

Stubblefield et al. (1997), as cited by USEPA (2000), determined that water hardness significantly affects Mn chronic toxicity, with toxicity decreasing with increasing hardness. Using early life stage brown trout (*Salmo trutta*), Stubblefield et al. (1997) derived 62-day 25th percentile inhibitory concentration (IC25) values, based on the combined endpoints (i.e., survival and body weight), were 4.67, 5.59, and 8.68 mg/L

(based on measured Mn concentrations) at hardness levels of approximately 30, 150, and 450 mg/L as $CaCO_3$, respectively. NOEC values (62-day) for mortality and growth were 4.41 mg/L and 4.55 mg/L, respectively.

No toxicity data were available on the effects of Mn on saltwater fish species.

13.7 Amphibians

13.7.1 MMT

No toxicity data were available on the effects of MMT on amphibians.

13.7.2 Manganese

Acute toxicity data were available for one frog species. Rao et al. (1987), as cited by USEPA, 2000, derived 24-, 48-, 72- and 96-hour LC50 values for Mn for tadpoles of ornate narrow-mouthed Frog *Microhyla ornata* in the range between 17.5 to 14.3 mg/L.

13.8 Summary of environmental effects

13.8.1 MMT

Following the guidelines from Mensink et al. (1995) and laboratory-derived aquatic toxicity data, MMT may generally be regarded as highly toxic to aquatic invertebrates and fish, with acute LC(EC)50 values in the range of <1 mg/L. Effects of MMT in aquatic animals may include mortality, immobility, fitful activity, gradual loss of equilibrium (horizontally usually first, than vertically), excess mucous production except in the lowest test concentrations, and finally gulping at the surface with fitful swimming.

A predicted no effect concentration (PNEC) for MMT to freshwater organisms of 0.014 mg/L has been derived by applying a standard assessment factor of 10 to the lowest available NOEC data of 0.14 mg/L for freshwater fish (Kem-Tech Laboratories, 1977).

There is currently no environmental hazard classification system in Australia. In accordance with the OECD Globally Harmonized System of Classification and Labelling of Chemicals (OECD 2002), MMT would be classified Chronic 1 Very Toxic to Aquatic Life with Long-lasting Effects.

13.8.2 Manganese

Aquatic toxicity of MMT is high relative to Mn, which may be regarded as slightly to moderately toxic to aquatic organisms with chronic exposure effects in the 1 to 10 mg/L concentration range (Mensink et al., 1995).

Manganese is a naturally occurring element and essential for nutrition in plants and animals. Typical concentrations of Mn in marine and freshwaters approximate 0.003 to 0.38 and 1.5 µg/L, respectively (ANZECC and ARMCANZ, 2000).

ANZECC and ARMCANZ (2000) provide a quality guideline (trigger level) for Mn for the protection of freshwater ecosystems of 1.7 mg/L. They calculated this moderate reliability trigger value for Mn using a statistical distribution method with 95%

protection and an acute to chronic ratio (ACR) of 9.1. This trigger level is considered to be a suitable predicted no effect concentration ($PNEC_{Freshwater}$) for this assessment.

Insufficient toxicity data were available for marine organisms for ANZECC and ARMCANZ (2000) to derive a marine trigger value. They derived a marine interim indicative working level (IIWL) for Mn of 0.8 mg/L. This IIWL was derived by dividing the lowest available acute LC(EC)50 by a standard assessment factor of 20 (Bonnell and Atkinson, 1999, as cited by ANZECC and ARMCANZ, 2000). The lowest acute 48-hour LC50 was 16 mg/L for the American oyster *C. virginica* (Calabrese et al., 1973, as cited by USEPA, 2000). The value of 0.8 mg/L is considered a suitable $PNEC_{Marine}$ for this assessment.

The $PNEC_{Marine}$ and $PNEC_{Freshwater}$ values are not widely dissimilar in magnitude; however, there is greater uncertainty in the $PNEC_{Marine}$ than the $PNEC_{Freshwater}$ due to the lesser amount of marine aquatic toxicity data available (ANZECC and ARMCANZ, 2000).

14. Risk Characterisation

In this section, the results of the health hazard and occupational exposure assessments are integrated to characterise the risk of adverse effects to workers potentially exposed to MMT.

14.1 Environmental risk

This section provides a characterisation of risks to the environment from use of fuels containing MMT as an AVSR.

A hazard quotient (HQ) approach has been used to predict the hazard to terrestrial and aquatic organisms. To predict a low environmental risk, the ratio of PEC to PNEC needs to be 1 or less (i.e. HQ ≤ 1).

14.1.1 Terrestrial risk

Most of the MMT used each year will be destroyed during combustion within internal combustion engine cylinders. MMT is unstable to photochemical degradation in the atmosphere with an estimated half-life of 8 to 18 seconds (Ter Haar et al. 1975). In water bodies, MMT is likely to degrade in sunlight with a half-life of approximately 1 minute. However, in deeper waters, photodegradation may be reduced and hydrolysis slow.

Following combustion, the Mn component in MMT is converted to a mixture of Mn compounds (Mn phosphates, oxides and sulphates), and most will apparently remain in the exhaust train. However, approximately 20% of these Mn compounds may be emitted with exhaust gases associated with very fine particles (< 2.5 μm). These particles have a low quiescent air sedimentation velocity, and may remain suspended in air for a prolonged period. Ultimately, settlement to the earth surface (land and water) will occur, with Mn becoming associated with soils, waters and aquatic sediments.

A predicted no effect concentration ($PNEC_{mammals}$) of 6.2 mg/m^3 (inhalation) has been derived for mammals exposed to MMT (Section 10.4). Concentrations of MMT in air at a petrol station using MMT in Canada approximated 12 ng/m^3 and concentrations were lower in other areas sampled (see Table 5). Given this air MMT concentration at a high use area, and that MMT degrades rapidly when exposed to sunlight, terrestrial wildlife are unlikely to be exposed to MMT in air at levels of concern.

Conservative estimation of potential Mn levels in air indicates an Mn concentration (PEC) of up to 49 ng/m^3 (Table 6) for the Present Use scenario. This PEC is several orders of magnitude lower than the conservatively estimated $PNEC_{mammals}$ of 11.6$\mu g/m^3$ for Mn in air.

Although no published phytotoxicity data were available on the acceptable concentration of Mn in air for terrestrial plants, no records of adverse effects on plants have been noted in the literature in MMT use areas. The information available indicates that Mn is an essential nutrient for plants and of low toxicity but exposure to high to very high soil Mn concentrations combined with low pH soil conditions, or excessive

foliar Mn may lead to adverse effects in plants. However, plants have a propensity to tolerate foliar exposure to Mn and recommended foliar concentrations of Mn typically approximate 1 mg/L, which is several orders of magnitude higher than the estimated concentration of Mn in stormwater in MMT use areas (Section 8.3.4). Aerial deposition of Mn-bound particles onto plants in MMT use areas is unlikely to reach concentrations of concern.

Levels of Mn in soils (using the example of urban runoff in Sydney) are unlikely to reach levels of concern. With the MMT use scenarios developed in Section 8.2, the estimated concentration of Mn deposition from air to land is unlikely to result in unacceptable soil Mn concentrations. In concentration areas such as stormwater, runoff Mn may contain approximately 1.2 μg Mn/L in high MMT use areas (using the Sydney example from Section 8.3.4), several orders of magnitude less than phytotoxicological benchmark for Mn in soil solution of 4 mg/L.

14.1.2 Aquatic risk

A $PNEC_{Freshwater}$ for MMT of 0.014 mg/L has been derived based on the application of a standard assessment factor of 10 to the lowest available NOEC data of 0.14 mg/L. However, due to MMT's instability in the environment and subsequent low probability of discharge to water bodies during normal use of fuels containing MMT, further assessment of risk from MMT to aquatic organisms is not considered necessary.

PNECs for Mn in freshwater and marine waters of 1.7 and 0.8 mg/L, respectively, have been derived (ANZECC and ARMCANZ, 2000; Section 14.5).

As indicated above, the PEC for Mn in stormwater derived from urban runoff may approximate 0.0012 mg/L (refer Section 8.3.4).

Hazard quotients for estimated Mn discharge to freshwater and marine ecosystems from urban runoff have been summarised below:

Predicted Environmental Concentration of Manganese, PEC (mg/L)	**Predicted No Effect Concentration for Manganese, PNEC (mg/L)**		**Hazard Quotient, HQ**	
0.0012	$PNEC_{Freshwater}$	1.7	$HQ_{Freshwater}$	0.0007
0.0012	$PNEC_{Marine}$	0.8	HQ_{Marine}	0.0015

This evidence supports a conclusion of a low expected risk to the aquatic environment from use of AVSR products containing MMT for the uses prescribed and the volumetric use rates estimated. The abovementioned HQ values are based on current estimated LRP demand (Present Use scenario), and risks are likely to reduce further as demand for LRP decreases over time.

14.2 Occupational risk

A margin of exposure methodology is used frequently in international assessments to characterise risks to human health (European Commission, 1996). The risk characterisation is conducted by comparing quantitative information on exposure to the NOAEL and deriving a Margin of Exposure (MOE) as follows:

1. Identification of the critical effect(s);

2. Identification of the most appropriate/reliable NOAEL (if available) for the critical effect(s);

3. Where appropriate, comparison of the estimated or measured human dose or exposure (EHD) to provide a Margin of Exposure:

   MOE = NOAEL/EHD;

4. Characterisation of risk, by evaluating whether the Margin of Exposure indicates a concern for the human population under consideration.

The MOE provides a measure of the likelihood that a particular adverse health effect will occur under the conditions of exposure. As the MOE increases, the risk of potential adverse effects decreases. In deciding whether the MOE is of sufficient magnitude, expert judgement is required. Such judgements are usually made on a case-by-case basis, and should take into account uncertainties arising in the risk assessment process such as the completeness and quality of the database, the nature and severity of effect(s) and intra/inter species variability. Default uncertainty factors for intra- and inter-species variability are usually 10-fold each and so a MOE of less than 100 is usually considered a flag for concern.

14.2.1 Critical health effects

MMT

MMT is acutely toxic by all routes of exposure. The critical effects from acute exposure to MMT are neurological and pulmonary dysfunction. In humans, giddiness, headache, nausea, chest tightness, dyspnea and paresthesia are reported in anecdotal cases of acute occupational exposure. Acute lethal exposure to MMT in animals is associated with damage to the lungs, kidney, liver and spleen effects, tremors, convulsions, dyspnea and weakness. In both animals and humans, slight skin and eye irritation results from dermal and ocular exposure respectively.

Only limited repeated dose toxicity data are available. Repeated inhalation exposure to MMT is reported to result in degenerative changes in liver and kidneys. A NOAEL of 0.0062 mg/L for inhalation exposure was reported. MMT did not cause teratogenic or embryotoxic effects in developmental studies in rats.

Manganese

Given their production and widespread dissemination resulting from MMT combustion, the present assessment also considers the health effects of Mn and inorganic Mn compounds.

In animal studies, the critical effect following acute exposure to inorganic Mn compounds is neurological dysfunction. Decreased activity, alertness, muscle tone, touch response and respiration have been reported with oral administration. Pulmonary effects are also reported in inhalation studies, but these may at least in part reflect an inflammatory effect following inhalation of particulate matter rather than a result of pulmonary toxicity of Mn.

In repeated dose animal studies, the critical effect is also neurological dysfunction. Effects range from decreased motor activity to increased activity, aggression and movement tremors. In humans, chronic occupational exposure to respirable dusts (2-22 mg/m^3) leads to manganism, a progressive neurological disorder. Subclinical nervous system toxicity has been detected in repeated occupational exposures ranging from 0.14-1.0 mg/m^3. Reproductive effects including impotence and loss of libido in male workers have also been associated with high Mn exposures. However, a dose-response relationship for reproductive effects has not been established.

A principal epidemiological study of occupational inhalation exposure to Mn in which neurobehavioural endpoints were examined (Roels et al., 1992) was used to determine a dose-response relationship for neurological effects. A lower 95% confidence limit was estimated at the level of Mn exposure expected to result in a 5% response rate. This value (30 $\mu g/m^3$) was considered a surrogate for a NOAEL for neurological effects. It is important to base the risk characterisation on effects seen due to inhalational exposure, as there appears to be differences in toxicity based on route of exposure and absorbed dose.

14.2.2 Occupational health and safety risks

Although MMT is toxic by oral as well as dermal and inhalation routes, the likelihood of exposure by ingestion in occupational settings is expected to be low. Similarly, the low vapour pressure of MMT renders inhalation exposure to MMT vapours in occupational settings unlikely. Exposure is possible, however, via dermal and ocular routes and the toxicological profile of MMT indicates that contact with concentrated solutions may result in local irritation. Irritation is also likely upon contact with fuels or fuel additives containing MMT, but given the significant dilution of MMT with petroleum distillates, this is likely to be due to the irritant properties of the petroleum distillates more than the MMT itself.

Refineries

The blending of LRP is essentially an enclosed, automated process. Although exposure via the dermal and ocular routes is possible from slops, spills and residue during decanting of the imported MMT solution prior to LRP blending, exposure is expected to be infrequent, minimal and of short duration. Overall, the potential for exposure to MMT and hence Mn is low. Consequently, the risk to refinery workers from handling MMT is assessed as low.

Formulators

Formulation of imported MMT into aftermarket fuel additives is essentially also an enclosed, automated process that occurs even more intermittently than LRP blending. In a similar fashion to LRP blending, exposure is possible via the dermal and ocular routes from slops, spills and residue, but exposure would normally be minimal and of short duration. The potential for exposure to MMT and hence Mn during formulation is low. Consequently, the risk to formulation workers from MMT is assessed as low.

Petrol stations and maintenance workshops

Tanker drivers, petrol station attendants and auto mechanics may be exposed occupationally to MMT through contact with additised fuels and less frequently with

aftermarket fuel additives containing MMT. Although exposure to fuel vapours may be expected during a typical working day, the low vapour pressure of MMT and its high dilution in fuel renders inhalation exposure to MMT unlikely. Exposure to MMT via dermal and ocular routes is expected to be infrequent, minor and of short duration and also limited due to its dilution with solvents and other additives in the fuel and fuel additives. Therefore, the risk to these workers from MMT is assessed as low.

As reflected by overseas exposure data, auto mechanics at petrol stations and at dedicated maintenance workshops may have particular potential for repeated exposure to Mn from MMT and from Mn particulates associated with auto exhaust. Of overseas studies examining Mn exposure of garage mechanics, the highest mean personal exposure measured was 448 ng/m^3 (Sierra et al., 1995) for auto mechanics working in Montreal in mostly closed workshops (Section 8.5.1). Zayed et al. (1994) measured mean personal exposure levels of 314 and 152 ng/m^3 for garage mechanics in closed and open workshops respectively.

Bearing in mind the limitations associated with extrapolating these overseas data to local workplaces and given the likelihood that in the Sierra et al (1995) study only up to one third of airborne Mn resulted from MMT combustion (Section 8.5.1), 148 ng/m^3 (448 x 33%) is considered a worst case for Mn exposure from the use of MMT.

Assuming that all of the above Mn measured in the breathing zone of workers in the closed garages will be deposited and absorbed, then:

Margin of Exposure = 30,000/148 = 203

This is considered a sufficient Margin of Exposure as it is probable that for Australian auto mechanics the exposure to Mn would be much lower than calculated due to lower use of MMT in fuel, differences in working conditions (i.e. less closure of workshops) and the lower background levels of Mn in Australia. Therefore, the risk to these workers from Mn exposure is considered to be low.

Car park personnel, professional drivers and road maintenance workers

Occupational exposure to Mn particulates from automotive exhaust may occur for these workers but exposure is likely to be highly variable depending on the level of separation from the exhaust sources and traffic densities. Personal exposure data for Montreal taxi drivers show exposures that are lower than garage mechanics in the same study by an order of magnitude (Zayed et al., 1994). Therefore, despite the lack of personal exposure data for local workers, given the more restricted use of MMT and lower environmental levels of Mn locally, exposure of Australian professional drivers to MMT and Mn is likely to be significantly less than automechanics and so the risk to local workers is considered low. Similarly, exposure to and risk associated with Mn for car park and road maintenance workers is considered low.

14.2.3 Uncertainties

Uncertainties exist in the assessment of risk to local workers from MMT use as an AVSR. No Australian personal exposure data exist and only overseas data from a small number of limited studies are available and have been used for assessing risks associated with exposures to MMT in the workplace. The interpretation of these data for local conditions is complicated by factors such as differences in environmental conditions such as climate that may affect, for example, the enclosure of workplaces

and therefore ambient air levels of MMT and Mn combustion products. Also, local use patterns of MMT are likely to be significantly different to overseas where supplementation of fuels with MMT is presently more prevalent.

There is also substantial uncertainty associated with the limitations in the amount and quantity of toxicological data. For example, as there was no threshold for neurological effects identified in the study by Roels et al. (1992) there is some uncertainty associated with the derivation of surrogate NOAELs from this study. In addition, the study of Roels et al. (1992) has some disadvantages in that it was an occupational epidemiological study involving young or middle aged males and therefore applicability to the general population, including women, infants, the elderly, and those more susceptible because of illness, diet, or genetic predisposition, can only be achieved by the use of uncertainty factors. The study of Roels et al. (1992) involved exposure to Mn_3O_4 dust whereas recent data indicates that Mn sulphates and phosphates as well as oxides are likely to be present in exhaust emissions as a result of MMT combustion. Recent animal studies by Dorman et al. (2001) show that soluble Mn salts such as Mn sulphate have toxicokinetics that differ from insoluble Mn compounds such as Mn_3O_4, Studies by Vitarella et al. (2000b) and Brenneman et al (2000) show that Mn can be transported to the brain via the olfactory bulb in rats. These authors note significant differences in nasal and brain anatomy and physiology between rats and humans that question the toxicological significance of this manganese absorption pathway for humans. Therefore, there is also uncertainty related to potential differences in toxicokinetics and potential toxicity of different Mn salts that may be associated with human exposures to airborne Mn resulting from MMT combustion.

14.3 Public health risk

14.3.1 Acute effects

Direct public exposure to MMT is likely to occur primarily via the dermal route as a result of spills and splashes of LRP and aftermarket products. MMT is not expected to be a skin irritant at concentrations present in LRP. Dermal LD50's were in the range of 135-800 mg/kg bw (see Section 10.1) and an estimated dose received during exposure under a worst-case scenario was approximately 208 µg/kg bw. Therefore it can be concluded that there is a low risk of acute health effects in the general public as a result of dermal exposure to MMT in LRP.

Regarding the potential for acute health effects following exposure to aftermarket products containing MMT, skin irritation is not expected from exposure to MMT at the concentrations present (< 10% w/w equivalent to approximately < 7% v/v). Assuming that toxicokinetics and toxicodynamics of MMT are similar in rats and humans after dermal exposure, a comparison of the dermal LD50s with the exposure estimates in Section 8.6.1 suggests that there is some potential for acute health effects resulting from dermal exposure to MMT in aftermarket products. However, the LD50 values in rats were obtained after a constant 24-hour exposure to MMT and in contrast, much shorter exposures are expected following spillage. Overall, the risk of acute health effects is low given the small amounts to which people are likely to be exposed, the concentration of MMT likely to be lower than 7% v/v (approximately 10% w/w) and any spill on the skin is unlikely to reside untreated for long periods.

The risk of acute health effects as a result of accidental ocular exposure to MMT in LRP and aftermarket products is considered to be low since exposure to very small

amounts is expected to occur only infrequently and MMT is not expected to cause eye irritation at concentrations present in aftermarket products.

Acute health effects could also occur as a result of accidental ingestion by a child. Acute oral LD50s were in the range of approximately 9-905 mg/kg bw (see Table 11) with the rat being the most sensitive to the effects of MMT and having oral LD50s generally in the range of about 20-60 mg/kg bw. Assuming that toxicokinetics and toxicodynamics of MMT are similar in rats and humans after oral exposure and using the lowest LD50 of approximately 10 mg/kg bw, a child (10kg) ingesting about one mL of a product containing 10% w/w MMT could receive a potentially lethal dose. Children between one and a quarter and three and a half years of age can swallow approximately 4.5 mL of liquid (Gosselin et al., 1976), giving a potential dose several times higher than the lowest oral LD50 observed in laboratory animals. Aftermarket products are more likely to be stored in garages rather than in the home, these types of products are generally not "attractive" for ingestion by a child and the information provided by companies marketing these products states that they are supplied in packages with child resistant closures. These factors could reduce the potential risk associated with accidental ingestion of aftermarket products containing MMT. However, since very small volumes provide a potentially lethal dose, products containing MMT represent a significant acute health risk for children.

The risk to public health as a result of ingesting MMT in LRP is unlikely to be any greater than the public health risk associated with ingestion of petrol without the additive. Given the concentration of MMT currently in LRP (about 73mg/L), it can be estimated that a 70 kg adult would need to ingest about 10 L of MMT-LRP in order to receive a dose of MMT approaching the lowest acute oral LD50 observed in laboratory animal studies. Similarly, it can be estimated that a child of 10 kg bodyweight and a youth of about 35 kg bodyweight would need to ingest about 1 or 5 L respectively, of MMT-LRP in order to receive doses approaching the lowest LD50. Therefore, acute toxic effects as a result of accidental ingestion exposure to MMT in LRP are considered to be unlikely.

14.3.2 Chronic effects

Total Mn exposures (from all sources combined) are unlikely to be significantly changed by the use of MMT since exposure via food, water and other sources forms, by far, the greatest proportion of the total dose and these sources of exposure are not expected to change significantly as a result of the estimated use of MMT. However, the data in Table 9 show that the use of MMT according to the Present Use scenario of maintained LRP market share or 2004 scenario of diminished LRP market share will potentially significantly increase the Mn dose received by inhalation (excluding smoking).

The most significant adverse health effect from chronic (inhalation) exposure to Mn is neurotoxicity. A variety of inhalation health standards and guidance values have been promulgated in different countries based, in many cases, on an occupational epidemiological study conducted by Roels et al. (1992). Workers examined in this study demonstrated poor eye-hand coordination and hand steadiness and poor visual reaction times after exposures to Mn dust in a battery factory.

From this study, the NOAEL for neurological effects in humans was established at 30 μg/m^3 (Section 14.2.1) (WHO 1999). Converting intermittent exposures (5 days/week, 24 hours/day) to continuous exposures,

For Present Use scenario, where current LRP market share is maintained,

Margin of Exposure = (30 μg/m^3 x 5/7 x 8/24)/4.9 ng/m^3 = 1458

For 2004 scenario, where the LRP market share declines,

Margin of Exposure = (30 μg/m^3 x 5/7 x 8/24)/2 ng/m^3 = 3571

These margins of exposure are considered sufficient, taking into account conservative exposure estimates.

Australian estimated ambient exposures are also below overseas chronic reference values for Mn. Based on the study by Roels et al. (1992) and factoring for continuous exposures, interindividual variations and uncertain pharmacokinetic information on different Mn species especially regarding deposition in the brain, Wood and Egyed (1994) for the Environmental Health Directorate, Health Canada derived an air reference level of 110 ng/m^3. Using uncertainty factors for continuous exposures, interindividual variations, lack of data on developmental toxicity and toxicity of different forms of Mn, the USEPA (1993) set an inhalation reference concentration (RfC) at 50 ng/m^3 based on the study by Roels et al. (1992). In a re-evaluation of inhalation health risks associated with MMT in fuels in 1994, the USEPA derived chronic reference concentrations in the range of 90-200 ng/m^3 using a variety of methodologies (USEPA 1994).

Factoring for continuous exposures, interindividual variations and developmental effects in young children, WHO (1999) derived a guidance value of 150 ng/m^3 for Mn, based on the study of Roels et al. (1992). Similarly, and factoring for toxicity of different Mn species and possible reproductive effects in females, ATSDR (2000) devised a minimal risk level of 40 ng/m^3. Although based on the same epidemiological study, differences in these guidance values reflect differences in applied uncertainty factors and derived starting values.

There is currently no Australian ambient air standard for Mn. Comparing the estimated ambient air concentrations in Table 9 with the range of health standards set overseas indicates that the estimated air concentrations for both the Present Use scenario and the 2004 scenario are unlikely to represent a significant risk to public health. Air concentrations are much lower than the USEPA RfC for Mn, the guidance value derived by the ASTDR and the standards developed by WHO and Wood and Egyed (1994) for Health Canada.

The estimated ambient air concentrations of Mn due to MMT combustion are lower than a range of ambient air standards and a number of apparently conservative assumptions were used in the exposure assessment. Therefore, it could be concluded that, the risk to public health as a result of the use of MMT (as outlined in the Present Use scenario, Section 8.3.3 of this report) as an AVSR is expected to be low. However, as outlined below, there is considerable uncertainty associated with this risk assessment and there are likely to be sub-populations that have higher exposures and hence are at greater risk than the general population. For example, exposure of people in Launceston is of potential concern since the ambient air concentration of total (but not respirable) Mn even without the contribution from MMT combustion is higher than some of the

ambient air standards developed overseas and the use of MMT would add to environmental Mn levels in this region.

14.3.3 Uncertainties

In the assessment of potential acute health effects, there is uncertainty associated with the estimation of potential doses that may be received and extrapolation from animal data to humans. There is likely to be considerable variation in doses received and toxic responses are likely to vary both between species and among individuals within a species.

Like uncertainties associated with occupational risk assessment, uncertainties involved in the chronic health risk assessment are derived in part from significant database limitations. There is a lack of suitable Australian air Mn data upon which to base a realistic exposure assessment and there is very limited data that could be used to determine the contribution that MMT combustion might make to ambient air levels of respirable Mn. There are no Australian data on indoor concentrations of Mn and, since Australians generally spend a significant amount of time indoors, the indoor concentration of Mn could significantly influence personal exposures. In addition, there are no Australian data for ambient air concentrations of Mn that could be used to estimate exposures for individuals who live (or work) in areas with high traffic densities and there are no data on air concentrations of Mn inside cars or in homes that may have attached garages. Manganese concentrations in these microenvironments could significantly influence public exposures.

15. Risk Management

15.1 Assessment of current control measures

According to the NOHSC *National Model Regulations for the Control of Workplace Hazardous Substances* (NOHSC 1994c), exposure to hazardous substances should be prevented or, when this is not practicable, adequately controlled, so as to minimise risks to health and safety. The NOHSC *National Code of Practice for the Control of Workplace Hazardous Substances* (NOHSC 1994) provides further guidance in the form of a hierarchy of control strategies, namely, elimination, substitution, isolation, engineering controls, safe work practices and personal protective equipment (PPE).

15.1.1 Elimination and substitution

Elimination is the removal of a chemical from a process and should be the first option considered when minimising risks to health. In situations where it is not feasible or practical to eliminate the use of a chemical, substitution should be considered. Substitution includes replacing with a less hazardous substance or the same substance in a less hazardous form.

As indicated in Section 7.2.1, there is a declining market for LRP sales and hence AVSR additives due to attrition from the Australian motor fleet of vehicles designed to run on leaded petrol.

By 2004, bulk sales of LRP are expected to decline to less than 5 % of total petrol sales (Australian Petroleum Gazette, 1999). The general provision and sale of bulk LRP by the oil refineries and terminals will become uneconomical at some point. This will eliminate the requirement for refinery or terminal addition of MMT as an AVSR to fuel.

When bulk LRP is phased out, aftermarket addition of AVSR fuel additives rather than bulk treatment by the oil refineries and terminals will become the only option for motorists with vehicles designed to run on leaded petrol. Given the likelihood of a base population of vehicles for which mechanical alteration of engine components to run on unleaded petrol may be prohibitive e.g. vintage vehicles, the total elimination of AVSRs from the Australian fuel market is unlikely and the use of MMT as an aftermarket additive may continue indefinitely.

Several AVSR additives that are potential substitutes for MMT are available on the Australian market (Section 1.1). However, users need to consider the efficacy, cost, health, safety and environmental effects of each in considering these as alternatives for MMT.

15.1.2 Isolation and engineering controls

Isolation as a control measure aims to separate employees, as far as practicable, from the chemical hazard. This can be achieved by distance, use of barriers or enclosure. Engineering Controls are plant or processes which minimise the generation and release

of hazardous substances. They include total or partial enclosure, local exhaust ventilation and automation of processes.

Refineries and terminals

At refineries, MMT is isolated by containment of the MMT isotainer in a special bunded enclosure distant from worker control areas. Engineering controls consist of automatic metering of MMT from the isotainer through enclosed transfer lines to the enclosed blending manifold and finished product tank and similar automatic, enclosed transfer from the LRP finished product tank to terminals or to road tankers. The connection to the dip leg of the isotainer to which transfer lines are fastened is located at the top of the isotainer above fluid level, preventing inadvertent gravity flow and spillage of MMT concentrate during manipulation.

The main isolation and engineering control measure in laboratory areas where quality analyses are conducted is confinement of handling procedures to a ventilated fume cupboard.

Third party formulators

At third party formulators, isolation of MMT occurs by the opening of import drums or cylinders in bunded enclosures. Engineering controls for MMT during formulation consist of pumping via enclosed transfer lines to a closed mixing or storage vessel and subsequent enclosed feeding to automated filling/packing plant. Access bungs are located at the top of the drums or cylinders above fluid level, preventing inadvertent spillage through gravity flow of MMT concentrate during emptying.

In a similar fashion to refineries, the main isolation and engineering control measure in laboratory areas where quality analyses are conducted is confinement of handling procedures to a ventilated fume cupboard.

Petrol stations

At petrol stations, isolation and engineering controls of exposure for MMT are achieved through enclosed transfer hoses for transferring LRP containing MMT from road tankers and storage in underground tanks.

With regards to USTs, there are currently no existing leak prevention or detection requirements for operators of underground fuel storage tanks in all states to detect and control leakages from UST facilities. UST leak detection systems are implemented on a voluntary basis by industry, particularly by major petroleum suppliers.

Aftermarket product use

Engineering controls of exposure for the public and occupational users of aftermarket products containing MMT consist presently of containers with childproof screw caps and long spouts. These long spouts enable sufficient insertion into the fuel filler of the vehicle to minimise backflow and spillage during addition to unleaded fuel.

15.1.3 Safe work practices

Safe work practices are administrative practices that require people to work in safe ways.

Refineries

Refineries operate under a permit-to-work system, which requires job safety audits before work can commence. Professional occupational health and safety personnel available on site typically oversee these. A HiTEC 3062 Product Handling Manual supplied by Ethyl Corporation is used at refineries to provide guidance on storage requirements, blending procedures, handling precautions, maintenance procedures and decontamination and disposal procedures.

Third party formulators

The blending and packaging of aftermarket additives are conducted at formulator sites in accordance with internal written standard operating procedures. These procedures incorporate safety and quality control instructions, PPE requirements and first aid directions.

15.1.4 Personal protective equipment

Refineries

The Ethyl Corporation HiTEC 3062 Product Handling Manual used by refineries recommends personal protective equipment for use when handling bulk MMT solution. For normal operations with good ventilation, PPE recommendations include safety glasses or chemical goggles, face shield (when making or breaking connections), light coloured overalls and neoprene, PVC or butyl rubber gloves and boots. In poorly ventilated environments, an organic vapour cartridge respirator is recommended also. In practice at the refinery, rubber gloves, nomex clothing, safety shoes goggles and respirator with an organic vapour cartridge are used during connection and disconnection of transfer lines with imported isotainers.

Third party formulators

PPE consisting of protective clothing, gloves and goggles are used during blending and packaging of aftermarket additives.

Petrol stations and maintenance workshops

At petrol stations during unloading of road tankers and the dipping of underground tanks, workers typically wear PPE consisting of protective clothing, footwear and gloves. Auto mechanics with potential exposure to MMT in fuel also use PPE consisting of protective clothing and footwear but gloves or protective eyewear are not typically worn.

15.2 Hazard communication

15.2.1 Labels

Labels for six aftermarket MMT products containing up to 10% w/w MMT, one MMT concentrate imported in bulk in isotainers and one MMT concentrate imported in drums both containing approximately 60% w/w MMT were available for assessment. A label for an additional imported drummed MMT concentrate was not available. Labelling for this product consisted of an attached MSDS.

Labels submitted for assessment were assessed for requirements under the NOHSC *National Code of Practice for the Labelling of Workplace Substances* (NOHSC, 1994). The assessment took the form of a qualitative appraisal of the following categories of information:

- Substance identification;
- Hazard category/Signal word;
- ADG Code classification/packaging group;
- Details of manufacturer or supplier;
- Risk Information (or phrase);
- Safety Information (or phrase);
- Information on spills/leaks or fires; and
- Reference to MSDS.

In accordance with the hazard classification of MMT against the current version of the NOHSC *Approved Criteria for Classifying Hazardous Substances* (NOHSC 1999a) (Section 13), MMT is classified as a Hazardous Substance. Depending on the concentration of MMT, labels for products containing MMT should contain the following hazard classification, risk and safety phrases:

Classification of mixtures containing MMT

MMT Concentration	Risk Phrases	Classification of Mixture
≥ 0.1% - < 1%	R20, R22	Harmful
≥ 1% - < 3%	R23, R25, R48/20	Toxic
≥ 3% - < 7%	R21, R23, R25, R48/20	Toxic
≥ 7% - < 10%	R21, R26, R28, R48/20	Very Toxic
≥ 10% - < 25%	R21, R26, R28, R48/23	Very Toxic
≥ 25%	R24, R26, R28, R48/23	Very Toxic

The most appropriate safety phrases are:

- S36: Wear Suitable Protective Clothing;
- S38: In Case of Insufficient Ventilation Wear Suitable Respiratory Equipment.

Additional risk and safety phrases may also be applicable in products depending on the presence of other hazardous ingredients.

MMT concentrates

Both labels available for assessment contained overseas but not local supplier contact details, the product name and disclosed the presence of MMT. However, neither

contained information on ingredient proportions, either as an exact concentration or as a range.

Signal words ("Warning" and "Danger: Poison") were found on both labels. As these products are to be used in the workplace, the signal word should be "Hazardous". Only one label contained information on an ADG code classification/packaging group.

Neither label contained the risk phrases recommended above. One label contained a risk phrase of equivalent hazard warning for acute effects ("May be fatal if swallowed, inhaled or absorbed through skin"). However, on this label there was no risk phrase covering effects of repeated exposure. The second label contained an appropriate risk phrase for repeated exposure ("May cause CNS, blood, liver and kidney damage after prolonged or repeated exposure"), although this warning was in relation to another ingredient in the mixture.

Neither label recommended the wearing of suitable protective clothing (S36) or the wearing of suitable respiratory equipment in cases of insufficient ventilation (S38). However, both contained adequate safety phrases regarding hazards of acute contact. Both labels contained adequate first aid instructions but one label only contained advice on spills/leaks.

Aftermarket products

In the case of labelling of hazardous substances of 500 mL capacity or less and where space on the containers is especially limited, the NOHSC Labelling Code describes the required minimum information as:

- Signal words and/or dangerous goods class;
- Product name; and
- Details of manufacturer or importer.

All labels for the present aftermarket products of 350 or 500 mL capacity contained local supplier contact details and the product name. However, despite MMT being above the cut-off of 0.1% in all products for classification as a hazardous ingredient, only two labels disclosed the presence of MMT and none contained information on the concentration of MMT present, either as an exact concentration or as a range.

Signal words were obvious only on 3 labels and no labels contained the risk or safety phrases recommended above. Alternative safety phrases were present to varying extents, pertaining to avoidance of dermal and ocular exposure, aspiration hazards or prevention of child exposures. All labels included some first aid instructions varying from advice regarding ingestion to additional advice regarding dermal exposure.

15.2.2 MSDS

Material Safety Data Sheets (MSDS) are the primary source of information for workers involved in the handling of chemicals. Under the NOHSC *National Model Regulations for the Control of Workplace Hazardous Substances* (NOHSC 1994c) and the corresponding State and Territory legislation, suppliers of a hazardous chemical for use at work are obliged to provide a current MSDS to their customers and employers must ensure that an MSDS is readily accessible to employees with potential for exposure to the chemical.

A total of 8 MSDS, 5 for aftermarket products and 3 for imported MMT concentrates were available for assessment against the NOHSC *National Code of Practice for the Preparation of Material Safety Data Sheets* (NOHSC 1994b). The results of the MSDS assessment are presented in Appendix 2.

On 6 MSDS, either no statement was found as to the hazardous nature of the product or statements incorrectly claimed that the product was not hazardous (one MSDS). On 5 MSDS, an emergency telephone number was missing. Local company details were missing on one MSDS.

Key health effects of MMT were included in the MSDS, although only 3 MSDS mentioned the possibility of kidney damage. Also, the First Aid section of some MSDS advised vomiting following ingestion whereas others advised (correctly) against vomiting. On 6 MSDS, exposure standards drawn from overseas sources rather than Australian sources (in this case they are the same) and there were no plain English explanation as to what the skin notation on the exposure standard meant.

One MSDS for an MMT concentrate incorporated ingredient details for 3 different possible formulations for the product targeted at the 3 different markets of USA, Canada and Europe whilst not indicating the formulation applicable for Australia.

A sample MSDS prepared in accordance with the findings of this assessment and the NOHSC *National Code of Practice for the Preparation of Material Safety Data Sheets* (NOHSC 1994b) is provided in Appendix 3.

15.2.3 Education and training

Guidelines for the induction and training of workers exposed to hazardous substances are provided in the NOHSC *National Model Regulations for the Control of Workplace Hazardous Substances* (NOHSC 1994c). Under these regulations, employers are obliged to provide training and education to workers handling hazardous substances. These regulations stipulate that training and induction should be appropriate for the workers concerned.

Refinery companies use the Ethyl Corporation HiTEC 3062 Product Handling Manual specifying storage requirements, blending procedures, handling precautions, maintenance procedures and decontamination and disposal procedures for refinery blending.

15.3 Occupational monitoring and regulatory controls

15.3.1 Atmospheric monitoring

Under the NOHSC Model Regulations (NOHSC, 1994c), employers are required to carry out an assessment of the workplace for all hazardous substances, the methodology of which is provided in the NOHSC *Guidance Note for the Assessment of Health Risks Arising from the Use of Hazardous Substances in the Workplace* (NOHSC, 1994d). When assessment indicates that the risk of exposure via inhalation is significant, atmospheric monitoring should be conducted to measure levels of the hazardous substances in the workplace as a precursor to the implementation of suitable control measures to reduce exposure. Subsequent monitoring is also required to ensure that such measures are effective.

No atmospheric monitoring programmes for MMT in workplaces have been identified.

15.3.2 Occupational exposure standards

Australia as well as other countries has set exposure standards for MMT and elemental and inorganic Mn.

Table 19. Occupational exposure limits for MMT and elemental and inorganic manganese compounds

	MMT		Elemental and Inorganic Mn	
Country	**8 h TWA (mg/m^3)**	**STEL (mg/m^3)**	**8 h TWA (mg/m^3)**	**STEL (mg/m^3)**
Australia	0.2 (as Mn)*	-	1	-
			1 (Mn fume)	3 (Mn fume)
Belgium	0.2*	-	1 (fume)	3 (fume)
Denmark	0.2*	-	2.5	-
			1 (fume)	
Finland	0.2*	0.6*	2.5	-
			1 (fume)	
France	0.2*	-	1 (fume)	-
Germany	-	-	0.5 (inhalable fraction)	-
Ireland	0.2*	0.6*	5 (as Mn)	-
			1 (Mn fume)	3 (Mn fume)
Japan	-	-	0.3 (except inorganic compounds)	-
Netherlands	0.2 (as Mn)*	-	1 (as Mn)	3 (as Mn)
The Philippines	-	-	5	-
Poland	-	-	0.3 (as Mn, dusts only)	5 (as Mn, dusts only)
Russia	-	-	-	0.2 (fume)
Sweden	-	-	2.5	-
Switzerland	0.2*		5	-
			1 (fume)	
Thailand	-	-	5	-
Turkey	-	-	5 (fume)	-
United Kingdom	0.2 (as Mn)*	0.6 (as Mn)*	5	-
			1 (Mn fume)	3 (Mn fume)
USA				
ACGIH	0.2 (as Mn)*	-	0.2	-
			0.2 (Mn fume)	
NIOSH	0.2 (as Mn)*	-	1	3
			1 (Mn fume)	3 (Mn fume)
OSHA	-	-	-	5 (Mn fume)

* skin notation

Based on ACGIH (2000). NIOSH = National Institute of Occupational Safety and Health (recommended limits). OSHA = Occupational Safety and Health Administration (statutory limits). STEL = short-term (15-min) exposure limit. TWA = time-weighted average. United Kingdom STEL = short-term (10-min) exposure limit. Germany STEL = short-term (30-min) exposure limit.

According to the NOHSC *Exposure Standards for Atmospheric Contaminants in the Occupational Environment*, the current Australian national occupational exposure standard for MMT (as Mn) is 0.2 mg/m^3, expressed as an 8 h TWA airborne concentration (NOHSC, 1995b). A skin notation, meaning that absorption through the skin may be a significant mode of exposure, accompanies this value. In Australia, there is no short-term exposure limit (STEL) for MMT. However, according to the NOHSC Exposure Standards (NOHSC, 1995b) a process is not considered to be under reasonable control if short-term exposures exceed three times the TWA exposure standard for more than 30 minutes per 8 h working day, or if a single short-term value exceeds five times the TWA exposure standard.

The Australian standard for Mn (as dust or fumes) is 1 mg/m^3 expressed as an 8 h TWA airborne concentration (NOHSC, 1995b). A short-term exposure limit (STEL) of 3 mg/m^3 as Mn exists for Mn fumes (NOHSC, 1995b). The standards for MMT and Mn as fumes were adopted from the ACGIH (1991) whilst that for Mn dust followed review by the Exposure Standards Expert Working Group (NOHSC, 1995a).

15.3.3 Health surveillance

In accordance with NOHSC Model Regulations (NOHSC, 1994c), employers have a responsibility to provide health surveillance in those workplaces where the workplace assessment indicates that exposure to a hazardous substance may lead to an identifiable substance-related disease or adverse health effect. MMT is not listed in Schedule 3 (list of substances requiring health surveillance) and as such there are no formal requirements for health surveillance programs for exposed workers.

No personal air monitoring or health surveillance programs have been reported in Australia. According to the Ethyl Corporation *Medical Guide for Use by Companies Handling HiTEC 3062 Octane Booster*, Ethyl Corporation recommends monitoring the level of Mn in the urine of exposed workers as an indicator of MMT exposure and considers that a level of Mn above 20 µg/L of urine might indicate exposure to Mn from sources other than food. They consider urine Mn levels of up to 50 µg/L not an immediate health concern, although if there is reason to suggest industrial exposure related to the elevated reading, they recommend that the source should be found and eliminated. Ethyl Corporation considers a urine Mn concentration above 50 µg/L strong evidence for exposure to Mn and advises that any worker with such a urine Mn reading be removed from the source of exposure, that the cause is identified and removed and that the worker not be permitted to return to a job where exposure to MMT is possible until two consecutive Mn urine measurements below 20 µg/L are registered.

15.3.4 National transportation regulations

Although MMT is not listed in the Australian Code for the Transport of Dangerous Goods (ADG) Code, it meets the criteria for classification as a dangerous good, Class 6.1, Packing Group I (FORS, 1998). MMT can be ascribed a Proper Shipping Name under the General Entry "Toxic Liquid, Organic, NOS" or Specific Entry "Metal

Carbonyls, NOS". The ADG Code containing guidance for the transport of dangerous goods is therefore applicable for the transportation of MMT.

15.3.5 National storage and handling regulations

MMT meets the criteria for a dangerous good and so national storage and handling regulations for dangerous goods are applicable for MMT. Storage and handling requirements are described in the NOHSC *National Standard for the Storage and Handling of Workplace Dangerous Goods* (NOHSC 2001a) and NOHSC *National Code of Practice for the Storage and Handling of Workplace Dangerous Goods* (NOHSC 2001b).

15.3.6 Control of major hazard facilities

According to the NOHSC *National Standard for the Control of Major Hazard Facilities* (NOHSC, 1996), MMT is not one of the specifically identified chemicals that must be considered when determining whether a site is a major hazard facility. However, according to Tables 2 and 3 of the NOHSC *National Standard for the Control of Major Hazard Facilities*, as MMT is classified as toxic, facilities that exceed the threshold quantity of 200 tonnes of MMT qualify as a major hazard facility. The purpose of this standard is to prevent and minimise the effects of major accidents and near misses by requiring the person in control of the facility to:

- Identify and assess all hazards and implement control measures to reduce the likelihood and effects of a major accident;
- Provide information to the relevant public authority and the community, including other closely located facilities, regarding the nature of hazards of a major hazard facility and emergency procedures in the event of a major accident;
- Report and investigate major accidents and near misses, and take appropriate corrective action; and
- Record and discuss the lessons learnt and the analysis of major accidents and near misses with employees and employee representatives.

15.4 Public health regulatory controls

Since consumer (aftermarket) products containing MMT represent a potential public health risk, some public health regulatory controls are warranted. MMT is not currently included in a Schedule of the *Standard for the Uniform Scheduling of Drugs and Poisons* (SUSDP). According to the Guidelines for National Drugs and Poisons Schedule Committee (NDPSC), the acute toxicity profile for MMT is consistent with a Schedule 7 entry in the SUSDP. The NDPSC may also consider appropriate cut-offs to lower schedules to accommodate products containing MMT at lower concentrations. It is recommended that consumer products containing MMT should be required to be contained in packages with child resistant closures.

15.5 Environmental regulatory controls

This section provides information with reference to international initiatives on the environmental regulatory controls in Australia applicable to MMT and also Mn. In summary, the management of environmental pollution and waste in Australia is regulated through individual State and Territory regulatory systems rather than at a National level and each State and Territory has legislative frameworks and strategies for managing emissions and environmental pollution to air, land and waters.

15.5.1 Air quality management

Australia

Potential air quality issues from combustion of fuels containing MMT include exhaust emissions of various Mn compounds (e.g. Mn oxides, Mn phosphate, Mn sulphate) and small particles (estimated in the 0.056 to 3.1 μm range; Roos et al., 2000).

Emissions of 'air toxics' (defined below) in Australia are regulated through individual State and Territory regulatory systems rather than at a National level and each State and Territory has established legislative frameworks and strategies for monitoring and managing air quality. National-level strategies are or have been developed to allow consistent management of ambient air quality throughout Australia.

Air toxics are gaseous, aerosol or particulate pollutants that are present in the air in low concentrations with characteristics such as toxicity or persistence so as to be hazardous to human, plant or animal life. The terms 'air toxics' and 'hazardous air pollutants' (HAPs) are used interchangeably. Air toxics include volatile and semi-volatile organic compounds, polycyclic aromatic hydrocarbons, metals and aldehydes (NEPC, 2002). Specific emission limitations and maximum ground level concentrations for individual sources are used in some States to control emissions from industrial sources (NEPC, 2002).

Emissions of air toxics from new motor vehicles are controlled through Australian Design Rules that set emission standards for a range of pollutants (not including Mn). These standards are set at a National level rather than State or Territory level. Recently the Australian Government introduced National fuel quality standards that will also reduce the level of some air toxics in ambient air. Manganese is not regulated by these standards and MMT is not listed currently on the register of prohibited fuel additives.

At a National level, at least two National Environment Protection Measures (NEPMs) apply to air quality including the National Pollutant Inventory (NPI) NEPM (NEPC, 1998a) and the Ambient Air Quality NEPM (NEPC, 1998b). An additional NEPM (Ambient Air Toxics) is also being developed (NEPC, 2002).

At a National level, particulates are included in the Ambient Air Quality National Environment Protection Measure (NEPC, 1998b), which sets national standards for the six air pollutants including airborne particles (as PM10, and PM2.5 is proposed to be included). The National standard for particulates (as PM10) in ambient air is 50 $\mu g/m^3$ (1 day average with 5 allowable daily exceedences per year), for implementation throughout Australia by 2008 (NEPC, 2002).

Manganese compounds are not specifically included in either the Ambient Air Quality NEPM (NEPC, 1998b) or the Ambient Air Toxics NEPM being developed (NEPC,

2002). An inventory of emissions of Mn and compounds, Mn fumes and particulate matter (PM10) from significant emission facilities are included in the National Pollutant Inventory NEPM (NEPC, 1998a). For the reporting period 2000 to 2001, the NPI database indicates that those industrial reporting facilities throughout Australia that provided data reported emissions of 140 tonnes of manganese to air, 30 tonnes to land and 1100 tonnes to waters. Emissions from sources other than reporting facilities (smaller companies and non-industrial sources) for the same period totalled an additional 380 tonnes of manganese to air. Total air emissions to the Sydney, Newcastle and Wollongong airshed (2000-2001 period) consisted of 15 tonnes of manganese.

Although the NPI database contains air, land and water emissions data for manganese from some NPI reporting facilities, the current year (2001-2002) is the first reporting period for facilities meeting a reporting criteria for manganese and manganese compounds (ie. use of >10 tonnes per annum) and so many more industrial emissions sources are expected to report for this period. The emissions data for the reporting period 2001-2002 will be available in early 2003.

International air quality management

Several international organisations have introduced regulations or policies that aim to limit the exposure of the general public to air particulates. This is relevant to the use of MMT as an AVSR as combustion of MMT results in particulate inorganic Mn compounds. The Organisation for Economic Cooperation and Development has implemented the Advanced Air Quality Indicators and Reporting Project in OECD member countries, including Australia (OECD, 1999). The project focuses on six major urban air pollutants, including particulate matter.

In the United States, air quality is managed and regulated under the Clean Air Act (CAA) 1970. The National Air Toxics Program: The Integrated Urban Air Strategy outlines a strategy for addressing cumulative health risks from identified HAPs, including Mn compounds in urban areas (USEPA, 1999). The Strategy also establishes air monitoring requirements for motor vehicle emissions including vehicles using fuels containing MMT and sets standards for HAPs emitted from motor vehicles and fuels.

In Canada, a range of air toxics including particulates PM10 and PM2.5 are measured and analysed within the National Air Pollution Surveillance (NAPS) Network. The NAPS network was established in 1969 to monitor and assess the quality of ambient air in Canadian urban areas.

In the United Kingdom, airborne particulates are managed by the Department of Environment, Transport and Regions (UKDETR), which established a benchmark standard for particles in air.

15.5.2 Aquatic ecosystem management

The Australian water quality guidelines (ANZECC and ARMCANZ, 2000), established under the National Water Quality Management Strategy, provide water and sediment quality guidelines (trigger levels) for freshwater and marine ecosystems throughout Australian States and territories. The guidelines provide a decision-tree framework for the assessment and management of risks from chemicals to water and sediment quality. No trigger values are available for MMT; however, ANZECC and ARMCANZ (2000) provide an ambient trigger level for Mn for the protection of freshwater ecosystems of 1.7 mg/L. Insufficient toxicity data were available from marine organisms for

ANZECC and ARMCANZ (2000) to derive a marine trigger value. Therefore ANZECC and ARMCANZ (2000) have derived a marine interim indicative working level (IIWL) of 0.8 mg Mn/L. Each State and Territory has legislative frameworks and strategies for managing water pollution.

15.5.3 Disposal and waste treatment

Each Australian State and Territory provides statutory controls on waste generation and management. MMT and Mn-containing materials classified as wastes should be sent to licensed waste disposal contractors in accordance with State and Territory requirements. No specific waste disposal guidelines, standards or management issues were identified for MMT or Mn wastes. Due to the toxicity of MMT, care should be exercised in disposing of contaminated wastes to avoid pollution of the environment. For example, in NSW, transporters conveying MMT waste in quantities greater than 200 kg per load or waste facilities treating MMT waste require a licence under the Protection of the Environment Operations Act (1997) issued by the NSW EPA.

15.6 Emergency procedures

Fire and spill responses for MMT are included in MSDS for bulk HiTEC 3062 (Ethyl Corporation) and drummed MMT concentrates TK-660 (Nulon Products Australia Pty Ltd) and Wynn's Octane Booster Concentrate. Emergency response information is also available from ILO (1999), NIEHS (2001) and the Ethyl Corporation HiTEC 3062 Octane Booster Product Handling Guide (2001).

Recommendations from the Ethyl Corporation Product Handling Guide for dealing with fire or spills of HiTEC 3062 consisting of 62% MMT in petroleum distillate (and applicable for the similar drummed MMT concentrates) state:

Personnel

- Personnel engaged in cleanup operations should be equipped with clothing and protective gear as suggested in the MSDS – chemical resistant gloves, suit and boots and safety glasses with side shields;
- For minor spills, respirators must be worn; for significant spills, air-supplied respiratory equipment or self-contained breathing apparatus is required.

Small spills and leaks

- Use absorbent materials to remove free liquid from the spill area;
- Clean smooth contaminated areas with a solvent, such as kerosene and collect rinsate with absorbent materials;
- Remove contaminated soils and/or absorbents with appropriate tools such as shovels;
- Thoroughly scrub smooth contaminated areas with soap and water.

Large spills

- Take immediate action to stop, contain and isolate the spill;

- Eliminate all sources of ignition;
- Barricade and restrict unauthorised personnel from the general area;
- Notify regulatory authorities immediately in the event of imminent danger to human health or to the environment;
- Contain spills with dykes or absorbent material to prevent migration and entry into sewers or streams;
- Use water sprays to reduce vapours. Avoid flushing the liquid into a stream or an open sewer system. Blanketing the spill with high-density (low expansion type) foam is also effective to reduce evaporation. Commercial absorbents, activated charcoal, petroleum coke or fine soils can also be used to contain and collect the spill and reduce evaporation;
- Pump all possible liquid from the spill area into steel closed-head drums or other suitable metal containers that can be sealed;
- Finish collecting residual spilled material with absorbents. Remove contaminated soils and/or absorbents with appropriate tools and place in sealed metal containers or drums.

Fire response

Use foam, water spray or dry chemicals to extinguish.

16. Discussion and Conclusions

MMT has been introduced recently onto the Australian market as an anti-valve seat recession additive and MMT used for this purpose is the subject of the present assessment. AVSR fuel additives are added to fuel to prevent excessive valve seat wear and consequent recession into the automotive engine head. Until its phase out, tetraethyl lead was the most common AVSR additive.

With the national phase out of lead in petrol, there are now four types of AVSR additives presently marketed in Australia. MMT, phosphorus-based and sodium-based AVSRs are presently being assessed by NICNAS as Priority Existing Chemicals and a potassium-based AVSR was assessed by NICNAS as a New Industrial Chemical. These AVSRs are delivered either pre-blended into LRP or are available as an aftermarket fuel supplement for addition to unleaded fuel by consumers.

Due to commercial sensitivities of information on market share for individual AVSRs, exposure and risk assessments for each individual AVSR assume 100% market share. Additionally, given that the use of AVSRs is governed by a declining population of older vehicles requiring these fuel additives, risk assessments were conducted under two separate scenarios based on AVSR use patterns. The first scenario "Present Use" assumes a continuation of the present LRP market of 2500 ML per year with 90% of AVSRs delivered in bulk LRP and 10% delivered as aftermarket fuel additives. The second scenario "2004" assumes a decline of the LRP market to 1000 ML with the AVSR delivered totally as an aftermarket fuel additive. These scenarios are based on motor vehicle statistics and forecasts from the Australia Bureau of Statistics and Australian Institute of Petroleum. The occupational health and safety, public health and environmental consequences of these volumes and modes of delivery of AVSRs are considered accordingly.

MMT is manufactured overseas and assuming MMT has 100% of the AVSR market, less than 180 tonnes is being imported to Australia per year. The majority of this amount is used to blend LRP, with only a minor quantity (< 10 tonnes/year) used for the formulation of aftermarket fuel additives. Concentrated MMT (approximately 60% MMT w/w) is imported in bulk for formulation into LRP containing a recommended 72.6 mg MMT/L (approximately < 0.01% MMT w/w) and formulation of aftermarket products containing < 150 mg MMT/L (< 10% w/w MMT). A small amount is also imported in pre-packaged aftermarket products containing < 10% w/w MMT.

16.1 Health hazards

In fuel, MMT is combusted and converted to a mixture of Mn oxides such as Mn_3O_4 and salts including Mn phosphate ($Mn_3[PO_4]_2$) and Mn sulphate ($MnSO_4$). A proportion of these inorganic derivatives are released in association with particulate material in vehicle exhaust. The balance (around 80%) is accumulated in engines or exhaust systems. Therefore, the health hazards associated with the use of MMT also include those associated with inorganic Mn compounds.

MMT is acutely toxic by all routes of exposure. The critical effects from acute exposure to MMT are neurological and pulmonary dysfunction. In humans, giddiness, headache,

nausea, chest tightness, dyspnea and paresthesia are reported in anecdotal cases of acute occupational exposure. Acute lethal exposure to MMT in animals is associated with damage to the lungs, kidney, liver and spleen effects, tremors, convulsions, dyspnea and weakness. In both animals and humans, slight skin and eye irritation results from dermal and ocular exposure respectively.

Limited data show that repeated inhalation exposure to MMT in animals results in degenerative changes in liver and kidneys. A NOAEL of 0.0062 mg/L for inhalation exposure was reported.

Manganese has been the subject of several extensive reviews and the summary of Mn toxicity for this present report is based predominantly on the WHO Concise International Chemical Assessment Document - *Manganese and Its Compounds*. In humans, Mn is an essential element. In animal studies, the critical effect following acute exposure to inorganic Mn compounds is neurological dysfunction. Decreased activity, alertness, muscle tone, touch response and respiration have been reported with oral administration. Pulmonary effects are also reported in inhalation studies, but these may at least in part reflect an inflammatory effect following inhalation of particulate matter rather than a result of pulmonary toxicity of Mn.

In repeated dose animal studies of Mn toxicity, the critical effect is also neurological dysfunction, and effects range from decreased motor activity to increased activity, aggression and movement tremors. In humans, chronic occupational exposure to respirable Mn dusts is associated with subclinical nervous system toxicity through to overt manganism, a progressive neurological disorder. Reproductive effects including impotence and loss of libido in male workers have also been associated with high Mn exposures.

It is generally agreed that the critical study for neurological effects due to Mn exposure is Roels et al., (1992). This principal neuroepidemiological study of occupational inhalation exposure to Mn was used by WHO (1999) to determine a dose-response relationship for neurological effects. A lower 95% confidence limit was estimated for the level of Mn exposure expected to result in a 5% response rate. This value (30 $\mu g/m^3$) was considered a surrogate for a NOAEL for neurological effects in the present assessment.

MMT (as Mn) is currently listed in the NOHSC *List of Designated Hazardous Substances* (NOHSC, 1999b) with no classification. In accordance with the NOHSC *Approved Criteria for Classifying Hazardous Substances* (NOHSC, 1999a), It is recommended that MMT is classified "Hazardous" with the following risk phrases:

- R26 - Very Toxic by Inhalation;
- R28 – Very Toxic if Swallowed;
- R24 – Toxic in Contact with Skin;
- R48/23 – Toxic: Danger of Serious Damage to Health by Prolonged Exposure Through Inhalation.

As a result of this classification, the following additional safety phrases are also recommended:

- S36 – Wear Suitable Protective Clothing;

- S38 – In Case of Insufficient Ventilation Wear Suitable Respiratory Equipment.

Based on a toxicity profile from animal experiments, MMT meets the criteria of the ADG Code (FORS, 1998) for classification as a toxic substance Class 6.1, Packing Group I. MMT can be ascribed a Proper Shipping Name using the General Entry "Toxic Liquid, Organic, NOS" or Specific Entry "Metal Carbonyls, NOS". MMT is currently not listed in the SUSDP. However, according to the Guidelines for the National Drugs and Poisons Schedule Committee, its domestic use and toxicity profile are also consistent with a Schedule 7 entry in the SUSDP. Consequently, this report will be referred for consideration of scheduling by the NDPSC.

16.2 Environmental hazards and risks

MMT is highly toxic to aquatic organisms and spill incidents and leaks to water bodies and land should be managed through existing Federal, State and Territory legislative frameworks and protocols to mitigate adverse effects to the aquatic environment. Such incidents may potentially occur during shipment into Australia, bulk handling and storage and leakage of underground storage tanks.

All States and Territories have general environment protection legislation pertaining to pollution and contaminated land. However, there are currently no existing leak prevention or leak detection requirements for operators of underground fuel storage tanks in NSW, and probably other States and Territories, to detect and control leakages from UST facilities. UST leak detection systems are implemented on a voluntary basis by industry, particularly by major petroleum suppliers.

Use of MMT in internal combustion engines as a fuel additive and subsequent degradation through combustion, and its short persistence in the environment, indicate that aquatic and terrestrial organisms are unlikely to be exposed to MMT at or above levels of concern through existing use as an AVSR. A low environmental risk is predicted.

Manganese, the principle degradation by-product from combustion of MMT, is naturally occurring and ubiquitous in the environment. It is an essential nutrient of plants and animals. Environmental exposure to Mn compounds will mostly arise through the gaseous phase. Eventually, these will deposit to land and waters. The emission of Mn into the environment from use of fuels containing MMT is unlikely to develop to levels of concern and therefore poses a low risk for terrestrial or aquatic environments.

The findings of this assessment highlight the potential for leaking USTs to pose an unacceptable risk to the environment. Such leakages represent localised, point source discharge, but have the potential to detrimentally affect significant areas of the environment. Although a large number of USTs have been replaced or have had leak detection systems or other measures installed, most USTs do not have leak detection systems, and many that are currently in service are old and have the potential to leak in the future if not decommissioned or replaced.

Although there is potential for risk to the environment from leakage of fuel (which may or may not contain MMT) from USTs, the risk would be site specific.

There is currently no environmental hazard classification system in Australia. In accordance with the OECD Globally Harmonized System of Classification and Labelling of Chemicals, MMT would be classified Chronic 1 Very Toxic to Aquatic Life with Long-lasting Effects (OECD, 2002).

16.3 Occupational health and safety risks

Occupational exposure to MMT mainly via the dermal route may be envisaged for refinery and formulator workers during blending of LRP or aftermarket fuel additives. Occupational exposure to MMT is possible also for those workers in downstream processes that handle fuel, fuel additives and automotive fuel system components e.g. petrol station and automotive maintenance workers. In addition, occupational exposure to Mn, mainly via inhalation, is possible for these and other workers associated with or in the vicinity of automotive usage e.g. service station attendants, professional drivers, car park and road maintenance personnel.

Although MMT is toxic by oral, dermal and inhalation routes, the enclosed processes used predominantly for blending of fuel or fuel additives where concentrates are handled renders the possibility of exposure low. Mild irritation is possible upon contact with fuels or fuel additives containing MMT but given the significant dilution of MMT with petroleum distillates, irritation is likely due to the irritant properties of the petroleum distillates more than the MMT itself.

Exposure to MMT is possible during handling of additised fuels, fuel additives and automotive fuel system components but is expected to be infrequent, minor and of short duration and limited due to its dilution with solvents and other additives in the fuel and fuel additives. Overall, the risks to workers posed by MMT during formulation and during handling of fuels, fuel additives containing MMT and automotive fuel system components contaminated with MMT is low.

The main route of exposure to Mn particulates is inhalation and in occupations where automotive usage is ubiquitous, chronic inhalation of inorganic Mn species may result. A worst-case scenario was considered for Mn exposure of Australian auto mechanics from the use of MMT. Using overseas personal inhalational exposure estimates, a Margin of Exposure of 203 for local mechanics was derived. This is considered a sufficient Margin of Exposure given the conservative exposure estimates derived from data from Canada where MMT is used widely as an octane enhancer in fuels and ambient air levels of Mn are higher and calculations assuming 100% market share for MMT. Therefore, the occupational health risks associated with Mn exposure from MMT combustion are assessed as low.

MSDS and labels for imported MMT concentrates and formulated aftermarket additives were assessed qualitatively against the NOHSC MSDS and Labelling Codes. In general, labels were lacking ingredient information and although some relevant hazard warnings were present, the recommended risk and safety phrases from this assessment were missing. Signal words and disclosure of the presence of MMT were also missing from some labels. Local contact details were absent from labels of imported concentrates. MSDS in general contained relevant health effect information but also did not include recommended risk and safety phrases. Most also had other important elements missing such as correct hazard statements and emergency telephone numbers. A sample MSDS for MMT is included in Appendix 3.

MMT (as Mn) is listed in the NOHSC *Exposure Standards for Atmospheric Contaminants in the Occupational Environment* with an exposure standard of 0.2 mg/m^3, (8 h TWA), skin notation (NOHSC 1995b).

16.4 Public health risks

Direct public exposure to MMT is likely to occur primarily via the dermal route as a result of spills and splashes of LRP and aftermarket products.

In LRP, MMT is not expected to be a skin irritant at present concentrations. Estimated dermal doses of MMT to be received under a worst case scenario of LRP spillage were several orders of magnitude below comparable animal dermal LD50s. Therefore, there is a low risk of acute health effects for the general public as a result of dermal exposure to MMT in LRP.

Similarly, in aftermarket products, MMT at concentrations presently reported is not expected to be a skin irritant. A comparison of dermal LD50 values with exposure estimates suggests some potential for acute toxicity resulting from dermal exposure to MMT in aftermarket products. However, LD50 values in rats were obtained after a constant 24-hour exposure to MMT and in contrast, much shorter exposures are expected following spillage. Overall, the risk of acute dermal effects in consumers is low given the small amounts of additive to which people are likely to be exposed, the low concentration of MMT present with the fuel additive and that any spill on the skin is unlikely to reside untreated for long periods.

The risk of acute health effects as a result of accidental ocular exposure to MMT in LRP and aftermarket products is also considered to be low since exposure to very small amounts of product is expected to occur only infrequently and MMT is not expected to cause eye irritation at low concentrations present in these products.

Acute health effects could occur as a result of accidental ingestion of MMT by a child or by adults when siphoning fuel. The health risk to adults from accidental ingestion of LRP containing MMT during siphoning or to children following ingestion of LRP stored inappropriately around the home is considered low, given the low level of MMT (< 0.01% w/w) in LRP. However, assuming comparable toxicokinetics of MMT in rats and humans after oral exposure and using the lowest rat LD50 for MMT of approximately 10 mg/kg bw, a child (10kg) ingesting about one mL of an aftermarket product containing 10% w/w MMT could receive a potentially lethal dose. Children between one and a quarter and three and a half years of age can swallow approximately 4.5 mL of liquid, giving a potential dose several times higher than the lowest oral LD50 observed in laboratory animals.

The potential risk associated with accidental ingestion of aftermarket products containing MMT is lessened by the likely storage of aftermarket products in garages, products being generally not “attractive” for ingestion by a child and products as assessed packaged with child resistant closures. However, since very small volumes provide a potentially lethal dose, products containing MMT represent a significant acute health risk for children.

Manganese is a ubiquitous element and chronic Mn exposures (from all sources combined) are unlikely to be significantly changed by the use of MMT. Exposure via food and water forms, by far, the greatest proportion of the total human Mn dose, and are not expected to change significantly as a result of the estimated use of MMT.

However, MMT used according to the Present Use scenario of maintained LRP market share or the 2004 scenario of diminished LRP market share will potentially significantly increase the Mn dose received by inhalation (excluding smoking).

Based on the study of Roels et al (1992), the NOAEL for neurological effects in humans was established at 30 μg/m^3 and Margins of Exposure were calculated in this report converting intermittent Mn exposures (5 days/week, 24 hours/day) to continuous exposures. For the Present Use scenario, where current LRP market share is maintained with a calculated ambient air concentration for Mn of 4.9 ng/m^3, the Margin of Exposure was calculated at 1458. For the 2004 scenario, where the LRP market share declines with a calculated ambient air concentration for Mn of 20 ng/m^3, the Margin of Exposure was calculated at 3571. These Margins of Exposure are considered sufficient, taking into account the conservative exposure estimates used.

It is noted that the estimated ambient air concentration of Mn due to MMT combustion is at the lower end of a range of overseas inhalation health standards and guidance values. However, a number of conservative assumptions were used in this present exposure assessment. Consequently, the risk to public health as a result of the use of MMT as an AVSR is expected to be low. However, there are uncertainties associated with this risk assessment and there are likely to be sub-populations that have higher exposures and hence are at greater risk than the general population. For example, although the measured ambient air concentration of respirable Mn is probably unrelated to the use of MMT, exposure of people in Launceston is of potential concern since the ambient air concentration of total (but not respirable) Mn in that city is higher than some of the ambient air standards developed overseas. The use of MMT would add potentially to environmental Mn levels in this region.

16.5 Data gaps

For the purposes of risk assessment, this report identified a number of significant data gaps. These include:

- data on potential skin or respiratory sensitisation and effects associated with chronic MMT exposure;
- definitive information on the speciation of Mn compounds emitted during MMT combustion under different driving conditions;
- the toxicokinetics and potential adverse effects of different inorganic Mn compounds resulting from the combustion of MMT;
- health effects associated with chronic, low level Mn exposure, especially in susceptible populations such as children or individuals with compromised liver function; and
- Australian exposure data (personal and ambient air monitoring data) for determining public exposures to Mn especially in environments such as indoors, inside cars, areas of high traffic density and areas with Mn emitting industries.

This report notes certain projects planned or underway that will address some of these data gaps. For example the project entitled “Metal Emissions from Petrol and the Future Health of Children” by Macquarie University Graduate School of the

Environment, Australian Government Analytical Laboratories, Commonwealth Scientific and Industrial Research Organisation, United States Environmental Protection Agency and Australian Nuclear Science and Technology Organisation is presently examining fuel-related Mn emissions on susceptible subpopulations. Also, Environment Australia are planning a project entitled "Fine Particle Composition in Four Major Australian Cities" where the sampling, elemental and chemical compositional analysis of PM_{10} and $PM_{2.5}$ particles including analysis for manganese in major Australian cities will be conducted.

17. Recommendations

This section provides the recommendations arising from the priority existing chemical assessment of MMT. Recommendations are directed principally at regulatory bodies and importers and formulators of MMT and MMT products. Implicit in these recommendations is that best practice is implemented to minimise occupational and public exposure and environmental impact.

17.1 Recommendations for regulatory bodies

17.1.1 NOHSC

MMT (as Mn) is currently listed in the NOHSC *List of Designated Hazardous Substances* (NOHSC, 1999b) with no classification.

In accordance with the NOHSC *Approved Criteria for Classifying Hazardous Substances* (NOHSC, 1999a), MMT is classified "Hazardous" with the following risk phrases:

- R26 – Very Toxic by Inhalation;
- R28 – Very Toxic if Swallowed;
- R24 – Toxic in Contact with Skin;
- R48/23 – Toxic: Danger of Serious Damage to Health by Prolonged Exposure Through Inhalation.

The following safety phrases are also recommended for MMT:

- S36 – Wear Suitable Protective Clothing;
- S38 – In Case of Insufficient Ventilation Wear Suitable Respiratory Equipment.

It is recommended that this classification for MMT be adopted by NOHSC as part of their process for updating the *List of Designated Hazardous Substances* (NOHSC 1999b).

17.1.2 National Drugs and Poisons Schedule Committee

Given the acute toxicity profile of MMT and the potential for consumer exposure to products containing MMT, it is recommended that the NDPSC consider scheduling of MMT in the *Standard for the Uniform Scheduling of Drugs and Poisons*. A copy of the final report will be forwarded to the NDPSC for their consideration.

17.1.3 Tasmanian Department of Primary Industries, Water and Environment

This report notes a pilot study of atmospheric particulates conducted prior to the use of MMT in automotive fuels that cites elevated atmospheric manganese levels in

Launceston, Tasmania at certain periods compared to other cities. Given the potential for the combustion of MMT in automotive fuels to add to atmospheric manganese levels, a copy of this report will be forwarded to the Tasmanian Department of Primary Industries, Water and Environment for their consideration.

17.2 Recommendations for MMT importers and formulators of MMT products

17.2.1 Hazard communication – MSDS

This assessment found that MSDS for products containing MMT did not conform to the requirements of the NOHSC *National Code of Practice for the Preparation of Material Safety Data Sheets* (NOHSC 1994b). In order to ensure conformity with this code, it is recommended that importers of MMT review their MSDS for compliance and pay particular attention to the following points:

- risk phrases and hazard information should be updated to reflect the hazard classification in Recommendation 17.1.1;
- MSDS should carry correct hazard statements;
- emergency telephone numbers should be included; and
- the Australian exposure standard for MMT should be listed with an explanation for skin notation; and
- only ingredients relevant to the product should be included.

A sample MSDS can be found in Appendix 3.

17.2.2 Hazard communication – labels

This assessment found that labels for MMT products did not conform to the requirements of the *National Code of Practice for the Labelling of Workplace Substances* (NOHSC 1994a) or the Australian Dangerous Goods Code. In order to ensure conformity with these codes, it is recommended that importers of MMT review their labels for compliance and pay particular attention to the following points:

- risk phrases and hazard information should be updated to reflect the hazard classification in Recommendation 17.1.1;
- safety phrases should be included as noted in Recommendation 17.1.1;
- contact details of the local supplier should be included;
- hazard category or signal words should be included; and
- labels should be attached to product containers.

17.2.3 Packaging

It is recommended that all consumer products containing MMT be packaged in containers with childproof closures.

To prevent backflow and spillage of MMT by consumers when using aftermarket MMT products, it is also recommended that all consumer products designed to be added directly to fuel tanks should be enclosed in containers with spouts of sufficient length to ensure good insertion of the spout into the fuel filler.

If products containing multiple shots of additive are produced for consumer use, it is recommended also that where possible these should be packaged in containers with a measuring capacity or ideally with an automatic measuring and dispensing capacity. Appropriate consideration of the light sensitivity of MMT would also be required.

17.2.4 Emergency procedures

Any spills of product containing MMT should not be allowed to enter stormwater, sewers or natural waters.

18. Secondary Notification

Under Section 64 of the *Industrial Chemicals (Notification and Assessment) Act 1989*, the secondary notification of a chemical that has been assessed under the Act may be required where an introducer (manufacturer or importer) of a chemical becomes aware of any circumstances that may warrant a reassessment of its hazards and risks. In the case of MMT, specific circumstances include:

- use of MMT in bulk transport fuels other than LRP;
- the manufacture of MMT has begun in Australia;
- additional information has become available to the introducers as to adverse health and/or environmental effects of MMT;

The Director (Chemicals Notification and Assessment) must be notified within 28 days of the introducer becoming aware of any of the above or other circumstances prescribed under Section 64(2) of the Act.

Appendix 1 - Calculation of LRP Volumes for 2004

The weekly fill-up rate for vehicles using lead replacement petrol (LRP) was calculated from sales volumes of lead and lead replacement petrol (LRP) in July 2000 to June 2001 of 2 937.36 ML (Department of Industry, Science and Research, 2001) and from the number of vehicles using leaded petrol at 31 March 2001 of 2 904 342 (Australian Bureau of Statistics Motor Vehicle Census, 2001) as:

2 937.36 x 106 litres/year ÷ 2 904 342 vehicles = 1 011 litres/year/vehicle

= 19.4 litres/week/vehicle

LRP volumes in 2004 for 1 000 000 VSR susceptible vehicles were calculated by using a 19.4 litre LRP fill-up rate per week per vehicle, i.e., 1011 litres/year:

1 000 000 vehicles x 1011 litres/year/vehicle = 1 011 000 000 litres/year

~ 1 000 ML/year of LRP in 2004

Appendix 2 - MSDS Assessment Summary

Information	Number of MSDS containing correct information	Comments
Introductory And Company Details		
Date of issue (mon/year)	8/8	Two MSDS had dates in the wrong format.
Statement of hazardous nature	2/8	Of the remainder, 4/8 had a statement that the product was not hazardous; 2/8 didn't have a statement.
Name of Australian company and address	7/8	
Telephone number	7/8	
Emergency telephone number (Australian number stating hours available)	3/8	The number given for these 3 was the Australian Poisons Line.
Identification		
Product name	8/8	
Recommended uses and methods of application	7/8	
Ingredients – exact proportion or range	7/8	One MSDS listed 3 separate formulations for 3 different markets – European, US, Canadian without indicating the Australian formulation.
Health Hazard Information		
Damage to kidneys	3/8	
Damage to liver	6/8	
Damage to lung	8/8	Only MSDS for MMT concentrates warned of risk of acute pulmonary irritation as well as chronic pulmonary damage
CNS effects	8/8	

First Aid Statements for ingestion, inhalation, skin and eye exposure	8/8	One MSDS did not contain advice to contact a doctor following eye exposure.
Precautions For Use		
Personal Protective Equipment	8/8	
Correct atmospheric exposure standard for MMT of 0.2 mg/m^3 (TWA)	7/8	Most MSDS refer to the ACGIH standard for MMT (identical to that of NOHSC).
Skin notation explained	2/8	Skin notation was present in 7 MSDS but only 2 provided an accompanying explanation.
Contact Point		
Direct telephone number	7/8	Three of these 7 MSDS containing a Contact Point referred only to the Australian Poisons Information Centre.

Appendix 3 - Sample Material Safety Data Sheet for Methylcyclopentadienyl Manganese Tricarbonyl (MMT)

MMT is classified as hazardous according to the National Occupational Health and Safety Commission's *Approved Criteria for Classifying Hazardous Substances* [NOHSC:1008(1994)].

Company Details

Company name

Address

State Postcode

Telephone number

Emergency telephone number

Identification

Product Name

Methylcyclopentadienyl manganese tricarbonyl

Other names

Manganese tricarbonyl [(1,2,3,4,5-)-1-methyl-2,4-cyclopentadien-1-yl]-

MMT

Methylcymantrene

Manufacturer's product code

UN Number

2810 Toxic liquid, organic, nos

Dangerous goods class and subsidiary risk

Class 6.1 Packing Group I

Hazchem code

2X

Poisons Schedule Number

None allocated

Use

Physical description and properties

Appearance

Dark orange or yellow liquid

Boiling Point	Freezing Point
231.7°C	2.2°C

Vapour pressure

0.01 kPa at 20°C

Specific Gravity

1.39 at 20°C

Flashpoint

96°C (closed cup)

Flammability Limits

Lower: 0.3% at 153°C

Upper: 26% at 175°C

Solubility in water

0.029 g/L at 25°C

Other properties

Odour: herbaceous

Autoignition temperature: 257°C

Partition coefficient (log Pow): 3.4

Solubility: MMT is miscible in most hydrocarbon solvents.

Stability: MMT decomposes when exposed to light.

Polymerisation: MMT will not undergo hazardous polymerisation.

Ingredients/impurities

Chemical entitiy	CAS Number	Proportion
MMT	12108-13-3	100%
Impurities		

Health hazard information

HEALTH EFFECTS

Acute

Swallowed: Very toxic in animals by the oral route.

Eye: Slight eye irritant.

Skin: MMT is toxic in contact with skin and a slight skin irritant. MMT penetrates the skin.

Inhaled: Very toxic in animals via inhalation.

Acute toxicity studies in rats, rabbits and mice have shown MMT to induce damage to the lungs, kidney, liver and spleen effects, tremors, convulsions, dyspnea and weakness.

In humans, the acute effects of MMT by skin or inhalation exposure are reported to be burning of the skin, a metallic taste in the mouth, "thick tongue", giddiness, headache, nausea, chest tightness, gastrointestinal upset, laboured breathing and abnormal sensation.

Chronic

Swallowed: In rats and mice, repeated oral exposure was associated with weight loss and mild neurological and developmental effects.

Inhaled: In rats and mice, repeated exposure via inhalation was associated with severe weight loss and death with degenerative changes in the lungs, liver and kidney.

There are no human case reports or studies detailing symptoms resulting from prolonged exposure to MMT. However, at chronic low doses of MMT, neurological and psychological disturbances may occur due to exposure to manganese.

FIRST AID

If swallowed, do NOT induce vomiting. Give a glass of water.

If in eyes, wash out immediately with water.

If skin contact occurs, remove contaminated clothing and wash skin thoroughly.

Remove from contaminated area. Apply artificial respiration if not breathing.

ADVICE TO DOCTOR

Treat symptomatically. No specific antidote. Aspiration of vomitis can cause chemical pneumonitis which can be fatal.

Precautions for use

EXPOSURE STANDARD

Australian Exposure Standard (NOHSC) 0.2 mg/m^3 8 hour TWA (as Mn) with skin notation.

The "skin notation" (Sk) indicates that absorption through the

skin may be a significant source of exposure.

ENGINEERING CONTROLS

Use only with adequate ventilation. Local exhaust ventilation may be necessary for some operations. Airborne concentrations should be controlled to below the NOHSC exposure standard.

PERSONAL PROTECTION

Use suitable protective clothing to avoid skin contact. Chemical resistant overalls (preferably disposable), neoprene, PVC or butyl rubber gloves and boots, safety glasses or chemical goggles should be used. If necessary, use a respirator with an organic vapour cartridge to avoid breathing vapours in confined spaces or in other places with limited ventilation.

Ensure good personal hygiene.

Fire fighting: wear self-contained breathing apparatus and complete protective clothing.

Safe handling information

STORAGE AND TRANSPORT

Store in a cool dry place away from heat sources, ignition sources and direct sunlight. Keep container closed.

Shipping Name: Metal Carbonyls NOS, Methylcyclopentadienyl manganese tricarbonyl

Transport Label Required: Toxic liquid, organic, nos

Packing Group: 1

Initial Emergency Response Guide:

SPILLS AND DISPOSAL

Remove all sources of ignition. Use protective gloves to avoid skin contact. Avoid breathing of vapours. Do not hose spills down drains, sewers or waterways. Dyke and contain spilled material and remove with inert absorbent. Store in closed container until product can be properly disposed of. Contact local waste disposal authority for advice or pass to a licensed waste disposal company for disposal.

FIRE/EXPLOSION HAZARD

Keep containers tightly closed. Isolate from heat and flames. Use self-contained breathing apparatus and complete protective clothing. Use water fog or fine spray to extinguish.

Other information

TOXICOLOGICAL INFORMATION

Acute

Oral LD50 9–176 mg/kg bw (rat)

Dermal LD50 140–795 mg/kg bw (rat)

Inhalation LC50 220–247 mg/m^3 bw (rat, 1 hour); >2–76 mg/m^3 (rat, 4 hour)

Repeat Dose

NOAEL (inhalation) 6.2 mg/m^3 (rats and mice)

Environmental Data

MMT is subject to rapid photochemical degradation in the atmosphere with a reported atmospheric half-life of 8-18 seconds.

MMT can adsorb to and become immobilised in soils reducing its potential for photo-degradation.

Degradation of MMT in dark, anaerobic aqueous environments is slow.

Aquatic Toxicity

MMT is toxic to aquatic organisms.

Daphnia Magna (4 and 48 hour EC50) 0.87 mg/L and 0.83 mg/L respectively.

Bluegill sunfish TLm (LC50) (12 h) 0.2 mg/L.

Fathead Minnow TLm (LC50) (12 h) 0.23 - 0.36 mg/L.

Classification

R26 - Very Toxic by Inhalation

R28 - Very Toxic if Swallowed

R24 - Toxic in Contact with Skin

R48/23 - Toxic: Danger of Serious Damage to Health by Prolonged Exposure Through Inhalation

S36: Wear Suitable Protective Clothing

S38: In Case of Insufficient Ventilation Wear Suitable Respiratory Equipment.

Further Information

National Industrial Chemicals Notification and Assessment Scheme (NICNAS) Assessment Report on Methylcyclopentadienyl Manganese Tricarbonyl: Priority Existing Chemical Assessment Report.

The full report can be downloaded from

http://www.nicnas.gov.au

Contact Point

Contact name	Telephone number
Position title	
Address	
State Postcode Country	

Appendix 4 – Classification under the Globally Harmonized System for Hazard Classification and Communication

In this report, MMT has been classified against the NOHSC *Approved Criteria for Classifying Hazardous Substances* (Approved Criteria) (NOHSC, 1999a) and, in the case of physicochemical hazards, the *Australian Dangerous Goods Code* (ADG Code) (FORS, 1998). However, classifications under the Globally Harmonized System for Hazard Classification and Communication (GHS) (OECD 2002) will come into force when the GHS is adopted by the Australian Government and promulgated into Commonwealth legislation. GHS documentation is available at

http://www.unece.org/trans/danger/publi/ghs/officialtext.html

The classification of MMT against the GHS can be found below.

Health and Environmental Hazards	Classification	Hazard Communication
Acute toxicity	**Acute Toxicity Category 1**	**Symbol:** Skull and Crossbones **Signal word:** Danger **Hazard Statements:** Fatal if Swallowed Fatal in Contact with Skin Fatal if Inhaled
Systemic toxicity-repeated exposure	**Repeated Exposure Category 1**	**Symbol:** New Health Hazard Symbol **Signal word:** Danger **Hazard Statement:** Causes Damage to Organs Through Prolonged or Repeated Exposure by Inhalation.
Ecotoxicity	**Category: Chronic 1**	**Symbol:** Fish and Tree **Signal word:** Warning **Hazard Statement:** Very Toxic to Aquatic Life with Long-Lasting Effects.

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