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Manganese CASRN 7439-96-5

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0373
Manganese; CASRN 7439-96-5

Health assessment information on a chemical substance is included in IRIS only after a comprehensive review of chronic toxicity data by U.S. EPA health scientists from several Program Offices and the Office of Research and Development. The summaries presented in Sections I and II represent a consensus reached in the review process. Background information and explanations of the methods used to derive the values given in IRIS are provided in the Background Documents.

STATUS OF DATA FOR Manganese

File On-Line 09/26/1988

Category (section)	Status	Last Revised
Oral RfD Assessment (I.A.)	on-line	05/01/1996
Inhalation RfC Assessment (I.B.)	on-line	12/01/1993
Carcinogenicity Assessment (II.)	on-line	12/01/1996

I. CHRONIC HEALTH HAZARD ASSESSMENTS FOR NONCARCINOGENIC EFFECTS**I.A. REFERENCE DOSE FOR CHRONIC ORAL EXPOSURE (RfD)**

Substance Name -- Manganese
 CASRN -- 7439-96-5
 Last Revised -- 05/01/1996

The oral Reference Dose (RfD) is based on the assumption that thresholds exist for certain toxic effects such as cellular necrosis. It is expressed in units of mg/kg-day. In general, the RfD is an estimate (with uncertainty spanning perhaps an order of magnitude) of a daily exposure to the human population (including sensitive subgroups) that is likely to be without an appreciable risk of deleterious effects during a lifetime. Please refer to the Background Document for an elaboration of these concepts. RfDs can also be derived for the noncarcinogenic health effects of substances that are also carcinogens. Therefore, it is essential to refer to other sources of information concerning the carcinogenicity of this substance. If the U.S. EPA has evaluated this substance for potential human carcinogenicity, a summary of that evaluation will be contained in Section II of this file.

NOTE: This reference dose is for the total oral intake of manganese. As discussed in the Principal and Supporting Studies and Uncertainty and Modifying Factors Sections, it is recommended that a modifying factor of 3 be applied if this RfD is used for assessments involving nondietary exposures.

I.A.1. ORAL RfD SUMMARY

Critical Effect	Experimental Doses*	UF	MF	RfD
CNS effects	NOAEL (food): 0.14 mg/kg-day	1	1	1.4E-1 mg/kg-day
Human Chronic Ingestion Data	LOAEL: None			

NRC, 1989; Freeland-Graves et al., 1987;
 WHO, 1973;

*Conversion Factors and Assumptions -- The NOAEL of 10 mg/day (0.14 mg/kg-day for 70 kg adult) for chronic human consumption of manganese in the diet is based on a composite of data from several studies.

I.A.2. PRINCIPAL AND SUPPORTING STUDIES (ORAL RfD)

Freeland-Graves, J.H., C.W. Bales and F. Behmardi. 1987. Manganese requirements of humans. In: Nutritional Bioavailability of Manganese, C. Kies, ed. American Chemical Society, Washington, DC. p. 90-104.

NRC (National Research Council). 1989. Recommended Dietary Allowances, 10th ed. Food and Nutrition Board, National Research Council, National Academy

Press, Washington, DC. p. 230-235.

WHO (World Health Organization). 1973. Trace Elements in Human Nutrition: Manganese. Report of a WHO Expert Committee. Technical Report Service, 532, WHO, Geneva, Switzerland. p. 34-36.

Manganese is a ubiquitous element that is essential for normal physiologic functioning in all animal species. Several disease states in humans have been associated with both deficiencies and excess intakes of manganese. Thus any quantitative risk assessment for manganese must take into account aspects of both the essentiality and the toxicity of manganese. In humans, many data are available providing information about the range of essentiality for manganese. In addition, there are many reports of toxicity to humans exposed to manganese by inhalation; much less is known, however, about oral intakes resulting in toxicity. As discussed in the Additional Studies / Comments Section, rodents do not provide a good experimental model for manganese toxicity, and only one limited study in primates by the oral route of exposure is available. The following assessment, therefore, focuses more on what is known to be a safe oral intake of manganese for the general human population. Finally, it is important to emphasize that individual requirements for, as well as adverse reactions to, manganese may be highly variable. The reference dose is estimated to be an intake for the general population that is not associated with adverse health effects; this is not meant to imply that intakes above the reference dose are necessarily associated with toxicity. Some individuals may, in fact, consume a diet that contributes more than 10 mg Mn/day without any cause for concern.

The Food and Nutrition Board of the National Research Council (NRC, 1989) determined an "estimated safe and adequate daily dietary intake" (ESADDI) of manganese to be 2-5 mg/day for adults. The lower end of this range was based on a study by McLeod and Robinson (1972), who reported equilibrium or positive balances at intakes of 2.5 mg Mn/day or higher. The range of the ESADDI also includes an "extra margin of safety" from the level of 10 mg/day, which the NRC considered to be safe for an occasional intake.

While the NRC determined an ESADDI for manganese of 2-5 mg/day, some nutritionists feel that this level may be too low. Freeland-Graves et al. (1987) have suggested a range of 3.5-7 mg/day for adults based on a review of human studies. It is noted that dietary habits have evolved in recent years to include a larger proportion of meats and refined foods in conjunction with a lower intake of whole grains. The net result of such dietary changes includes a lower intake of manganese such that many individuals may have suboptimal manganese status. This is discussed in more detail in the Additional Studies / Comments Section.

The World Health Organization (WHO, 1973) reviewed several investigations of adult diets and reported the average daily consumption of manganese to range from 2.0-8.8 mg Mn/day. Higher manganese intakes are associated with diets high in whole-grain cereals, nuts, green leafy vegetables, and tea. From manganese balance studies, the WHO concluded that 2-3 mg/day is adequate for adults and 8-9 mg/day is "perfectly safe."

Evaluations of standard diets from the United States, England, and Holland reveal average daily intakes of 2.3-8.8 mg Mn/day. Depending on individual diets, however, a normal intake may be well over 10 mg Mn/day, especially from a vegetarian diet. While the actual intake is higher, the bioavailability of manganese from a vegetarian diet is lower, thereby decreasing the actual absorbed dose. This is discussed in more detail in the Additional Studies / Comments Section.

From this information taken together, EPA concludes that an appropriate reference dose for manganese is 10 mg/day (0.14 mg/kg-day). In applying the reference dose for manganese to a risk assessment, it is important that the assessor consider the ubiquitous nature of manganese, specifically that most individuals will be consuming about 2-5 mg Mn/day in their diet. This is particularly important when one is using the reference dose to determine acceptable concentrations of manganese in water and soils.

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 ug/L in area A, 81.6-252.6 ug/L in area B, and 1600-2300 ug/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 ug/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 (\bar{x}) and range (r) of neurologic scores were as follows: Area A (males: $\bar{x}=2.4$, $r=0-21$; females: $\bar{x}=3.0$, $r=0-18$; both $\bar{x}=2.7$, $r=0-21$); Area B (males $\bar{x}=1.6$, $r=0-6$; females: $\bar{x}=5.7$, $r=0-43$; both: $\bar{x}=3.9$, $r=0-43$); and Area C (males: $\bar{x}=4.9$, $r=0-29$; females: $\bar{x}=5.5$, $r=0-21$; both $\bar{x}=5.2$, $r=0-29$). 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).

The individuals examined in the Kondakis study also had exposure to manganese in their diet. This was originally estimated to be 10-15 mg/day because of the high intake of vegetables (Kondakis, 1990). This estimate was subsequently lowered to 5-6 mg/day (Kondakis, 1993). Because of the uncertainty in the amount of manganese in the diet and the amount of water consumed, it is impossible to estimate the total oral intake of manganese in this study. These limitations preclude the use of this study to determine a quantitative dose-response relationship for the toxicity of manganese in humans.

This study, nevertheless, raises significant concerns about possible adverse neurological effects at doses not far from the range of essentially. Because of this concern, it is recommended that a modifying factor of 3 be applied when assessing risk from manganese in drinking water or soil. This is discussed more fully in the Uncertainty and Modifying Factors Section.

I.A.3. UNCERTAINTY AND MODIFYING FACTORS (ORAL RfD)

UF -- The information used to determine the RfD for manganese was taken from many large populations consuming normal diets over an extended period of time with no adverse health effects. As long as physiologic systems are not overwhelmed, humans exert an efficient homeostatic control over manganese such that body burdens are kept constant with variation in the manganese content of the diet. The information providing a chronic NOAEL in many cross-sections of human populations, taken in conjunction with the essentiality of manganese, warrants an uncertainty factor of 1.

MF -- When assessing exposure to manganese from food, the modifying factor is 1; however, when assessing exposure to manganese from drinking water or soil, a modifying factor of 3 is recommended. As discussed more fully in the Additional Studies/Comments Section, there are four reasons for this

recommendation. First, while the data suggest that there is no significant difference between absorption of manganese as a function of the form in which it is ingested (i.e., food versus water), there is some degree of increased uptake of manganese from water in fasted individuals. Second, the study by Kondakis et al. (1989) raises some concern for possible adverse health effects associated with a lifetime consumption of drinking water containing about 2 mg/L of manganese. Third, although toxicity has not been demonstrated, there is concern for infants fed formula that typically has a much higher concentration of manganese than does human milk. If powdered formula is made with drinking water, the manganese in the water would represent an additional source of intake. Finally, there is some evidence that neonates absorb more manganese from the gastrointestinal tract, that neonates are less able to excrete absorbed manganese, and that in the neonate the absorbed manganese more easily passes the blood-brain barrier. These findings may be related to the fact that manganese in formula is in a different ionic form and a different physical state than in human milk. These considerations concerning increased exposure in an important population group, in addition to the likelihood that any adverse neurological effects of manganese are likely to be irreversible and not manifested for many years after exposure, warrant caution until more definitive data are available.

IA.4. ADDITIONAL STUDIES / COMMENTS (ORAL RfD)

The biochemical role of manganese is to serve as an activator of several enzymes including hydrolases, kinases, decarboxylases and transferases. It is also required for the activity of three metalloenzymes: arginase, pyruvate carboxylase and mitochondrial superoxide dismutase. A review of the biochemical and nutritional roles of manganese in human health, as well as a list of disease states related to manganese deficiency or excess, is provided by Wedler (1994).

Because of the ubiquitous nature of manganese in foodstuffs, actual manganese deficiency has not been observed in the general population. There are, however, only two reports in the literature of experimentally induced manganese deficiency in humans. The first was a report by Doisy (1972), who inadvertently omitted manganese from a formulated diet. One of two subjects developed a slight reddening of the hair, a scaly transient dermatitis, marked hypocholesterolemia, and moderate weight loss. The diet was subsequently determined to contribute 0.34 mg Mn/day, a level that resulted in manganese deficiency. The second report was a metabolic balance study conducted by Friedman et al. (1987) in which seven male volunteers were fed a semipurified diet containing 0.11 mg Mn/day for 39 days. Transient dermatitis developed in five of the seven subjects by the 35th day, which the authors speculate was a result of decreased activity of glycosyltransferases or prolidase, manganese-requiring enzymes that are necessary for dermal maintenance. Hypocholesterolemia was also observed in this study, which the authors suggest was a result of the need for manganese at several steps in the cholesterol biosynthesis pathway.

While an outright manganese deficiency has not been observed in the general human population, suboptimal manganese status may be more of a concern. As reviewed by Freeland-Graves and Llanes (1994), several disease states have been associated with low levels of serum manganese. These include epilepsy, exocrine pancreatic insufficiency, multiple sclerosis, cataracts, and osteoporosis. In addition, several inborn errors of metabolism have been associated with poor manganese status (e.g., phenylketonuria, maple syrup urine disease). While a correlation has been shown for low levels of serum manganese and these disease states, a causal relationship has not been demonstrated, and this remains an area in which additional research is needed.

To better understand the consequences of manganese deficiency, several animal models have been studied. These have also been reviewed by Freeland-Graves and Llanes (1994). Experiments in several species have shown a deficiency in dietary manganese to result in disorders in lipid and

carbohydrate metabolism, impaired growth and reproductive function, and ataxia and skeletal abnormalities in neonates.

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).

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.

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

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a problem.

Although conclusive evidence is lacking, some investigators have also linked increased intakes of manganese with violent behavior. Gottschalk et al. (1991) found statistically significant elevated levels of manganese in the hair of convicted felons (1.62 +/- 0.173 ppm in prisoners compared with 0.35 +/- 0.020 ppm in controls). The authors suggest that "a combination of cofactors, such as the abuse of alcohol or other chemical substances, as well as psychosocial factors, acting in concert with mild manganese toxicity may promote violent behavior." Caution should be exercised to prevent reading too much into these data, but support for this hypothesis is provided by studies of a population of Aborigines in Groote Eylandt. Several clinical symptoms consistent with manganese intoxication are present in about 1% of the inhabitants of this Australian island, and it may not be coincidental that the proportion of arrests in this native population is the highest in Australia (Cawte and Florence, 1989; Kilburn, 1987). The soil in this region is very high in manganese (40,000-50,000 ppm), and the fruits and vegetables grown in the region also are reported to be high in manganese. Quantitative data on oral intakes have not been reported, but elevated concentrations of manganese have been determined in the blood and hair of the Aborigines (Stauber et al., 1987). In addition to the high levels of environmental manganese, other factors common to this population may further increase the propensity for manganism: high alcohol intake, anemia, and a diet deficient in zinc and several vitamins (Florence and Stauber, 1989).

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.

Several oral studies have been performed in rodents, also demonstrating biochemical changes in the brain following administration of 1 mg MnCl₂·4H₂O/mL in drinking water (approximately 38.9 mg Mn/kg-day) (Chandra and Shukla, 1981; Lai et al., 1981, 1982; Leung et al., 1981). However, rodents do not exhibit the same neurologic deficits that humans do following exposure to manganese; thus the relevance of these biochemical changes has been challenged. The problem with using rodents is exemplified by the disease of parkinsonism, which is characterized by effects very similar to those seen in manganese poisoning. Marsden and Jenner (1987) hypothesize that the ability of certain drugs to induce parkinsonism in primates but not in rodents is due to the relative lack of neuromelanin in rodents. Because manganese selectively accumulates in pigmented regions of the brain (e.g., the substantia nigra), this species difference is fundamentally important.

EPA initiated an investigation of the literature to determine the relative bioavailability of manganese in food and water (Ruoff, 1995). The conclusions from this research were that under a wide variety of exposure scenarios in humans, the bioavailability of manganese ingested in water was essentially equal to the bioavailability of manganese in food. Total diet, rather than the actual medium of exposure, appears to be more of a determining factor for the uptake of manganese from the GI tract. Specifically, the relative bioavailability of manganese from food compared with that from drinking water was determined to be 0.7, and not statistically significantly different. When the data were reanalyzed to include only the ingestion of manganese in drinking water by fasted individuals, the relative bioavailability was 0.5, indicating roughly a 2-fold greater uptake of manganese from drinking water compared with uptake from food.

Another issue of great importance to consider in the risk assessment for manganese concerns the bioavailability of different forms of manganese consumed under different exposure conditions. Various dietary factors as well

as the form of manganese can have a significant bearing on the dose absorbed from the GI tract. Many constituents of a vegetarian diet (e.g., tannins, oxalates, phytates, fiber) have been found to inhibit manganese absorption presumably by forming insoluble complexes in the gut. In addition, high dietary levels of calcium or phosphorus have been reported to decrease manganese absorption. Individuals who are deficient in iron demonstrate an increase in manganese absorption. It is also recognized that manganese uptake and elimination are under homeostatic control, generally allowing for a wide range of dietary intakes considered to be safe. These factors and others are described in a review by Kies (1987). In addition to the influence of extrinsic variables, significant interindividual differences in manganese absorption and retention have been reported. In humans administered a dose of radiolabeled manganese in an infant formula, the mean absorption was 5.9 +/- 4.8%, but the range was 0.8-16%, a 20-fold difference (Davidsson et al., 1989). Retention at day 10 was 2.9 +/- 1.8%, but the range was 0.6-9.2%, again indicating substantial differences between individuals.

In a 100-day dietary study in 6-week-old male mice, Komura and Sakamoto (1991) demonstrated significant differences in tissue levels of manganese in mice fed equivalent amounts of manganese as $MnCl_2 \cdot 4H_2O$, $Mn(Ac)_2 \cdot 4H_2O$, $MnCO_3$ and MnO_2 . Mice receiving the two soluble forms of manganese (the chloride and acetate salts) were found to gain significantly less weight than controls, while mice consuming the insoluble forms of manganese (the carbonate and dioxide salts) appeared to actually gain slightly more weight than controls. The acetate and carbonate groups, however, had significantly higher manganese levels in the liver and kidney compared with the chloride and dioxide groups, both of which were elevated above control levels. Reduced locomotor activity in the carbonate and acetate groups was also reported, perhaps related to the higher tissue levels of manganese. This study points out a need for understanding the effects of the various chemical species of manganese, of which relatively little is known. More information on manganese speciation can be found in the RfC file on IRIS.

It is also recognized that neonates may be at increased risk of toxicity resulting from exposure to manganese because of a higher level of uptake from the GI tract and a decreased ability to excrete absorbed manganese. The uptake and retention of manganese have been reviewed by Lonnerdal et al. (1987). In rats, manganese absorption decreased dramatically as the animals matured. While 24-hour retention values are as high as 80% in 14-day-old pups, this value drops to about 30% by day 18. Low levels of manganese absorption (about 3-4%) have also been reported for mature humans, but few data are available for infants.

No reports of actual manganese toxicity or deficiency have been reported for infants. As with adults, however, the potential for effects resulting from excess manganese or suboptimal manganese appears to exist (reviewed by Lonnerdal, 1994). In particular, suboptimal manganese may be a problem for preterm infants given calcium supplementation, which is known to inhibit the absorption of manganese. Because manganese is required for adequate bone mineralization, it is suggested that insufficient absorption of manganese in preterm infants may contribute to poor bone growth. On the other hand, excess manganese may be a problem for infants with low iron status, as this is known to increase the absorption of manganese.

An additional concern for infants has been expressed because of the often high levels of manganese in infant formulas, particularly compared with breast milk. Also, manganese in human milk is in the trivalent form bound to lactoferrin, the major iron-binding protein. Lactoferrin receptors are located in the brush border membranes of epithelial cells throughout the length of the small intestine, thus allowing for regulation of the uptake of manganese. In infant formulas, however, because manganese is in the divalent state, absorption through the GI tract cannot be regulated by lactoferrin receptors. Collipp et al. (1983) found that hair manganese levels in newborn infants increased significantly from birth (0.19 ug/g) to 6 weeks of age (0.865 ug/g) and 4 months of age (0.685 ug/g) when the infants were given formula, but that the increase was not significant in babies who were breast-fed (0.330 ug/g at 4 months). While human breast milk is relatively low in manganese (7-15 ug/L), levels in infant formulas are much higher (50-300

ug/L). It was further reported in this study that the level of manganese in the hair of learning-disabled children (0.434 ug/g) was significantly increased in comparison with that of normal children (0.268 ug/g). Other investigators also have reported an association between elevated levels of manganese in hair and learning disabilities in children (Barlow and Kapel, 1979; Pihl and Parkes, 1977). Although no causal relationship has been determined for learning disabilities and manganese intake, further research in this area is warranted. High levels of manganese in infant formulas may be of concern because of the increased absorption and retention of manganese that has been reported in neonatal animals (Lonnerdal et al., 1987). Also, manganese has been shown to cross the blood-brain barrier, with the rate of penetration in animal experiments being 4 times higher in neonates than in adults (Mena, 1974).

I.A.5. CONFIDENCE IN THE ORAL RfD

Study -- Medium
Data Base -- Medium
RfD -- Medium

Many studies have reported similar findings with regard to the normal dietary intake of manganese by humans. These data are considered to be superior to any data obtained from animal toxicity studies, especially as the physiologic requirements for manganese vary quite a bit among different species, with man requiring less than rodents. There is no single study used to derive the dietary RfD for manganese. While several studies have determined average levels of manganese in various diets, no quantitative information is available to indicate toxic levels of manganese in the diet of humans. Because of the homeostatic control humans maintain over manganese, it is generally not considered to be very toxic when ingested with the diet. It is important to recognize that while the RfD process involves the determination of a point estimate of an oral intake, it is also stated that this estimate is associated "with uncertainty spanning perhaps an order of magnitude." Numerous factors, both environmental factors (e.g., the presence or absence of many dietary constituents) and biological or host factors (e.g., age, alcohol consumption, anemia, liver function, general nutritional status) can significantly influence an individual's manganese status. As discussed in the Additional Studies / Comments Section, there is significant variability in the absorption and elimination of manganese by humans. Confidence in the data base is medium and confidence in the dietary RfD for manganese is also medium.

I.A.6. EPA DOCUMENTATION AND REVIEW OF THE ORAL RfD

Source Document -- This assessment is not presented in any existing EPA documentation.

This summary has been peer reviewed by three external scientists and has also received internal EPA review. The review was completed on 07/06/1995. The comments of the reviewers have been carefully evaluated and considered in the revision and finalization of this IRIS summary. A record of these comments is included in the IRIS documentation files.

Other EPA Documentation -- U.S. EPA, 1984

Agency Work Group Review -- 05/17/1990, 06/21/1990, 06/24/1992, 09/22/1992, 03/31/12/14/1993, 05/12/1995

Verification Date -- 05/12/1995

I.A.7. EPA CONTACTS (ORAL RfD)

Please contact the Risk Information Hotline for all questions concerning this assessment or IRIS, in general, at (513)569-7254 (phone), (513)569-7159 (FAX) or RIH.IRIS@EPAMAIL.EPA.GOV (internet address).

I.B. REFERENCE CONCENTRATION FOR CHRONIC INHALATION EXPOSURE (RfC)

Substance Name -- Manganese
CASRN -- 7439-96-5
Last Revised -- 12/01/1993

The inhalation Reference Concentration (RfC) is analogous to the oral RfD and is likewise based on the assumption that thresholds exist for certain toxic effects such as cellular necrosis. The inhalation RfC considers toxic effects for both the respiratory system (portal-of-entry) and for effects peripheral to the respiratory system (extrarespiratory effects). It is expressed in units of mg/cu.m. In general, the RfC is an estimate (with uncertainty spanning perhaps an order of magnitude) of a daily inhalation exposure of the human population (including sensitive subgroups) that is likely to be without an appreciable risk of deleterious effects during a lifetime. Inhalation RfCs were derived according to the Interim Methods for Development of Inhalation Reference Doses (EPA/600/8-88/066F August 1989) and subsequently, according to Methods for Derivation of Inhalation Reference Concentrations and Application of Inhalation Dosimetry (EPA/600/8-90/066F October 1994). RfCs can also be derived for the noncarcinogenic health effects of substances that are carcinogens. Therefore, it is essential to refer to other sources of information concerning the carcinogenicity of this substance. If the U.S. EPA has evaluated this substance for potential human carcinogenicity, a summary of that evaluation will be contained in Section II of this file.

I.B.1. INHALATION RfC SUMMARY

Critical Effect	Exposures*	UF	MF	RfC
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Impairment of neuro-behavioral function	NOAEL: None	1000	1	5E-5 mg/cu.m
	LOAEL: 0.15 mg/cu.m			
Occupational exposure to manganese dioxide	LOAEL(ADJ): 0.05 mg/cu.m			
	LOAEL(HEC): 0.05 mg/cu.m			
Roels et al., 1992				
Impairment of neuro-behavioral function	NOAEL: None			
	LOAEL: 0.97 mg/cu.m			
Occupational exposure to manganese oxides and salts	LOAEL(ADJ): 0.34 mg/cu.m			
	LOAEL(HEC): 0.34 mg/cu.m			
Roels et al., 1987				

*Conversion Factors and Assumptions: Roels et al., 1992: The LOAEL is derived from an occupational-lifetime integrated respirable dust (IRD) concentration of manganese dioxide (MnO₂) (based on 8-hour TWA occupational exposure multiplied by individual work histories in years) expressed as mg manganese (Mn)/cu.m x years. The IRD concentrations ranged from 0.040 to 4.433 mg Mn/cu.m x years, with a geometric mean of 0.793 mg Mn/cu.m x years and a geometric standard deviation of 2.907. The geometric mean concentration (0.793 mg/cu.m x years) was divided by the average duration of MnO₂ exposure (5.3 years) to obtain a LOAEL TWA of 0.15 mg/cu.m. The LOAEL refers to an extrarrespiratory effect of particulate exposure and is based on an 8-hour TWA occupational exposure. MVho = 10 cu.m/day, MVh = 20 cu.m/day. LOAEL(HEC) = 0.15 mg/cu.m x (MVho/MVh) x 5 days/7 days = 0.05 mg/cu.m.

Roels et al., 1987: The LOAEL is based on an 8-hour TWA occupational exposure. The TWA of total airborne manganese dust ranged from 0.07 to 8.61 mg/cu.m, and the median was 0.97 mg/cu.m. This is an extrarrespiratory effect of a particulate exposure. MVho = 10 cu.m/day, MVh = 20 cu.m/day. LOAEL(HEC) = 0.97 mg/cu.m x (MVho/MVh) x 5 days/7 days = 0.34 mg/cu.m.

I.B.2. PRINCIPAL AND SUPPORTING STUDIES (INHALATION RfC)

Roels, H., R. Lauwerys, J.-P. Buchet et al. 1987. Epidemiological survey among workers exposed to manganese: Effects on lung, central nervous system, and some biological indices. *Am. J. Ind. Med.* 11: 307-327.

Roels, H.A., P. Ghyselen, J.P. Buchet, E. Ceulemans, and R.R. Lauwerys. 1992. Assessment of the permissible exposure level to manganese in workers exposed to manganese dioxide dust. *Br. J. Ind. Med.* 49: 25-34.

Roels et al. (1992) conducted a cross-sectional study of 92 male workers exposed to manganese dioxide (MnO₂) dust in a Belgian alkaline battery plant. A control group of 101 male workers was matched for age, height, weight, work schedule, coffee and alcohol consumption, and smoking; educational level was slightly higher in the control group (p = 0.046 by chi square test).

The manganese (Mn)-exposed group had been exposed to MnO₂ for an average of 5.3 years (range: 0.2-17.7 years). The geometric means of the workers' TWA airborne Mn concentrations, as determined by personal sampler monitoring at the breathing zone, were 0.215 mg Mn/cu.m for respirable dust and 0.948 mg Mn/cu.m for total dust. No data on particle size or purity were presented, but the median cut point for the respirable dust fraction was 5 μ m according to information provided by Roels et al. (1992) and Roels (1993). Total and respirable dust concentrations were highly correlated (r = 0.90, p < 0.001), with the Mn content of the respirable fraction representing on average 25% of the Mn content in the total dust. The authors noted that the personal monitoring data were representative of the usual exposure of the workers because work practices had not changed during the last 15 years of the operation of the plant.

Occupational-lifetime integrated exposure to Mn was estimated for each worker by multiplying the current airborne Mn concentration for the worker's job classification by the number of years for which that classification was held and adding the resulting (arithmetic) products for each job position a worker had held. The geometric mean occupational-lifetime integrated respirable dust (IRD) concentration was 0.793 mg Mn/cu.m x years (range: 0.040-4.433 mg Mn/cu.m x years), with a geometric standard deviation of 2.907 mg Mn/cu.m x years, based on information provided by Roels (1993). The geometric mean occupational-lifetime integrated total dust (ITD) concentration was 3.505 mg Mn/cu.m x years (range: 0.191-27.465 mg Mn/cu.m x years). Geometric mean concentrations of blood Mn (MnB) (0.81 μ g/dL) and urinary Mn (MnU) (0.84 μ g/g creatinine) were significantly higher in the Mn-exposed group than in the control group, but on an individual basis no significant correlation was found between either MnB or MnU and various external exposure parameters. Current respirable and total Mn dust concentrations correlated

significantly with geometric mean MnU on a group basis (Spearman $r = 0.83$, $p < 0.05$).

A self-administered questionnaire focused on occupational and medical history, neurological complaints, and respiratory symptoms. Lung function was evaluated by standard spirographic measures. Neurobehavioral function was evaluated by tests of audio-verbal short-term memory, visual simple reaction time, hand steadiness, and eye-hand coordination. Blood samples were assayed for several hematological parameters (erythrocyte count, leukocyte count, hemoglobin, hematocrit, mean corpuscular volume, mean corpuscular hemoglobin, platelets, and differential leukocyte count); Mn; lead; zinc protoporphyrin; and serum levels of calcium, iron, follicle stimulating hormone (FSH), luteinizing hormone (LH), and prolactin. Urinary Mn, cadmium, and mercury concentrations were also determined.

Responses to the questionnaire indicated no significant differences between groups in either respiratory or neurological symptoms, nor were spirometric, hormonal, or calcium metabolism measurements significantly different for the two groups. In addition, a separate report (Gennart et al., 1992) indicated no significant difference in the fertility of 70 of these workers, in contrast to earlier findings in 85 workers exposed not only to MnO₂ but also to other Mn oxides and salts at higher concentrations (Lauwerys et al., 1985). Erythropoietic parameters and serum iron concentrations were consistently and significantly lower in the Mn-exposed workers, albeit within the normal range of values.

Of particular note, Mn workers performed worse than controls on several measures of neurobehavioral function. Visual reaction time was consistently and significantly slower in the Mn-exposed workers measured in four 2-minute periods, with more pronounced slowing over the total 8-minute period and significantly greater variability in reaction times for the Mn-exposed group. Abnormal values for mean reaction times (defined as greater than or equal to the 95th percentile of the control group) also were significantly more prevalent in the Mn-exposed group during three of four 2-minute intervals of the 8-minute testing period.

Five measures of eye-hand coordination (precision, percent precision, imprecision, percent imprecision, and uncertainty) reflected more erratic control of fine hand-forearm movement in the Mn-exposed group than in the controls, with mean scores on all five measures being highly significantly different for the two groups. There was also a significantly greater prevalence of abnormal values for these five measures in the Mn-exposed group. The hole tremormeter test of hand steadiness indicated a consistently greater amount of tremor in the Mn-exposed workers, with performance for two of the five hole sizes showing statistically significant impairment.

Roels et al. (1992) performed an exposure-response analysis by classifying IRD values into three groups (<0.6, 0.6-1.2, and >1.2 mg Mn/cu.m x years) and comparing the prevalence of abnormal scores for visual reaction time, hand steadiness, and eye-hand coordination with controls. This analysis indicated that the prevalence of abnormal eye-hand coordination values was significantly greater in workers whose IRD levels were less than 0.6 mg Mn/cu.m x years. However, the relationship between exposure and response was not linear across groups. Visual reaction time and hand steadiness showed linear exposure-related trends but did not achieve statistical significance except at levels of >1.2 mg Mn/cu.m x years. As noted by the authors, "analysis of the data on a group basis ... does not permit us to identify a threshold effect level for airborne Mn." Although suggestive of a LOAEL of <0.6 mg Mn/cu.m x years, the exposure-response analysis by Roels et al. (1992) possibly could reflect the small disparity in educational level between exposed and control workers that was noted above with regard to the matching criteria for this study. If educational level were in fact a covariate of exposure as well as neurobehavioral performance, it could confound the exposure-response analysis. Although it is not clear that such was the case, the possibility of confounding suggests that the LOAEL should not be based on the results of the exposure-response analysis until these results can be confirmed by other studies. Also, statistical correction for multiple comparisons should be included in the exposure response analysis.

A LOAEL may be derived from the Roels et al. (1992) study by using the IRD concentration of MnO₂, expressed as mg Mn/cu.m x years (based on 8-hour TWA occupational exposures for various job classifications, multiplied by individual work histories in years). Dividing the geometric mean IRD concentration (0.793 mg/cu.m x years) by the average duration of the workers' exposure to MnO₂ (5.3 years) yields a LOAEL of 0.15 mg/cu.m. The LOAEL(HEC) is 0.05 mg/cu.m.

Roels et al. (1987) conducted a cross-sectional study in 141 male workers exposed to MnO₂, manganese tetroxide (Mn₃O₄), and various Mn salts (sulfate, carbonate, and nitrate). A matched group of 104 male workers was selected as a control group. The two groups were matched for socioeconomic status and background environmental factors; in addition, both groups had comparable work-load and work-shift characteristics.

The TWA of total airborne Mn dust ranged from 0.07 to 8.61 mg/cu.m, with an overall arithmetic mean of 1.33 mg/cu.m, a median of 0.97 mg/cu.m, and a geometric mean of 0.94 mg/cu.m. The duration of employment ranged from 1 to 19 years, with a mean of 7.1 years. The particle size and purity of the dust were not reported. Neurological examination, neurobehavioral function tests (simple reaction time, short-term memory, eye-hand coordination, and hand tremor), spirographic measurements, blood and urine tests, and a self-administered questionnaire were used to assess possible toxic effects of Mn exposure. The questionnaire was designed to detect CNS and respiratory symptoms.

Significant differences in mean scores between Mn-exposed and reference subjects were found for objective measures of visual reaction time, eye-hand coordination, hand steadiness, and audio-verbal short-term memory. The prevalence of abnormal scores on eye-hand coordination and hand steadiness tests showed a dose-response relationship with blood Mn levels; short-term memory scores were related to years of Mn exposure but not to blood Mn levels. The prevalence of subjective symptoms was greater in the exposed group than in controls for 20 of 25 items on the questionnaire, with four items being statistically significant: fatigue, tinnitus, trembling of fingers, and irritability.

A significantly greater prevalence of coughs during the cold season, dyspnea during exercise, and recent episodes of acute bronchitis was self-reported in the exposed group. Lung function parameters were only slightly (<10%) lower in the Mn-exposed workers, with the only significant alterations evident in Mn-exposed smokers. These mild changes in Mn-exposed workers (apart from the effects of smoking) and the absence of respiratory effects in the more recent study by Roels et al. (1992) suggest that the nervous system is a more sensitive target for Mn toxicity.

Based upon the findings of impaired neurobehavioral function in workers whose average Mn exposure was estimated by the geometric mean TWA of total airborne Mn dust at the time of the study, a LOAEL of 0.97 mg/cu.m was identified, with a LOAEL(HEC) of 0.34 mg/cu.m. Note that this LOAEL(HEC) is based on total Mn dust of mixed forms, whereas the LOAEL(HEC) from the more recent Roels et al. (1992) study is based on the measured respirable dust fraction of MnO₂ only. However, the geometric mean total dust concentrations in the 1987 and 1992 studies by Roels et al. were approximately the same (0.94 and 0.95 mg/cu.m, respectively).

The findings of Roels et al. (1987, 1992) are supported by other recent reports that provide comparable and consistent indications of neurobehavioral dysfunction in Mn-exposed workers (Mergler et al., 1993; Iregren, 1990; Wennberg et al., 1991, 1992).

Mergler et al. (1993) conducted a cross-sectional study of 115 male ferromanganese and silicomanganese alloy workers in southwest Quebec. A matched-pair design was employed because of presumptively high environmental pollutant levels; 74 pairs of workers and referents were matched on age, educational level, smoking status, number of children, and length of residency in the region.

Air concentrations of respirable and total dust were sampled by stationary monitors during silicomanganese production. The geometric mean of a series of 8-hour TWAs was 0.035 mg Mn/cu.m (range: 0.001-1.273 mg Mn/cu.m) for respirable dust and 0.225 mg Mn/cu.m (range: 0.014-11.480 mg Mn/cu.m) for total dust. The authors noted that past dust levels at certain job sites had been considerably higher. The mean duration of the workers' Mn exposure was 16.7 years and included Mn fumes as well as mixed oxides and salts of Mn. Geometric mean MnB was significantly higher in the Mn alloy workers, but MnU did not differ significantly between exposed workers and controls.

The number of discordant pairs, in which workers reported undesirable symptoms on a self-administered questionnaire but their matched pairs did not, was statistically significant for 33 of 46 items, including the following: fatigue; emotional state; memory, attention, and concentration difficulties; nightmares; sweating in the absence of physical exertion; sexual dysfunction; lower back pain; joint pain; and tinnitus. Workers did not report symptoms typical of advanced Mn poisoning (e.g., hand tremor, changes in handwriting, loss of balance when turning, difficulty in reaching a fixed point) significantly more than referents, which suggests that the other reported symptoms were probably not due to bias on the part of the workers.

The greatest differences in neurobehavioral function were evident in tests of motor function, especially tests requiring coordinated alternating and/or rapid movements. Workers performed significantly worse on the motor scale of a neuropsychological test battery both in overall score and in eight subscales of rapid sequential or alternating movements. Worker performance also was significantly worse on tests of hand steadiness, parallel-line drawing performance, and ability to rapidly identify and mark specified alphabetic characters within strings of letters. Performance on a variety of other tests of psychomotor function, including simple reaction time, was worse in Mn-exposed workers but marginally significant ($0.05 < p < 0.10$). In addition, Mn alloy workers differed significantly from referents on measures of cognitive flexibility and emotional state. Olfactory perception also was significantly enhanced in the Mn-alloy workers.

The matched-pair design of Mergler et al. (1993) helped reduce differences between exposed and referent subjects that might otherwise have confounded the study. However, to the extent that the referents also may have had significant exposure to Mn in the ambient atmosphere, such exposure may have reduced the differences in neurobehavioral performance between workers and referents. This possibility is supported by the fact that the finger-tapping speed of both workers and referents on a computerized test was slower than that of Mn-exposed workers assessed on the same test by Iregren (1990) in Sweden. In the absence of a NOEL, the LOEL from the study of Mergler et al. (1993) is based on the geometric mean respirable dust level (0.035 mg Mn/cu.m), with a LOEL(HEC) of approximately 0.01 mg/cu.m, which is about five-fold lower than the LOEL(HEC) identified in the study by Roels et al. (1992).

Workers exposed to Mn in two Swedish foundries (15 from each plant) were evaluated in a study first reported by Iregren (1990). The exposure to Mn varied from 0.02 to 1.40 mg/cu.m (mean = 0.25 mg/cu.m; median = 0.14 mg/cu.m) for 1-35 years (mean = 9.9 years). Earlier monitoring measurements made in both factories suggested that essentially no changes in exposure had occurred in either factory for the preceding 18 years. Each exposed worker was matched for age, geographical area, and type of work to two workers not exposed to Mn in other industries. Neurobehavioral function was assessed by eight computerized tests and two manual dexterity tests. There were significant differences between exposed and control groups for simple reaction time, the standard deviation of reaction time, and finger-tapping speed of the dominant hand. In addition, digit-span short-term memory, speed of mental addition, and verbal (vocabulary) understanding differed significantly between exposed and control groups. The difference in verbal understanding suggested that the two groups were not well matched for general cognitive abilities. With verbal performance used as an additional matching criterion, differences between the groups in simple reaction time, the standard deviation of reaction time, and finger-tapping speed remained statistically significant, despite a decrease in

statistical power due to reducing the size of the reference group to 30 workers. Further analyses using verbal test scores as a covariate also indicated that these same three measures of neurobehavioral function were statistically different in exposed and control workers. No significant correlation was found within the exposed group to establish a concentration-response relationship.

Additional reports of neurobehavioral and electrophysiological evaluations of these same workers have been published by Wennberg et al. (1991, 1992). Although none of the latter results achieved statistical significance at $p = 0.05$, increased frequency of self-reported health symptoms, increased prevalence of abnormal electroencephalograms, slower brain-stem auditory-evoked potential latencies, and slower diadochokinesometric performance were found in the exposed workers. Diadochokinesis refers to the ability to perform rapidly alternating movements such as supination and pronation of the forearm, and is an indicator of extrapyramidal function (see Additional Comments/Studies). Also, an increase in P-300 latency, as suggested by these results, has been observed in patients with parkinsonism according to Wennberg et al. (1991), who viewed these results in Mn-exposed workers as early (preclinical) signs of disturbances similar to parkinsonism. Based on the impairments in reaction time and finger-tapping speed reported in the Swedish studies (Iregren, 1990; Wennberg et al., 1991, 1992), the LOEL(HEC) is calculated to be 0.05 mg/cu.m. Although numerically the same value as that derived from Roels et al. (1992), the Swedish study measured total dust. However, Wennberg et al. (1991) stated that the respirable dust level was 20-80% of total dust, which implies that the LOEL(HEC) from the Swedish studies could be somewhat lower than that from Roels et al. (1992).

All of the above studies taken together provide a consistent pattern of evidence indicating that neurotoxicity is associated with low-level occupational Mn exposure. The fact that the speed and coordination of motor function are especially impaired is consistent with other epidemiological, clinical, and experimental animal evidence of Mn intoxication (see Additional Comments/Studies). Moreover, the LOEL(HEC)s obtained from these studies are not appreciably different. Nevertheless, some differences between the studies are evident in the durations of exposure and forms of Mn to which workers were exposed. In the Roels et al. (1992) study, the mean period of exposure was 5.3 years (range: 0.2-17.7 years), and exposure was limited to MnO₂. In the other studies, mixed forms of Mn were present, and the mean durations of exposure were longer: 7.1 years in Roels et al. (1987), 9.9 years in Iregren (1990), and 16.7 years in Mergler et al. (1993). The findings of Mergler et al. (1993) suggest that the LOEL(HEC) could be at least as low as approximately 0.01 mg/cu.m. However, the variable concentrations and mixed compounds of Mn to which workers were exposed make it difficult to rely primarily upon the findings of Mergler et al. (1993) in deriving the RfC. Nevertheless, their results provide support for the findings of Roels et al. (1992) and suggest that the longer period of exposure (16.7 years in Mergler et al. (1993) vs. 5.3 years in Roels et al., 1992) may have contributed to the apparent differences in sensitivity. Although analyses by Roels et al. (1987, 1992) and Iregren (1990) generally did not indicate that duration of exposure correlated significantly with neurobehavioral outcomes, none of these studies involved average exposures as long as those in the Mergler et al. (1993) study. Also, the oldest worker in the Roels et al. (1992) study was less than 50 years old, and the average age in that study was only 31.3 years vs. 34.3 years in Roels et al. (1987), 43.4 years in Mergler et al. (1993), and 46.4 in Iregren (1990). These points suggest that chronic exposure to Mn and/or interactions with aging could result in effects at lower concentrations than would be detected after shorter periods of exposure and/or in younger workers.

Based on the findings of neurobehavioral impairment by Roels et al. (1987, 1992), with supporting evidence from Mergler et al. (1993) and the Swedish reports (Iregren, 1990; Wennberg et al., 1991, 1992), the LOEL for derivation of the RfC is 0.15 mg/cu.m, and the LOEL(HEC) is 0.05 mg/cu.m.

LB.3. UNCERTAINTY AND MODIFYING FACTORS (INHALATION RfC)

UF -- An uncertainty factor of 1000 reflects 10 to protect sensitive individuals, 10 for use of a LOAEL, and 10 for database limitations reflecting both the less-than-chronic periods of exposure and the lack of developmental data, as well as potential but unquantified differences in the toxicity of different forms of Mn.

MF -- None

LB.4. ADDITIONAL STUDIES / COMMENTS (INHALATION RfC)

Manganese toxicity varies depending upon the route of exposure. When ingested, Mn is considered to be among the least toxic of the trace elements. In the normal adult, between 3 and 10% of dietary Mn is absorbed. Total body stores normally are controlled by a complex homeostatic mechanism regulating absorption and excretion. As detailed in the Uncertainty Factor Text and the Additional Comments/Studies for the oral RfD, toxicity from ingested Mn is rarely observed. However, deficiencies of calcium and iron have been noted to increase Mn absorption (Mena et al., 1969; Murphy et al., 1991). Also, Mena et al. (1969) found that anemic subjects absorbed 7.5% of ingested Mn, whereas normal subjects absorbed 3%. Interestingly, manganism patients absorbed 4%, and apparently healthy Mn miners absorbed only 3%. These differences suggest that certain subpopulations, such as children, pregnant women, elderly persons, iron- or calcium-deficient individuals, and individuals with liver impairment, may have an increased potential for excessive Mn body burdens due to increased absorption or altered clearance mechanisms, which may be of particular importance for those exposed to Mn by multiple routes.

As a route of Mn exposure, the respiratory tract is the most important portal of entry. The inhalation toxicity of Mn is in part a function of particle dosimetry and subsequent pharmacokinetic events. Particle size determines the site of deposition in the respiratory tract. Generally, in humans, fine mode particles (<2.5 μm) preferentially deposit in the pulmonary region, and coarse mode particles (>2.5 μm) deposit in the tracheobronchial and extrathoracic regions. Those particles depositing in the extrathoracic and tracheobronchial regions are predominantly cleared by the mucociliary escalator into the gastrointestinal tract where absorption is quite low (about 3%). Particles deposited in the pulmonary region are cleared predominantly to the systemic compartment by absorption into the blood and lymph circulation. Disregarding the possibility of counteracting mechanisms, 100% absorption of particles deposited in the pulmonary region is assumed. Another possible route of exposure may exist. Studies such as those of Perl and Good (1987) and Evans and Hastings (1992) have indicated that neurotoxic metals such as aluminum and cadmium can be directly transported to the brain olfactory bulbs via nasal olfactory pathways (i.e., from extrathoracic deposition). The alteration in olfactory perception that Mergler et al. (1993) found in Mn-exposed workers lends support to the speculation that this pathway may also operate for Mn, which would further complicate understanding of target-site dosimetry.

The human health effects data base on Mn does not include quantitative inhalation pharmacokinetics information on the major oxides of Mn. Two of the studies described in the Principal and Support Studies (Roels et al., 1992; Mergler et al., 1993) measured respirable as well as total Mn dust, and one study (Roels et al., 1992) dealt with workers exposed to only one form of Mn, namely MnO₂. However, this information does not allow quantitative determinations of the dose delivered to the respiratory tract or estimates of target-site doses. After absorption via the respiratory tract, Mn is transported through the blood stream directly to the brain, bypassing the liver and the opportunity for first-pass hepatic clearance. This direct path from the respiratory tract to the brain is the primary reason for the differential toxicity of inhaled and ingested Mn. Pharmacokinetic analyses based on inhalation of manganese chloride (MnCl₂) by macaque monkeys (Newland

et al., 1987) indicated that clearance from the brain was slower than from the respiratory tract and that the rate of clearance depended on the route of exposure. Brain half-times were 223-267 days after inhalation vs. 53 days following subcutaneous administration (Newland et al., 1987) or 54 days in humans given Mn intravenously (Cotzias et al., 1968). These long half-times were thought to reflect both slower clearance of brain stores and replenishment from other organs, particularly the respiratory tract. In rats, Drown et al. (1986) also observed slower clearance of labeled Mn from brain than from the respiratory tract. Several occupational physicians have reported large individual differences in workers' susceptibility to Mn intoxication, which Rodier (1955) speculated might be due in part to differences in the ability to clear particulate Mn from the lung.

The bioavailability of different forms of Mn is another matter for consideration. Roels et al. (1992) noted that geometric mean blood and urinary Mn levels of workers exposed only to MnO₂ in their 1992 report were lower (MnB: 0.81 ug/dL; MnU: 0.84 ug/g creatinine) than those of workers exposed to mixed oxides and salts in their 1987 report (MnB: 1.22 ug/dL; MnU: 1.59 ug/g creatinine), even though airborne total dust levels were approximately the same (geometric means of 0.94 and 0.95 mg/cu.m, respectively). Mena et al. (1969) observed no difference between the absorption of 1 um particles of MnCl₂ and manganese sesquioxide (Mn₂O₃) in healthy adults. Drown et al. (1986) found that following intratracheal instillation of MnCl₂ and Mn₃O₄ in rats, the soluble chloride cleared four times faster than the insoluble oxide from the respiratory tract. However, despite this initial difference, after 2 weeks the amounts of labeled Mn in the respiratory tract were similar for the two compounds. Recent work by Komura and Sakamoto (1993) comparing different forms of Mn in mouse diet suggested that less soluble forms such as MnO₂ were taken up to a significantly greater degree in cerebral cortex than the more soluble forms of MnCl₂ and manganese acetate [Mn(CH₃COO)₂]; however, the corpus striatal binding characteristics of the +4 valence state of Mn in MnO₂ were not substantially different from those of the divalent forms in MnCl₂, Mn(CH₃COO)₂, and manganese carbonate. Different oxidation states of certain metals (e.g., chromium, nickel, mercury) are known to have different toxicities, and some researchers have suggested that endogenous Mn can have quite different roles in Mn neurotoxicity depending on its oxidation state (e.g., Archibald and Tyree, 1987; Donaldson et al., 1982). There have been unsubstantiated claims that the higher valence states of Mn (Mn⁺³, Mn⁺⁴) and the higher oxides in ores (Mn₂O₃ and Mn₃O₄) are more toxic (Oberdoerster and Cherian, 1988). At present, however, insufficient information exists by which to determine the relative toxicities of different forms of Mn, and thus, for the purpose of deriving an RfC for Mn, no distinction is made among various compounds of Mn.

Because Mn is an essential element and is commonly ingested in diet, total Mn exposure is an issue. It would be desirable to know the effective target-site doses and apportion the dose to both the inhalation and oral routes of exposure. However, given the lack of data regarding oral and inhalation pharmacokinetics under environmental conditions, such quantitative apportionment is not possible at present.

Among the primary effects associated with Mn toxicity from inhalation exposure in humans are signs and symptoms of CNS toxicity. The first medical description of chronic Mn neurotoxicity (manganism) in workers is generally credited to Couper in the 1830s (NAS, 1973). Although the course and degree of Mn intoxication can vary greatly among individuals, manganism is generally considered to consist of two or three phases (Rodier, 1955). The first is the psychiatric aspect, which includes disturbances such as excessive weeping and laughing, sleep disturbance, irritability, apathy, and anorexia. These symptoms can occur independently of the second phase, neurological signs. The latter may include gait disturbances, dysarthria, clumsiness, muscle cramps, tremor, and mask-like facial expression. In addition, there may be a final stage of Mn intoxication involving symptoms of irreversible dystonia and hyperflexion of muscles that may not appear until many years after the onset of exposure (Cotzias et al., 1968). Cotzias et al. (1976) noted a parallel between these stages of symptoms and the biphasic pattern of dopamine levels over time in the Mn-exposed individuals noted above. Indeed, various specific features of Mn toxicity show biphasic patterns in which there is generally

first an increase then a decrease in performance (e.g., a notable increase in libido followed by impotence, or excitement followed by somnolence) (Rodier, 1955).

In addition to studies described in the Principal and Supporting Studies, numerous investigators have reported CNS effects in workers exposed to Mn dust or fumes (Sjoegren et al., 1990; Huang et al., 1989; Wang et al., 1989; Badawy and Shakour, 1984; Siegl and Bergert, 1982; Chandra et al., 1981; Saric et al., 1977; Cook et al., 1974; Smyth et al., 1973; Emará et al., 1971; Tanaka and Lieben, 1969; Schuler et al., 1957; Rodier, 1955; Flinn et al., 1941). Limitations in these studies generally preclude describing a quantitative concentration-response relationship. Exposure information is often quite limited, with inadequate information on the historical pattern of Mn concentrations or on the chemical composition and particle size distribution of the dust. In addition, exposure to other chemicals in the workplace is often not adequately characterized. Despite these limitations, such studies collectively point to neurobehavioral dysfunction as a primary endpoint for Mn toxicity.

The neuropathological bases for manganism have been investigated by many researchers and have indicated the involvement of the corpus striatum and the extrapyramidal motor system (e.g., Archibald and Tyree, 1987; Donaldson and Barbeau, 1985; Donaldson et al., 1982; Eriksson et al., 1987, 1992). Neuropathological lesions have generally been associated with the basal ganglia, specifically involving neuronal degeneration in the putamen and globus pallidus (e.g., Newland et al., 1987). Brain imaging studies (e.g., Wolters et al., 1989; Nelson et al., 1993) more recently have begun to provide additional insight into the brain structures involved in Mn toxicity.

In terms of the neurochemistry of Mn toxicity, several studies have shown that dopamine levels are affected by Mn exposure in humans, monkeys, and rodents, with various indications of an initial increase in dopamine followed by a longer term decrease (e.g., Cotzias et al., 1976; Bird et al., 1984; Barbeau, 1984; Brouillet et al., 1993). Some theories of Mn neurotoxicity have focused on the role of excessive Mn in the oxidation of dopamine resulting in free radicals and cytotoxicity (e.g., Donaldson et al., 1982; Barbeau, 1984). In addition, the fundamental role of mitochondrial energy metabolism in Mn toxicity has been indicated by the studies of Aschner and Aschner (1991), Gavin et al. (1992), and others. Brouillet et al. (1993) have suggested that the mitochondrial dysfunctional effects of Mn result in various oxidative stresses to cellular defense mechanisms (e.g., glutathione) and, secondarily, free radical damage to mitochondrial DNA. In view of the slow release of Mn from mitochondria (Gavin et al., 1992), such an indirect effect would help account for a progressive loss of function in the absence of ongoing Mn exposure (Brouillet et al., 1993), as Mn toxicity has been known to continue to progress in humans despite the termination of exposure (Cotzias et al., 1968; Rodier, 1955).

Because of the involvement of the dopaminergic system and extrapyramidal motor system in both Parkinson's disease and manganism, symptoms of the two diseases are somewhat similar, and several writers have suggested the possibility of a common etiology; however, many neurological specialists make a clear distinction in the etiologies and clinical features of Parkinson's disease and manganism (Barbeau, 1984; Langston et al., 1987).

Another primary endpoint of Mn toxicity has been male reproductive dysfunction, often manifesting in symptoms such as loss of libido, impotence, and similar complaints (e.g., Rodier, 1955; Cook et al., 1974). Some neuropathological evidence suggests that the hypothalamus is a site of Mn accumulation (Donaldson et al., 1973); thus, disturbance of the hypothalamic-pituitary-gonadal axis hormones might be expected (Deskin et al., 1981) and has been examined in a few occupational studies. Lauwerys et al. (1985) reported the results of a fertility questionnaire administered to male factory workers (n = 85) exposed to Mn dust. This study involved the same population of workers for which Roels et al. (1987) reported neurobehavioral disturbances. The range of Mn levels in the breathing zone was 0.07-8.61 mg/cu.m, with a median concentration of 0.97 mg/cu.m. Average length of exposure was 7.9 years (range of 1-19 years). A group of workers (n = 81)

with a similar workload was used as a control group. The number of births expected during different age intervals of the workers (16-25, 26-35, and 36-45 years) was calculated on the basis of the reproductive experience of the control employees during the same period. A decrease in the number of children born to workers exposed to Mn dust during the ages of 16-25 and 26-35 was observed. No difference in the sex ratio of the children was found. The same apparent LOAEL(HEC) (0.34 mg/cu.m) that was identified in Roels et al. (1987) for neurobehavioral effects is identified in this study for human reproductive effects.

However, a more recent report from the same group of investigators (Gennart et al., 1992), based on 70 of the alkaline battery plant workers evaluated by Roels et al. (1992), indicated that the probability of live birth was not different between the Mn-exposed and control workers. Also, in the study by Roels et al. (1992), serum levels of certain hormones related to reproductive function (FSH, LH, and prolactin) were not significantly different for the full group of 92 Mn workers vs. 102 controls. The latter results are partially supported by a preliminary report by Alessio et al. (1989), who found that serum FSH and LH levels were not significantly different in 14 workers generally exposed to <1 mg Mn/cu.m compared to controls, although prolactin and cortisol levels were significantly higher in the Mn-exposed workers. It is possible that differences in the forms of Mn to which workers were exposed in these studies may have contributed to the similarities and differences in the results, but insufficient information exists to substantiate this speculation.

Average concentrations of airborne Mn differed slightly in the reports of Gennart et al. (1992) and Roels et al. (1992), evidently because only a subset of Mn workers, presumably with different job functions, was used in the Gennart et al. (1992) analysis. The median respirable dust concentration was 0.18 mg/cu.m, and the median total dust concentration (comparable to Roels et al., 1987, and Lauwerys et al., 1985) was 0.71 mg/cu.m. Thus, if 0.34 mg/cu.m is identified as a LOAEL(HEC) based on the reports of Lauwerys et al. (1985) and Roels et al. (1987), 0.25 mg/cu.m total dust is the NOAEL(HEC) for reproductive effects based on the report of negative findings by Gennart et al. (1992).

The respiratory system is another primary target for Mn toxicity; numerous reports of Mn pneumonitis and other effects on the respiratory system have appeared in the literature, dating back to 1921 (NAS, 1973). In their cross-sectional study of workers exposed to mixed Mn oxides and salts (described in the Principal and Supporting Studies), Roels et al. (1987) found that significantly greater prevalences of coughs during the cold season, dyspnea during exercise, and recent episodes of acute bronchitis were reported in the exposed group on a self-administered questionnaire. However, objectively measured lung function parameters were only slightly altered and only in Mn-exposed smokers (also see Saric and Lucic-Palaic, 1977, regarding a possible synergism between Mn and smoking in producing respiratory symptoms). In their more recent study, Roels et al. (1992) found no significant differences between MnO₂-exposed and control workers in responses to a questionnaire regarding respiratory symptoms. Nor were objective spirometric measurements significantly different for the two groups. The LOAEL(HEC) for respiratory effects is 0.34 mg/cu.m total dust, based on the Roels et al. (1987) study, and the NOAEL(HEC) is 0.05 mg/cu.m respirable dust, based on the Roels et al. (1992) study. In view of the near equivalence of the geometric mean total dust concentrations in the 1987 and 1992 studies by Roels et al. (0.94 and 0.95 mg/cu.m, respectively), there in fact may be little difference between the LOAEL(HEC) and the NOAEL(HEC) in terms of air concentrations; however, differences in the forms of Mn (MnO₂ vs. mixed Mn oxides and salts) to which the workers in the two studies were exposed make it difficult to compare these values quantitatively.

Nogawa et al. (1973) investigated an association between atmospheric Mn levels and respiratory endpoints in junior high school students. A questionnaire focusing on eye, nose, and throat symptoms and pulmonary function tests were given to students attending junior high schools that were 100 m (enrollment = 1258) and 7 km (enrollment = 648) from a ferromanganese plant. Approximately 97-99% of the students participated. Based on

measurements obtained at another time by a government agency, the 5-day average atmospheric Mn level 300 m from the plant was reported to be 0.0067 mg/cu.m.

Significant increases in past history of pneumonia, eye problems, clogged nose, nose colds, throat swelling and soreness, and other symptoms were noted among the students in the school 100 m from the plant. Those living closest to the plant reported more throat symptoms and past history of pneumonia than did students living farther away. Pulmonary function tests revealed statistically significant decreases in maximum expiratory flow, forced vital capacity (FVC), forced expiratory volume at 1 second (FEV-1), and the FVC:FEV-1 ratio in the students attending the school closer to the plant, with some measures suggesting a relationship between performance and distance of residence from the plant.

Although the results from the study of Nogawa et al. (1973) suggest an association between ambient Mn exposure and respiratory problems, limitations in the study make it difficult to interpret. No direct measurements were made of atmospheric Mn levels either in the schools or homes, and exposure levels were inferred from the distance from the plant and other indirect measures of Mn in the environment. Also, the authors did not note whether socioeconomic variables were controlled, and this factor could well be confounded with both distance from the plant and health problems. A follow-up study by Kagamimori et al. (1973) suggested that, following reductions in Mn emissions (with apparently no reduction in sulfur dioxide or total dust) from the ferromanganese plant, students nearest the plant showed improvements in subjective symptoms and pulmonary function tests. As before, however, exposure levels were not adequately characterized to allow clear-cut conclusions.

Lloyd-Davies (1946) reported an increased incidence of pneumonia in men employed at a potassium permanganate manufacturing facility over an 8-year period. During that period, the number of workers in the facility varied from 40 to 124. Dust measurements were well described in terms of collection conditions and particle size and composition, but actual exposure levels were not evaluated. Air concentrations ranged from 9.6 to 83.4 mg/cu.m as MnO₂, which constituted 41-66% of the dust. The incidence of pneumonia in the workers was 26 per 1000, compared to an average of 0.73 per 1000 in a reference group of over 5000 workers. Workers also complained of bronchitis and nasal irritation. In a continuation of this study, Lloyd-Davies and Harding (1949) reported the results of sputum and nasopharynx cultures for four men diagnosed as having lobar- or bronchopneumonia. With the exception of one of these cases, they concluded that Mn dust, without the presence of bacterial infection or other factors, caused the observed pneumonitis.

Evidence from several laboratory animal studies supports findings in Mn-exposed humans. For example, inhaled Mn has been shown to produce significant alterations in dopamine levels in the caudate and globus pallidus of Rhesus monkeys (Bird et al., 1984) and behavioral changes in mice (Morganti et al., 1985). However, species differences may complicate interpretation of certain neurobehavioral findings in laboratory animals. Unlike primates, rodents do not have pigmented substantia nigra, which is a brain region of relatively high Mn uptake and consequent involvement in neurobehavioral dysfunction. Nevertheless, rodent and primate studies show various neurochemical, neuropathological, and neurobehavioral effects resulting from Mn exposure. However, because most laboratory animal studies of Mn neurotoxicity involve exposure by routes other than inhalation, they are not described here.

Other endpoints of Mn toxicity also have been investigated with laboratory animal models of inhalation exposure. Experimental animal data qualitatively support human study findings of respiratory effects in that Mn exposure results in increased incidence of pneumonia in rats exposed to 68-219 mg/cu.m MnO₂ for 2 weeks (Shiotsuka, 1984), pulmonary emphysema in monkeys exposed to 0.7-3.0 mg/cu.m MnO₂ for 10 months (Suzuki et al., 1978), and bronchiolar lesions in rats and hamsters exposed to 0.117 mg/cu.m Mn₃O₄ for 56 days (Moore et al., 1975). Also, Lloyd-Davies and Harding (1949) induced bronchiolar epithelium inflammation, widespread pneumonia, and granulomatous reactions in rats administered 10 mg MnO₂ by intratracheal injection, and pulmonary edema

in rats administered 5-50 mg MnCl₂ in the same fashion. However, no significant pulmonary effects were detected in other studies of rats and monkeys exposed to as much as 1.15 mg Mn/cu.m as Mn₃O₄ for 9 months (Ulrich et al., 1979a,b,c) or rabbits exposed to as much as 3.9 mg Mn/cu.m as MnCl₂ for 4-6 weeks (Camner et al., 1985).

Laboratory animal studies also have shown that inhaled Mn may increase susceptibility to infectious agents such as *Streptococcus pyogenes* in mice (Adkins et al., 1980), *Enterobacter cloacae* in guinea pigs (Bergstrom, 1977), *Klebsiella pneumoniae* in mice (Maigetter et al., 1976), and *Streptococcus hemolyticus* in mice (Lloyd-Davies, 1946). In general, Mn concentrations were relatively high (>10 mg/cu.m) in these studies. However, Adkins et al. (1980) concluded that, based on the regression line of the relationship between concentration and mortality in Mn-exposed mice, exposure to <0.62 mg/cu.m would result in a mortality rate that differed from controls by at least 10%.

The developmental effects of Mn have been investigated primarily from the viewpoint of the nutritional role of this element and therefore have generally involved oral exposure. Some studies indicate that neonates of various species have a greater body burden of Mn than mature individuals have, possibly because neonates do not develop the ability to eliminate Mn--and thereby maintain Mn homeostasis--until some time after birth (Miller et al., 1975; Cotzias et al., 1976; Wilson et al., 1991). Moreover, some evidence suggests that the neonate's inability to maintain Mn homeostasis is due to a limitation in the elimination of Mn rather than in its gastrointestinal absorption (Bell et al., 1989), which would suggest a potentially greater vulnerability of young individuals to excessive Mn exposure regardless of the route of exposure.

Several studies have demonstrated neurochemical alterations in young rats and mice exposed postnatally to Mn by routes other than inhalation (e.g., Kontur and Fechter, 1988; Seth and Chandra, 1984; Deskin et al., 1981; Cotzias et al., 1976). The only inhalation study of the developmental toxicity of Mn appears to be that of Lown et al. (1984). Female mice were exposed to MnO₂ 7 hours/day, 5 days/week for 16 weeks prior to conception and for 17 days following conception (i.e., gestational days 1-18). For the first 12 weeks, the air concentration was 49.1 mg Mn/cu.m; all later exposures were at 85.3 mg Mn/cu.m. To separate prenatal and postnatal exposure effects, a cross-fostering design was used. Although mothers exposed to MnO₂ prior to conception produced significantly worse pups per litter, prenatally exposed offspring showed reduced scores on various activity measures (open field, roto-rod, and exploration) and retarded growth that persisted into adulthood. A decrease in roto-rod performance was also observed in the offspring of nonexposed mice that were fostered to Mn-exposed females during lactation. Thus, balance and coordination were affected by either gestational or postpartum exposure to MnO₂.

I.B.5. CONFIDENCE IN THE INHALATION RfC

Study -- Medium
Data Base -- Medium
RfC -- Medium

Confidence in the principal studies (Roels et al., 1987, 1992) is medium. Neither of the principal studies identified a NOAEL for neurobehavioral effects, nor did either study directly measure particle size or provide information on the particle size distribution. The 1992 study by Roels et al. did provide respirable and total dust measurements, but the 1987 study measured only total dust. These limitations of the studies are mitigated by the fact that the principal studies found similar indications of neurobehavioral dysfunction, and these findings were consistent with the results of other human studies (Mergler et al., 1993; Iregren, 1990; Wennberg et al., 1991, 1992; as well as various clinical studies). In addition, the exposure history of the workers in the 1992 study by Roels et al. was well

characterized and essentially had not changed over the preceding 15 years, thereby allowing calculation of integrated exposure levels for individual workers. However, individual integrated exposures were not established in the 1987 study of Roels et al.

Confidence in the data base is medium. The duration of exposure was relatively limited in all of the principal and supporting studies, ranging from means of 5.3 and 7.1 years in the co-principal studies by Roels et al. (1992 and 1987, respectively) to a maximum of 16.7 years in the study by Mergler et al. (1993). Moreover, the workers were relatively young, ranging from means of 31.3 and 34.3 years in the co-principal studies (Roels et al., 1992 and 1987, respectively) to a maximum of 46.4 years (Iregren, 1990). These temporal limitations raise concerns that longer durations of exposure and/or interactions with aging might result in the detection of effects at lower concentrations, as suggested by results from studies involving longer exposure durations and lower concentrations (Mergler et al., 1993; Iregren, 1990). In addition, except for the 1992 study by Roels et al., in which Mn exposure was limited to MnO₂, the other principal and supporting studies did not specify the species of Mn and the proportions of the different compounds of Mn to which workers were exposed. It is not clear whether certain compounds or oxidation states of Mn are more toxic than others. Thus, it is not possible to distinguish the relative toxicity of different Mn compounds in these studies, despite some indications in the literature regarding the differential toxicity of various oxidation states of Mn. Although the primary neurotoxicological effects of exposure to airborne Mn have been qualitatively well characterized by the general consistency of effects across studies, the exposure-effect relationship remains to be well quantified, and a no-effect level for neurotoxicity has not been identified in any of these studies thus far. Finally, the effects of Mn on development and reproduction have not been studied adequately. Insufficient information on the developmental toxicity of Mn by inhalation exposure exists, and the same is true for information on female reproductive function. The study of the reproductive toxicity of inhaled Mn in males also needs to be characterized more fully.

Reflecting medium confidence in the principal studies and medium confidence in the data base, confidence in the inhalation RfC is medium.

I.B.6. EPA DOCUMENTATION AND REVIEW OF THE INHALATION RfC

Source Document -- This assessment is not presented in any existing U.S. EPA document.

Other EPA Documentation -- U.S. EPA, 1984

Agency Work Group Review -- 08/23/1990, 09/19/1990, 09/23/1993

Verification Date -- 09/23/1993

I.B.7. EPA CONTACTS (INHALATION RfC)

Please contact the Risk Information Hotline for all questions concerning this assessment or IRIS, in general, at (513)569-7254 (phone), (513)569-7159 (FAX) or RIH.IRIS@EPAMAIL.EPA.GOV (internet address).

II. CARCINOGENICITY ASSESSMENT FOR LIFETIME EXPOSURE

Substance Name -- Manganese
CASRN -- 7439-96-5
Last Revised -- 12/01/1996

Section II provides information on three aspects of the carcinogenic assessment for the substance in question; the weight-of-evidence judgment of the likelihood that the substance is a human carcinogen, and quantitative estimates of risk from oral exposure and from inhalation exposure. The quantitative risk estimates are presented in three ways. The slope factor is the result of application of a low-dose extrapolation procedure and is presented as the risk per (mg/kg)/day. The unit risk is the quantitative estimate in terms of either risk per ug/L drinking water or risk per ug/cu.m air breathed. The third form in which risk is presented is a drinking water or air concentration providing cancer risks of 1 in 10,000, 1 in 100,000 or 1 in 1,000,000. The rationale and methods used to develop the carcinogenicity information in IRIS are described in The Risk Assessment Guidelines of 1986 (EPA/600/8-87/045) and in the IRIS Background Document. IRIS summaries developed since the publication of EPA's more recent Proposed Guidelines for Carcinogen Risk Assessment also utilize those Guidelines where indicated (Federal Register 61(79):17960-18011, April 23, 1996). Users are referred to Section I of this IRIS file for information on long-term toxic effects other than carcinogenicity.

NOTE: Manganese is an element considered essential to human health.

II.A. EVIDENCE FOR CLASSIFICATION AS TO HUMAN CARCINOGENICITY

II.A.1. WEIGHT-OF-EVIDENCE CLASSIFICATION

Classification -- D; not classifiable as to human carcinogenicity

Basis -- Existing studies are inadequate to assess the carcinogenicity of manganese.

II.A.2. HUMAN CARCINOGENICITY DATA

None.

II.A.3. ANIMAL CARCINOGENICITY DATA

Inadequate. DiPaolo (1964) subcutaneously or intraperitoneally injected DBA/1 mice with 0.1 mL of an aqueous solution 1% manganese chloride twice weekly for 6 months. A larger percentage of the mice exposed subcutaneously (24/36; 67%) and intraperitoneally (16/39; 41%) to manganese developed lymphosarcomas compared with controls injected with water (16/66; 24%). In addition, tumors appeared earlier in the exposed groups than in the control groups. The incidence of tumors other than lymphosarcomas (i.e., mammary

adenocarcinomas, leukemias, injection site tumors) did not differ significantly between the exposed groups and controls. A thorough evaluation of the results of this study was not possible because the results were published in abstract form.

Stoner et al. (1976) tested manganous sulfate in a mouse lung adenoma screening bioassay. Groups of strain A/Strong mice (10/sex), 6-8 weeks old, were exposed by intraperitoneal injection to 0, 6, 15 or 30 mg/kg manganous sulfate 3 times/week for 7 weeks (a total of 21 injections). The animals were observed for an additional 22 weeks after the dosing period, before sacrifice at 30 weeks. Lung tumors were observed in 12/20, 7/20, and 7/20 animals in the high, medium, and low dosage groups, respectively. The percentage of mice with tumors was elevated, but not significantly, at the highest dose level (Fisher Exact test) compared with that observed in the vehicle controls. In addition, there was an apparent increase in the average number of pulmonary adenomas per mouse both at the mid and high doses, as compared with the vehicle controls (10 mice/sex), but the increase was significant only at the high dose (Student's t-test, $p < 0.05$).

In the mouse lung adenoma bioassay, certain specific criteria should be met in order for a response to be considered positive (Shimkin and Stoner, 1975). Among these criteria are an increase in the mean number of tumors per mouse and an evident dose-response relationship. While the results of this study are suggestive of carcinogenicity, the data cannot be considered conclusive since the mean number of tumors per mouse was significantly increased at only one dose, and the evidence for a dose-response relationship was marginal.

Furst (1978) exposed groups of F344 rats (25/sex) intramuscularly or by gavage to manganese powder, manganese dioxide, and manganese (II) acetylacetonate (MAA). Treatment consisted of either 9 i.m. doses of 10 mg each of manganese powder or manganese dioxide, 24 doses of 10 mg manganese powder by gavage, or 6 i.m. doses of 50 mg of MAA. In addition, female swiss mice (25/group) were exposed intramuscularly to manganese powder (single 10 mg dose) and manganese dioxide (6 doses of 3 or 5 mg each). There was an increased incidence of fibrosarcomas at the injection site in male (40%) and female (24%) rats exposed intramuscularly to MAA compared with vehicle controls (4% male, 4% female). EPA (1984) determined that these increases were statistically significant and noted that the study results regarding MAA, an organic manganese compound, cannot necessarily be extrapolated to pure manganese or other inorganic manganese compounds. No difference in tumor incidence was found between rats and mice exposed to manganese powder and manganese dioxide and controls.

Sunderman et al. (1974, 1976) exposed male 344 rats to 0.5 to 4.4 mg manganese dust intramuscularly and found that no tumors were induced at the injection site. It was further observed that co-administration of manganese with nickel subsulfide resulted in decreased sarcoma production by comparison to nickel subsulfide alone. Subsequent studies by Sunderman et al. (1980) suggest that manganese dust may inhibit local sarcoma induction by benzo(a)pyrene.

Witschi et al. (1981) exposed female A/J mice intraperitoneally to 80 mg/kg methylcyclopentadienyl manganese tricarbonyl (MMT) and found that although cell proliferation was produced in the lungs, lung tumor incidence did not increase.

II.A.4. SUPPORTING DATA FOR CARCINOGENICITY

None.

__II.B. QUANTITATIVE ESTIMATE OF CARCINOGENIC RISK FROM ORAL EXPOSURE

Not available.

__II.C. QUANTITATIVE ESTIMATE OF CARCINOGENIC RISK FROM INHALATION EXPOSURE

Not available.

__II.D. EPA DOCUMENTATION, REVIEW, AND CONTACTS (CARCINOGENICITY ASSESSMENT)

__II.D.1. EPA DOCUMENTATION

Source Document -- U.S. EPA, 1984, 1988

The Drinking Water Criteria Document for Manganese has received OHEA review.

__II.D.2. REVIEW (CARCINOGENICITY ASSESSMENT)

Agency Work Group Review -- 05/25/1988

Verification Date -- 05/25/1988

__II.D.3. U.S. EPA CONTACTS (CARCINOGENICITY ASSESSMENT)

Please contact the Risk Information Hotline for all questions concerning this assessment or IRIS, in general, at (513)569-7254 (phone), (513)569-7159 (FAX) or RIH.IRIS@EPAMAIL.EPA.GOV (internet address).

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Substance Name -- Manganese
CASRN -- 7439-96-5
Last Revised -- 11/01/1995

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VI.C. CARCINOGENICITY ASSESSMENT REFERENCES

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VII. REVISION HISTORY

Substance Name -- Manganese
CASRN -- 7439-96-5

Date	Section	Description
09/26/1988	II.	Carcinogen summary on-line
09/01/1989	VI.	Bibliography on-line
06/01/1990	I.A.	Oral RfD now under review
08/01/1990	I.A.	Oral RfD summary on-line
08/01/1990	II.	Text edited
08/01/1990	VI.	Oral RfD references added
09/01/1990	I.B.	Inhalation RfC now under review
12/06/1990	I.B.	Inhalation RfC on-line
12/06/1990	VI.B.	Inhalation RfC references added
01/01/1992	IV.	Regulatory Action section on-line
06/01/1992	VI.B.	Iregren, 1990 and Nishiyama et al., 1975 pages corrected
08/01/1992	I.A.	Oral RfD noted as pending change
08/01/1992	I.A.6.	Work group review date added
10/01/1992	I.A.	Oral RfD withdrawn; new summary in preparation
10/01/1992	I.A.6.	Work group review date added
10/01/1992	VI.A.	Oral RfD references withdrawn
01/01/1993	I.A.	Oral RfD replaced (RfD changed)
01/01/1993	VI.A.	Oral RfD references replaced
05/01/1993	I.A.	Work group review date added
07/01/1993	II.A.3.	'Inadequate' added to 1st paragraph
07/01/1993	II.D.1.	EPA Documentation clarified
11/01/1993	I.B.	Inhalation RfC noted as pending changed
11/01/1993	I.B.6.	Work group review date added

12/01/1993	I.B.	Inhalation RfC replaced; RfC changed
12/01/1993	VI.B.	Inhalation RfC references replaced
01/01/1994	I.A.	Oral RfD noted as pending change
01/01/1994	I.A.6.	Work group review date added
03/01/1994	II.D.3.	Primary contact changed
04/01/1994	I.A.2.	Text revised
04/01/1994	I.A.3.	Text revised
04/01/1994	I.A.4.	Text revised
04/01/1994	I.A.5.	Text revised
04/01/1994	VI.A.	Oral RfD references revised
06/01/1995	I.A.	Oral RfD noted as pending change
06/01/1995	I.A.6.	Work group review date added
11/01/1995	I.A.	Oral RfD assessment replaced
11/01/1995	VI.A.	Oral RfD references replaced
05/01/1996	I.A.7.	Secondary contact's phone number changed
12/01/1996	II.D.3.	Primary contact removed

VIII. SYNONYMS

Substance Name -- Manganese
CASRN -- 7439-96-5
Last Revised -- 09/26/1988

7439-96-5
COLLOIDAL MANGANESE
MAGNACAT
MANGAN
Manganese
MANGAN NITRIDOVANY
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