While manganese is clearly an essential element, it has also been demonstrated to be the causative agent in a syndrome of neurologic and psychiatric disorders that has been described in manganese miners. Donaldson (1987) provides a summary of this documented toxicity of manganese to humans, which has been primarily limited to workers exposed by inhalation. In contrast to inhaled manganese, ingested manganese has rarely been associated with toxicity. A review of manganese toxicity in humans and experimental animals has been provided by Keen and Zidenberg-Cherr (1994).


Epidemiological study


There is one epidemiologic study of manganese in drinking water, performed by Kondakis et al. (1989). Three areas in northwest Greece were chosen for this study, with manganese concentrations in natural well water of 3.6-14.6 µg/L in area A, 81.6-252.6 µg/L in area B, and 1600-2300 µg/L in area C. The total population of the three areas studied ranged from 3200 to 4350 people. The study included only individuals over the age of 50 drawn from a random sample of 10% of all households (n=62, 49 and 77 for areas A, B and C, respectively). The authors reported that "all areas were similar with respect to social and dietary characteristics," but few details were reported. The three areas are located within a 200-square km region. Although the amount of manganese in the diet was not reported, the authors indicated that most of the food was purchased from markets and is expected to be comparable for all three areas. Chemicals other than manganese in the well water were reported to be within Economic Community (EC) standards, except for hardness (120-130 mg calcium carbonate per liter). The individuals chosen were submitted to a neurologic examination, the score of which represents a composite of the presence and severity of 33 symptoms (e.g., weakness/fatigue, gait disturbances, tremors, dystonia). Whole blood and hair manganese concentrations also were determined. The mean concentration of manganese in hair was 3.51, 4.49 and 10.99 µg/g dry weight for areas A, B and C, respectively (p<0.0001 for area C versus A). The concentration of manganese in whole blood did not differ between the three areas, but this is not considered to be a reliable indicator of manganese exposure. The mean (x) and range (r) of neurologic scores were as follows: Area A (males: x=2.4, r=0-21; females: x=3.0, r=0-18; both x=2.7, r=0-21); Area B (males x=1.6, r=0-6; females: x=5.7 r=0-43; both: x=3.9, r=0-43); and Area C (males: x=4.9, r=0-29; females: x=5.5, r=0-21; both x=5.2, r=0-29). The authors indicate that the difference in mean scores for area C versus A was significantly increased (Mann-Whitney z=3.16, p=0.002 for both sexes combined). In a subsequent analysis, logistic regression indicated that there is a significant difference between areas A and C even when both age and sex are taken into account (Kondakis, 1990).
A report by Kawamura et al. (1941) is the only epidemiologic study describing toxicologic responses in humans consuming large amounts of manganese dissolved in drinking water. The manganese came from about 400 dry-cell batteries buried near a drinking water well, resulting in high levels of both manganese and zinc in the water. Twenty-five cases of manganese poisoning were reported, with symptoms including lethargy, increased muscle tonus, tremor and mental disturbances. The most severe symptoms were observed in elderly people, while children appeared to be unaffected. Three individuals died, one from suicide. The cause of death for the other two was not reported, but the autopsy of one individual revealed manganese concentration in the liver to be 2-3 times higher than in control autopsies. Zinc levels also were increased in the liver. The well water was not analyzed until 1 month after the outbreak, at which time it was found to contain approximately 14 mg Mn/L. When re-analyzed 1 month later, however, the levels were decreased by about half. Therefore, by retrospective extrapolation, the concentration of manganese at the time of exposure may have been as high as 28 mg Mn/L. No information regarding dietary levels of manganese was available in this study.

3. Long term exposure to manganese in rural well water has no neurological effects. There is debate on the neurological impact of chronic exposure to Manganese (MN). MN burden from rural well water was studied cross-sectionally in two proband cohorts from rural dwellings located in northern Germany. Both cohorts had exposure times for up to 40 years and were separated on the basis of well water MN content. Group A (41 subjects; mean age 57.5 years) was exposed to MN water contents of at least 0.300 mg/l (range 0.300 to 2.160), while group B (74 subjects; mean age 56.9 years) was exposed to concentrations of less than 0.050 mg/l. Both proband groups were homogenous with regard to age, sex, nutritional habits, and drug intake. Neurological assessments by clinical investigators blinded for proband's exposure status was done using structured questionnaires, standardized neurological examination with assessment of possible Parkinsonian signs by the Columbia University Rating Scale, and instrumental tests of fine motor coordination. No significant difference in any neurological measure was found between groups. Results were not confounded by demographic and dietary features. Exposure to high body burden of MN does not result in detectable neurological impairment. Exposure to MN in drinking water does not seem to be a risk factor for idiopathic Parkinson's disease.

Case reports: A few case studies have also pointed to the potential for manganese poisoning by routes other than inhalation.

One involved a 59-year-old male who was admitted to the hospital with symptoms of classical manganese poisoning, including dementia and a generalized extrapyramidal syndrome (Banta and Markesbery, 1977). The patient's serum, hair, urine, feces and brain were found to have manganese "elevated beyond toxic levels," perhaps a result
of his consumption of "large doses of vitamins and minerals for 4 to 5 years."
Unfortunately, no quantitative data were reported.


Another case study of manganese intoxication involved a 62-year-old male who had been receiving total parenteral nutrition that provided 2.2 mg of manganese (form not stated) daily for 23 months (Ejima et al., 1992). The patient's whole blood manganese was found to be elevated, and he was diagnosed as having parkinsonism, with dysarthria, mild rigidity, hypokinesia with masked face, a halting gait and severely impaired postural reflexes. To be able to compare the manganese load in this individual with that corresponding to an oral intake, the difference between the direct intravenous exposure and the relatively low level of absorption of manganese from the GI tract must be taken into account. Assuming an average absorption of roughly 5% of an oral dose, the intravenous dose of 2.2 mg Mn/day would be approximately equivalent to an oral intake of 40 mg Mn/day.


A third case study involved an 8-year old girl with Alagille's syndrome (an autosomal dominant disorder manifested principally by neonatal cholestasis and intrahepatic bile duct paucity) and end-stage liver disease (Devenyi et al., 1994). The patient had a stable peripheral neuropathy and for 2 months manifested with episodic, dystonic posturing and cramping of her hands and arms. Whole blood manganese was elevated (27 ug/L; normal range: 4-14 ug/L) and cranial T1-weighted magnetic resonance imaging (MRI) revealed symmetric hyperintense globus pallidi and subthalamic nuclei. These were taken as indications of manganese neurotoxicity. Following liver transplantation, the patient's manganese levels returned to normal, neurological symptoms improved and MRI appeared normal. It appeared, then, that the progression of liver dysfunction had resulted in inadequate excretion of manganese into the bile, ultimately leading to neurotoxicity. With restoration of liver function, this was remedied. This case study suggests that for individuals with impaired liver function, intakes of manganese that would otherwise be safe may present a problem.

Animal studies:


Only one limited oral study has been performed in a group of four Rhesus monkeys (Gupta et al., 1980). Muscular weakness and rigidity of the lower limbs developed
after 18 months of exposure to 6.9 mg Mn/kg-day (as MnCl2.4H2O). Histologic analysis showed degenerated neurons in the substantia nigra and scanty neuromelanin granules in some other pigmented cells. While it is clear that neurotoxicity resulting from excessive exposure to manganese is of primary concern, the exact mechanism is not clear. Histopathologically, the globus pallidus and substantia nigra appear to be most affected. Biochemically, deficiencies of striatal dopamine and norepinephrine appear to be fundamental. As reviewed by Aschner and Aschner (1991), multiple pathways that contribute to manganese-induced neurotoxicity are likely.