Dr Charles Kilburn takes blood samples for manganese analysis.

Tracking down the cause of a mysterious illness

While some manganese is necessary as a trace element in our food, with higher intake the element can become an insidious neurotoxin that only shows its debilitating effects years or even decades later.

On Groote Eylandt — the Dutch-named 'Great Island' in the Gulf of Carpentaria — most of the local Aboriginal population live on top of a high-grade manganese deposit. Covering some 80 sq. km, it's the world's largest. Next to the main settlement sit an open-cut mine and piles of crushed ore.

Lumps of black manganese ore (pyrolusite, or manganese oxide) can be picked up on roads, and a thin black film of manganese dust settles on furniture and anything else left undisturbed for more than a day or two.

Bark paintings from Groote Eylandt are distinctive: they show extensive use of a jet-black pigment — pyrolusite. Other Aboriginal cultures make do with charcoal instead. Nearby Blue Mud Bay, named by Matthew Flinders, owes its colour to a manganese compound.

The local Angurugu River (pronounced a-nu-ru-gu), which supplies the inhabitants with water, flows across an exposed bed of manganese ore. The black soil contains up to 4% manganese, and fruit and vegetables grown in it contain concentrations of the element up to a hundred times the world average. One 20-g yam can supply 13 mg of manganese — three times the recommended daily allowance.

The syndromes didn't appear before the community shifted to manganese-rich Angurugu.

A diet of 'bush tucker' could provide a manganese intake of 100–200 mg per day, (50–100 times larger than that of a Sydneysider). Since the local store opened in 1970, bush tucker no longer makes up the bulk of the Aborigines' diet. Flour, sugar, and tea are now the staples. However, damper is cooked in the earth and, as it happens, strong billy tea is intrinsically high in manganese — about 6 mg per litre.

More than 1000 Groote Eylandters have been living in this high-manganese environment since 1942, when war-time activities led them to shift 30 km north from a relatively manganese-free area. Nowhere else in the world has an entire population of men, women, children, and — significantly — infants and pregnant women been exposed to such high levels of manganese for an extended time. Has it had a detrimental effect?

According to Dr John Cawte, Professor of Psychiatry at the University of New South Wales, the Aborigines' new manganese-rich environment, allied to a genetic predisposition to manganese build-up in some susceptible individuals, is to blame for distressing motor-neurone defects and cerebellar dysfunctions that strike 1–2% of the population. Measurements of the manganese burden of the Groote Eylandters and of their environment by CSIRO scientists have put figures on the levels of manganese to which the people have been exposed.

One major syndrome — seen in people in their 40s and 50s — is an awkward high-stepping gait, like that of a bird. The tribe members refer to those afflicted as 'bird people', and anxiously watch out for this sign in themselves and their children. General unsteadiness and lack of co-ordination accompany it, and are reflected in outstretched arms that latch on to furniture or walls for support.

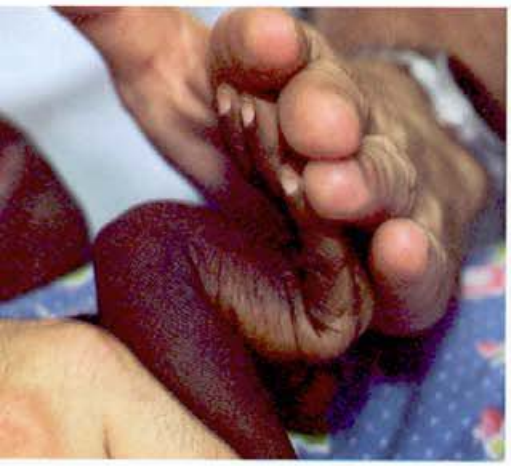
Other typical signs are flickering eyes, hand tremors, and muscle twitching. Mentally, states of excitement alternate with fixed gazes and unresponsiveness. A CAT-scan of one severely affected man brought to Sydney for treatment showed atrophy of his cerebellum.

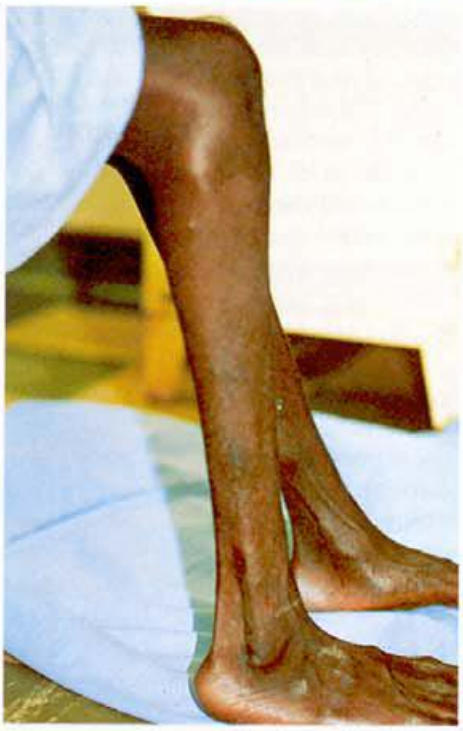
Another related syndrome, which begins in childhood, is a wasting and weakness of the muscles, particularly in the lower limbs. All those affected have minor foot and spine deformities, suggesting a congenital influence. An unusual disparity in the sex ratio of schoolchildren is apparent, with four girls for every three boys. An obvious laxity of the ligaments is also common.

Angurugu syndromes

Professor Cawte first became aware of some of these symptoms in 16 individuals about 10 years ago, and he named them 'Angurugu syndromes'. He came across them while working as an anthropologist and physician at nearby Elcho Island (where he has spent most of his vacations for the last 20 years).

In addition, he found that many Aborigines display an 'emotional incontinence' that is generally foreign to other Aboriginal tribes. Historically, Groote Eylandters have had a reputation for acute





***Top*: Lax ligaments in a child's hand — a prevalent symptom.**

***Lower*: Muscle wasting is another sign of the disease.**

excitement, angry outbursts, and aggression, and the record of arrest and jailing of the inhabitants is the highest, *per capita*, in the country. Teachers have noted that, compared with other groups of a similar age, Groote Eylandt children are considerably retarded in their educational development.

Many of those displaying Angurugu syndromes are closely related, and the problem does tend to 'run in families'. Originally Dr Cawte took this as a sign that the disease was a genetic one, quite a possibility in a small isolated population.

However, the affliction doesn't appear to follow the expected Mendelian pattern, and anthropologists in the 1920s, when the people were not living in such a high-manganese locality, had recorded no instance of neurological disease.

A key pointer is that in none of the cases presently diagnosed did the syndromes appear before the community shifted from Emerald River (relatively low in manganese) to Angurugu (manganese-rich).

Although the Groote Eylandt Mining Company began its open-cut mining operation at Angurugu in 1960, the mine itself, and the dust it scatters, cannot be identified as the primary cause of the problem. In about half the documented cases, symptoms arose before the mine was opened.

Nevertheless, Dr Cawte recognised that chronic manganese poisoning could be the culprit. The symptoms appeared similar, although not identical, to those that had been recorded in manganese-miners elsewhere, particularly in Chile. There, long-term exposure had led to a number of neurological disorders, many resembling Parkinson's disease and one being an easy arousal to rage.

In the Chilean situation, individual susceptibility to manganese again stood out as a vital factor. Less than 5% of the miners developed chronic manganese toxicity symptoms; while one miner succumbed, his workmate, with identical exposure, was not affected.

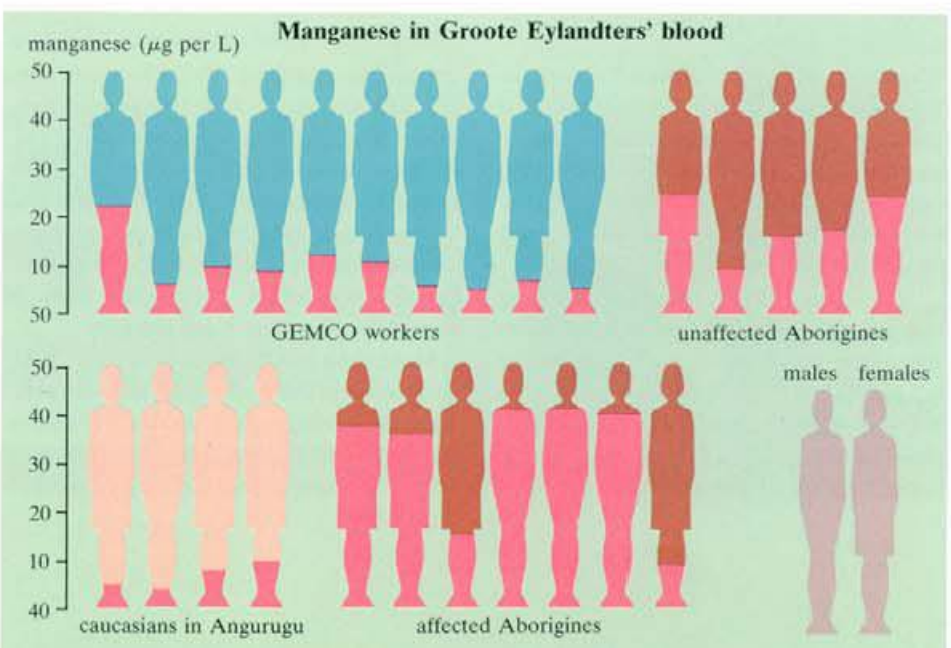
Possibly because of the apparent large variation in people's susceptibility to manganese poisoning, it took a long time for scientists to recognise the danger. Most manganese salts have low acute toxicity, and until the 1970s it was regarded as one of the most innocuous of elements.

Dr Cawte suggests that some differences in symptoms between Angurugu and Chile can be attributed to different patterns of exposure. In Chile, adult miners take in large quantities of manganese in the course of their work. At Angurugu, exposure may begin at conception due to the potentially high manganese burden of the mother, and continue through pregnancy into infancy and beyond. One disturbing habit is widespread clay-eating (medically called pica); children are known to take bags of clay to the pictures and eat it during the show.

Dr Mark Florence collecting hair samples.

Animal studies by Dr Bill Webster of Sydney University have shown that, during pregnancy and lactation, manganese absorption and excretion processes change. A pregnant female absorbs manganese at

Aborigines affected by Angurugu syndromes usually had very high levels of blood manganese.



Manganese in hair

subjects	mean manganese in hair at scalp (p.p.m.)
Sydney	0·5 ± 0·2
GEMCO workers	2·2 ± 0·8
caucasians in Angurugu	2·5 ± 0·7
unaffected Aborigines	15 ± 5
affected Aborigines	9 ± 3

Although levels of manganese in the hair of affected Aborigines were high, they didn't differ significantly from levels in the unaffected.

about twice the normal rate. The foetus and the newborn lack any mechanism for excreting the element. The growing brain also shows a tendency to concentrate manganese, particularly in the cerebellum.

Investigations begin

Strongly suspecting a link between Angurugu syndromes and manganese, Dr Cawte convened a conference in Darwin in 1983 to make known his concern. After it, GEMCO (through its parent, BHP) and the Angurugu Community Council provided funds for further investigations, and in 1985 a National Health and Medical Research Council research grant enabled Dr Charles Kilburn to spend 2 years at Angurugu as resident medical officer. He screened the local population closely, and took hair and blood samples for analysis.

Special equipment at the CSIRO Division of Fuel Technology provided an accurate way of analysing the trace metal composition of these samples and others collected by the CSIRO scientists. Dr Mark Florence and his Divisional colleagues used neutron activation analysis, anodic stripping voltammetry, and inductively coupled plasma emission spectroscopy for most of their measurements. Atomic absorption spectroscopy was best suited for blood analyses; this was carried out by Mr Graham Hams at the Prince of Wales Hospital, Sydney.

Because it's so easy to collect hair samples, Dr Florence hoped that scalp hair manganese would prove a reliable indicator of an individual's whole-body burden. The idea is that hair concentrates trace elements from blood supplying the hair follicle and so should give a record of manganese in blood over some months.

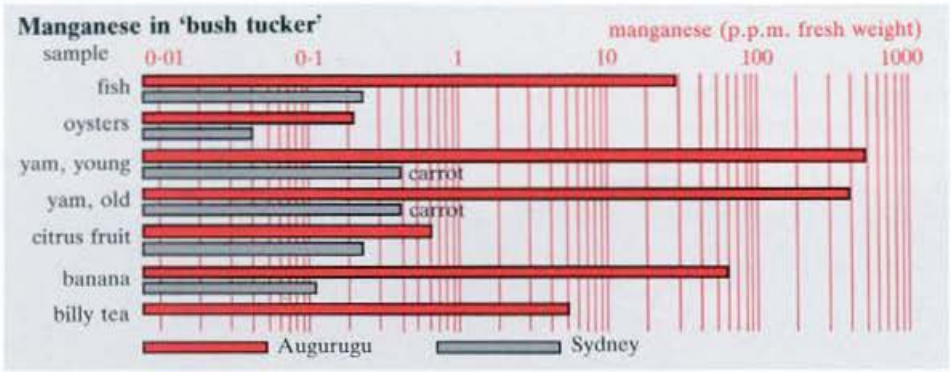
Hair samples from more than a hundred Groote Eylandters were analysed to see whether any distinct pattern could be demonstrated. Unexpectedly, Dr Florence found that manganese levels gradually increased along the length of all the samples. No, everybody wasn't progressively taking in less manganese; he explains it's a result of hair losing its protective waxy coating with age (and length). The longer the hair, the easier it is for sweat-dissolved manganese (from air-borne dust lodged in the hair) to enter the absorbent hair shaft.

Piles of manganese ore at Groote Eylandt.

Nowhere else has an entire population been exposed to such high levels of manganese for an extended time.

Angurugu village. Dr Kilburn consults with Digetty, a tribal elder.

Most of the Aborigines on Groote Eylandt live at Angurugu, right on top of a manganese outcrop.



Analysis of traditional foods revealed very high levels of manganese. One 20-g yam would supply three times the recommended daily intake.

To compensate for this effect, he plotted manganese concentration against distance from the scalp and extrapolated it to zero length. This gave a good estimate of the manganese content of emerging, uncontaminated, hair.

It quickly became clear that everybody living on the island had hair enriched in manganese. Aborigines had scalp-hair manganese concentrations ranging from 3 to 25 p.p.m., with a mean of 15 p.p.m. — much higher than the mean of 0·9 p.p.m. for Aborigines living in eastern Arnhem Land.

Caucasians living at Angurugu also had high levels of manganese in their hair (but much lower than the Aborigines), with an average of 2·5 p.p.m. A comparative figure obtained for Sydney whites was 0·5 p.p.m.

Unfortunately, hair readings provided no simple indicator of disease status. There was no significant difference in these readings between Aborigines affected with Angurugu syndromes and others, whereas sufferers had blood levels twice those of unaffected Aborigines. And, as a point of comparison, the latter had blood manganese levels about twice those of Groote Eylandt whites (which were normal — about 9 μg per L).

The main cause of high blood manganese in Aborigines may be their close-to-the-earth living. Sitting, eating, and sleeping on ground containing 4% manganese probably leads to the ingestion and inhalation of large amounts of the element.

Dr Florence concludes that blood readings are presently the best indicator we have for locating those individuals who have either enhanced manganese-uptake mechanisms or deficient clearance mechanisms. Levels of manganese in sweat and urine did not differ between sufferers and non-sufferers.

But even so, blood manganese can only give an indication of recent exposure, since manganese in the human body is excreted

How manganese can poison

Although a trace quantity of manganese is essential for proper nerve functioning, too much leads to serious toxic effects. In acute cases, *locura manganica* (manganese madness) can occur, with disorientation, memory loss, compulsive behaviour, and hallucinations. In chronic cases, such as are likely on Groote Eylandt, locomotor defects predominate.

Scientists believe manganese acts primarily as a catalyst in certain metallo-enzymes within nerve cells. In particular, they think that operation of the neurotransmitter dopamine depends on manganese, and that one metallo-enzyme, manganese superoxide dismutase, protects nerve membranes against damage by naturally occurring superoxide radicals (O_2^-).

Dr Florence has studied, in his CSIRO laboratory, the chemistry of manganese catalysis of dopamine oxidation. His results suggest that, in the presence of manganese, oxidation of dopamine proceeds by a series of identifiable steps, each of which produces neurotoxins. Of special concern, he believes, are the powerful neurotoxins dopamine quinone and hydrogen peroxide. As the main article mentioned, he has found that vitamin C and vitamin B_1 effectively inhibit dopamine oxidation.

However, no clear-cut description of what occurs in manganese poisoning has yet emerged. A remarkable feature of chronic manganese poisoning is that the symptoms resemble those of Parkinson's disease. The latter is caused by degeneration in the cerebellum, and evidence points to manganese disrupting nerve function in the same area. In another parallel, dosing with l-dopa (the treatment of choice for Parkinson's disease) also alleviates symptoms of manganese poisoning.

In both conditions, we find a diminished neuromelanin content in the *substantia nigra* ('black substance') of the cerebellum. Significantly, neuromelanin is formed directly from dopamine, and manganese has a strong affinity for melanin. Monkeys exposed to manganese for 18 months showed marked neuronal degeneration and loss of neuromelanin from the *substantia nigra*.

Apparently manganese wreaks havoc on the *substantia nigra* because this region of the body is one that is, biochemically, highly oxidative. And so manganese, which in its normal divalent state (Mn^{2+}) is relatively innocuous, here readily becomes oxidised to its trivalent form (Mn^{3+}). Manganese (III) has high toxicity because it is very reactive and, as we have seen, it can react with dopamine (also abundant in the *substantia nigra*) to produce those nasties, hydrogen peroxide and dopamine quinone.

And so scientists are beginning to think that excess manganese exerts its damaging effects through accelerating degeneration of areas in the cerebellum. If this proves right, the danger of manganese poisoning is that the effects may not manifest until many decades later.

Normally, we lose only a small fraction of the neurons in the *substantia nigra* each year. Only when 70–80% of the neurons are destroyed does Parkinson's disease begin to show itself. In some people, this level is never reached; others reach it in their sixties and seventies.

How insidious it would be if manganese played a role in accelerating neurone degeneration such that people in their forties and fifties began to suffer as a result of manganese they had absorbed a long time ago — even in their babyhood or intra-uterine life.

Experiments in animals have shown that, until the animal is some weeks old, almost no barrier exists to prevent manganese crossing from the gut through to the blood-stream.

Psychiatric *sequelae* of manganese exposure in the adult, foetal and neonatal nervous systems. J. Cawte. *Australian and New Zealand Journal of Psychiatry*, 1985, **19**, 211–17.

Manganese and human health. J. Donaldson. In 'Manganese in the Canadian Environment', chapter 5. (National Research Council of Canada: Ottawa 1988.)

from readily exchangeable pools in soft tissues after some days (by one route) or weeks (by another mechanism). Damaging manganese poisoning might have taken place years ago, perhaps at birth, or the manganese may now be locked up in inaccessible brain structures.

Aggravating factors

In this connection, one worrying result came from the measurement of high manganese in the umbilical cord of an Angurugu baby — 41 μg per L — even though the mother's blood was normal.

Another concern is that manganese toxicity is enhanced by a number of factors that are commonly found among Groote Eylandt Aborigines. A major one is a low level of iron in the blood (anaemia) — a result of inadequate diet and aggravated by widespread hook-worm infestation. Iron and manganese have similar uptake mechanisms, so when anaemic individuals increase their absorption of iron to try to compensate, they inadvertently increase their manganese absorption as well.

Chronic infections and a high alcohol intake decrease the body's ability to scavenge toxic substances, especially those that are produced by manganese as catalyst (see the box on page 6). In addition, alcohol enhances the intestinal uptake of manganese.

A low level of calcium in the diet is harmful, in that manganese can displace calcium from nerve endings and disrupt nerve functioning. This is more likely in individuals with high manganese and low calcium levels. Dr Florence found that soils in one-time gardens at Angurugu, while exceptionally high in manganese (up to a hundred times the world average), were also very low in calcium (a twenty-fifth of the world average). Calcium in the Angurugu River was again very low, 0·2 mg per L, about one-hundredth the levels regarded as typical elsewhere.

A crucial factor here is how much calcium the Aborigines obtain from the staples of flour and sugar they buy from the local store. These days, bush tucker comprises perhaps 10–20% of their diet, whereas prior to 1970 fruit and vegetables grown in the garden areas made up about 80% of their food intake.

Nobody has done a close dietary study to show what the calcium intake of the Aborigines may be. Similarly, we presume their manganese intake must be high, but we don't know the actual figure.

An Aboriginal miner holds a nugget of manganese ore. (Drawing by Aboriginal artist Billy Reid.)

Raising the dust during mining.

Looking for solutions

What can be done? A ready solution would be to move the community away from Angurugu, but that's not so simple now that it has settled down and established permanent buildings. Angurugu is now home, and has important tribal connections.

Application of ferrous sulfate to the vegetable gardens may help to prevent manganese uptake by the plants. Hawaiians use such a practice in their pineapple plantations to prevent a build-up of manganese in the fruit. The Angurugu Community Council plans to replace garden soil with low-manganese soil brought in from elsewhere, and to seal the roads to reduce dust levels.

Many metals can be removed from the body by administering substances — chela-

Manganese in air and water

sample	Angurugu	Sydney
tapwater (μgMn per L)	4·3 (Aug. 1985) 70 (Jan. 1987)	5·8
Angurugu River (μgMn per L)	27 (Aug. 1985) 97 (Jan. 1987)	
air (μgMn per cu.m)	23 (3 m from road) 1·2 (10 m from road)	0·05

These are minor sources, but there is some evidence that inhaled manganese is more toxic than that ingested.

Longevity and manganese at Walcha

The longevity of the residents of Walcha, a sleepy little town (population 1500) near Armidale, N.S.W., is legendary. It has 18 nonagenarians (statistically you would expect two), and two blithe spirits over 100.

Tales are told of undertakers doing poor business, and having to shoot people to generate activity at the cemetery.

The locals attribute their long life to manganese. In years gone by a manganese mine operated nearby.

With an interest in manganese derived from his Groote Eylandt work, Dr Florence became intrigued by these apocryphyal tales. He decided he'd see whether the claim that manganese was the elixir of life had any basis.

He journeyed to beautiful Walcha and took samples of water and soil. Back in the laboratory, analysis of them showed levels of manganese no different from those in most other places in Australia. The manganese hypothesis is a myth, destroyed by science.

Taking water samples from the Angurugu River.

tion agents — that have an affinity for the metal; they bind to it and are then excreted, taking the metal with them.

Three brothers from Angurugu were brought to Prince Henry Hospital in Sydney and treated with one chelation agent, EDTA, in an attempt to remove excess body manganese. Unfortunately, such a treatment is unlikely to reverse brain damage done by manganese early on.

Urine analysis showed that EDTA failed to remove any manganese in these three cases. One of the brothers had an advanced case of the syndrome, one a mild case, and the other was unaffected even though he too had somewhat elevated manganese levels in his blood.

A slightly more promising approach is to administer l-dopa, the precursor to dopamine. This substance has been successfully used to alleviate symptoms of manganese poisoning in Chilean miners by raising dopamine levels in the brain. It was first tried because their symptoms resembled those of Parkinson's disease, a complaint associated with low levels of brain dopamine and one that responds well to l-dopa.

Indeed, after taking l-dopa tablets, the affected brother walked faster and recovered his balance quicker. His speech and mood also improved. However, the tablets were discontinued when he returned to Angurugu, as the treatment is not easy to supervise (raising dopamine this way can deplete levels of the essential amino acids methionine and cystine).

Vitamin cure?

Dr Florence recently undertook some laboratory studies that have suggested another way of preventing Angurugu syndromes. His results suggest that giving large doses of vitamins B and C may prove successful.

Since manganese toxicity probably results from its action in aiding the depletion of dopamine (which produces the neurotoxins dopamine quinone and hydrogen peroxide), Dr Florence studied a wide range of compounds looking for those that would inhibit dopamine oxidation. In test-tube experiments, he found that ascorbic acid (vitamin C) and thiamine (vitamin B_1) were the most effective inhibitors, completely blocking oxidation in both the presence and absence of manganese.

Because many of the Groote Eylandt Aborigines are likely to be deficient in vitamin C (due to poor diet) and in vitamin B_1 (alcohol consumption), it seems a likely supposition that lack of these vitamins facilitates the disease.

Dr Florence is excited by the prospect of a simple preventive measure for the dreaded 'bird disease'. With collaborators at Macquarie University, he is planning a detailed study of the vitamin status of the Groote Eylandt Aborigines, which would, if appropriate, be followed by setting up an arrangement for providing vitamin supplements.

Andrew Bell

More about the topic

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Manganese as a petrol additive

A manganese compound, methylcyclopentadienyl manganese tricarbonyl (MMT), is used in Canada to raise the octane rating of unleaded petrol, and its possible use in Australia for this purpose is currently being considered by the Australian Environment Council (comprising Federal and State Environment Ministers).

Nearly a decade's use in Canada has shown it to be an economical octane booster. In the United States it is no longer used in unleaded petrol because of evidence that it may slightly increase hydrocarbon emissions, but it is added to leaded petrol.

United States and Canadian regulatory bodies consider the compound presents no threat to health, with calculated manganese doses from air containing vehicle emissions being very much less than the amounts taken in from other sources, mainly food and water. In Australia, the National Health and Medical Research Council has investigated the possible use of MMT and found no reason, on toxicological grounds, to oppose its introduction.

The manufacturers of MMT calculate that its addition to unleaded petrol in Australia at the envisaged rate of 17 mg per litre would raise manganese levels in city air by an average of about 0·02 μg per cu. m. This compares with a current level of some 0·05 μg per cu. m. measured by Dr Florence in Sydney and an average of 0·04 μg per cu. m. measured in Toronto, Canada, where unleaded petrol contains MMT. The Canadian occupational limit for manganese in air is 1000 or 5000 μg per cu. m, depending on whether the manganese is present as fume or dust.

At a concentration of 0·05 μg per cu. m, daily inhalation of manganese amounts to about 1 μg. Some evidence suggests that manganese that is inhaled persists in the body longer than ingested manganese. However, the quantities involved are much smaller; normal manganese intake from all sources by an adult averages 2–3000 μg per day.

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