TOXICITY SUMMARY FOR MANGANESE

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EXECUTIVE SUMMARY

Manganese is an essential trace element in humans that can elicit a variety of serious toxic responses upon prolonged exposure to elevated concentrations either orally or by inhalation. The central nervous system is the primary target. Initial symptoms are headache, insomnia, disorientation, anxiety, lethargy, and memory loss. These symptoms progress with continued exposure and eventually include motor disturbances, tremors, and difficulty in walking, symptoms similar to those seen with Parkinsonism. These motor difficulties are often irreversible. Based on human epidemiological studies, 0.8 mg/kg/day for drinking water exposure and 0.34 mg/m^3 in air for inhalation exposure have been estimated as lowest-observed-adverse-effect levels (LOAELs) for central nervous system effects.

Effects on reproduction (decreased fertility, impotence) have been observed in humans with inhalation exposure and in animals with oral exposure at the same or similar doses that initiate the central nervous system effects. An increased incidence of coughs, colds, dyspnea during exercise, bronchitis, and altered lung ventilatory parameters have also been seen in humans and animals with inhalation exposure. A possible effect on the immune system may account for some of these respiratory symptoms.

Because of the greater bioavailability of manganese from water, separate reference doses (RfD) for water and diet were calculated. A chronic (EPA 1995) and subchronic RfD (EPA 1994) for drinking water of 0.005 mg/kg/day has been calculated by EPA from a human no-observed-adverse-effect level (NOAEL) of 0.005 mg/kg/day; the NOAEL was determined from an epidemiological study of human populations exposed for a lifetime to manganese concentrations in drinking water ranging from 3.6–2300 μg/L (Kondakis et al. 1989). A chronic (EPA 1995) and subchronic RfD (EPA 1994) of 0.14 mg/kg/day for dietary exposure has been calculated by EPA from a human NOAEL of 0.14 mg/kg/day, which was determined from a series of epidemiological studies (Schroeder et al. 1966, WHO 1973, NRC 1989). Large populations with different concentrations of manganese in their diets were examined. No adverse effects that were attributable to manganese were seen in any of these groups. For both the drinking water and dietary values, the RfD was derived from these studies without uncertainty factors since manganese is essential in human nutrition and the exposure of the most sensitive groups was included in the populations examined. EPA (1995) indicates that the chronic RfD values are pending change.

A reference concentration (RfC) of 0.05 $\mu g/m^3$ (EPA 1995) for chronic inhalation exposure was calculated from a human LOAEL of 0.05 mg/m^3 for impairment of neurobehavioral function from an epidemiological study by Roels et al. (1992). The study population was occupationally exposed to airborne manganese dust with a median concentration of 0.948 mg/m^3 for 0.2 to 17.7 years with a mean duration of 5.3 years. Neurological examinations, psychomotor tests, lung function tests, blood tests, and urine tests were used to determine the possible effects of exposure. The LOAEL was derived from an occupational-lifetime integrated respirable dust concentration of manganese dioxide expressed as mg manganese/m^3 × years. Confidence in the inhalation RfC is rated medium by the EPA.

Some conflicting data exist on possible carcinogenesis following injections of manganese chloride and manganese sulfate in mice. However, the EPA weight-of-evidence classification

is: D, not classifiable as to human carcinogenicity based on no evidence in humans and inadequate evidence in animals (EPA 1995).

1. INTRODUCTION

Manganese (CAS registry number 7439-96-5) makes up about 0.10% of the earth's crust and is the 12th most abundant element. It can exist in oxidation states from -3 to +7, the most common being +4 in the chemical form of manganese dioxide (Keen and Leach 1988). The oxides and peroxides are used in industry as oxidizers, and the metal is used for manufacturing metal alloys to increase hardness and corrosion resistance. In living systems, manganese is an essential element that is found most often in the +2 valence (Keen and Leach 1988, Stokinger 1981).

Normal nutritional requirements of manganese are satisfied through the diet, which is the normal source of the element, with minor contributions from water and air (EPA 1984). The National Research Council (NRC 1989) recommends a dietary allowance of 2 to 5 mg/day for a safe and adequate intake of manganese for an adult human. Toxic exposures occur largely due to particulate material in the air from mining and manufacturing activity.

2. METABOLISM AND DISTRIBUTION

2.1ABSORPTION

Intestinal absorption has been estimated to be between 3 and 10% of the amount of manganese ingested and is a multiple-step process similar to and involving some of the same binding sites as in iron absorption (EPA 1995). Experiments with isolated rat intestines indicate that manganese absorption is carrier-mediated with saturation occurring at 0.5 mM (Testolin et al. 1993). The absorption of manganese by inhalation depends on the particle size. The larger particles are cleared from the respiratory tract by the cilia and swallowed; whereas, the fine particles (< 2.5 microns) are deposited in the lungs and must be cleared by absorption into the blood and lymph circulation (EPA 1995). It is estimated that 60 to 70% of the inhaled particles are eventually swallowed (Stokinger 1981).

2.2 DISTRIBUTION

Once absorbed, manganese is transported to organs rich in mitochondria (in particular the liver, pancreas, and pituitary) where it is rapidly concentrated. Accumulation of manganese in the central nervous system following an intraperitoneal or intramuscular injection occurs slowly reaching a maximum in about 30 days. Distribution is homogeneous in the brain with lower concentrations in the spinal cord. The average turnover time in the central nervous system is reported to be about 110 days following intraperitoneal injection and about 55 days for intramuscular injection (Stokinger 1981).

2.3 METABOLISM

Manganese does not undergo metabolism; it is absorbed and excreted unchanged. However, manganese is an essential trace element and is involved as an activator or cofactor with a number of diverse enzymes involved with energy metabolism, digestion, and lipid and protein metabolism (Orten and Neuhaus 1975).

2.4 EXCRETION

The normal adult body pool of about 20 mg is maintained by the liver, and excess manganese is excreted into the intestine via the bile. This control is achieved with a daily intake of 10 to 20% of the total pool; therefore, relatively large amounts are handled by this mechanism. The normal urinary level of manganese averages about 2.75 µg/L with a range of about 1.0 to 8.0 µg/L. Urinary levels over 10 µg/L are indicative of manganese overexposure (Stokinger 1981).

3. NONCARCINOGENIC HEALTH EFFECTS

3.1 ORAL EXPOSURES

3.1.1 Acute Toxicity

3.1.1.1 Human

Information on the acute oral toxicity of manganese in humans was unavailable.

3.1.1.2 Animal

Due to the control exerted by mammals over manganese absorption and excretion, acute oral toxicity is observed only after relatively large doses. However, several LD_{50} values have been calculated. In one oral study using Sprague-Dawley rats, manganese dichloride tetrahydrate was given by stomach tube, and the animals were observed for 14 days. The LD_{50} was calculated to be 1484 mg/kg or 7.5 mmole/kg. The manganese concentrations in the liver, kidney, spleen, heart, testes, brain, and blood of the surviving animals returned to control values within the 14-day period (Holbrook et al. 1975).

Other oral values include an LD_{50} of 1715 mg/kg for manganese dichloride in mice and 3730 mg/kg for manganese^{2+} acetate in rats (Lewis and Sweet 1984). Potassium permanganate, a strong oxidizing agent, is an irritant to mucosal tissues, is hemolytic, and damages capillaries regardless of the route. An oral LD_{50} of 1090 mg/kg has been determined for potassium permanganate in rats (Stokinger 1981).

However, rats maintained on manganese-deficient diets for 21 days had higher plasma ammonia and lower plasma urea concentrations in association with lowered hepatic manganese concentrations and decreased arginase activity as compared to rats on diets containing 48 µg manganese/g diet (Brock et al. 1994).

3.1.2 Subchronic Toxicity

3.1.2.1 Human

A number of epidemiological studies have been performed that document the response of human populations to subchronic or chronic exposure to elevated manganese concentrations. Signs of toxicity may appear within months and can continue for years. Initial signs of manganese toxicity usually include headache, disorientation, speech disturbances, memory loss, and acute anxiety. Prompt removal of the affected person from the source of manganese exposure usually results in reversal of most of the symptoms; however, the symptoms will increase and eventually become irreversible if the individual continues to be exposed to high manganese concentrations (Keen and Leach 1988). Section 3.1.3 provides discussions of individual studies.

3.1.2.2 Animal

A decrease in brain amines was observed in a study of the effects of manganese chloride on brain chemistry. Male Sprague-Dawley rats were given 0.1 or 1.0 mg manganese/mL in drinking water for 8 months after which the brains were removed, dissected, and analyzed for various brain amines. Effects were seen with both doses. Decreases in the following amines were observed: dihydroxyphenylacetic, noradrenaline, homovanillic acid, 5-hydroxyindolacetic acid, noradrenaline, and serotonin.

In a similar study, rats were given 0.54 mg $MnCl_2 \cdot 5H_2O$/mL in drinking water for 90 days (Subhash and Padmashree 1991). Manganese accumulation in various brain regions was two- to three-fold that of controls. In addition, inhibition of dopamine β-hydroxylase and monoamine oxidase, decreased and increased dopamine levels, and increased serotonin were observed in various brain regions.

Feedlot calves fed a diet supplemented with 50 ppm zinc methionine plus 40 ppm manganese methionine for 34 days had better response to disease challenge than control (no supplement) animals or calves supplemented with the oxide forms of zinc and manganese. Calves fed the organic form of the metals had lower temperatures, higher feed intake, and greater body weight gain following challenge with infectious bovine rhinotracheitis virus when compared to control or inorganic zinc and manganese supplemented calves (Chirase et al. 1994).

3.1.3 Chronic Toxicity

3.1.3.1 Human

An epidemiological study by Schroeder et al. (1966) on normal diets in the United States, England, and Holland, demonstrated that the average daily intake of manganese ranged from about 2.3 to 8.8 mg/day. Certain other diets (vegetarian) were possibly higher in manganese, but all were considered safe for chronic human consumption. In another portion of the study, patients were given 9 mg manganese/day as manganese citrate for many months. Assuming the average dietary intake of 2.5 mg/day, the total manganese intake was about 11.5 mg/day. No signs of toxicity were seen in either part of the study.

The World Health Organization reviewed the previous study and other dietary information and concluded that 2 to 3 mg manganese/day is adequate for adults and 8 to 9 mg/day is safe (WHO 1973). The Food and Nutrition Board of the National Research Council also examined the available

evidence and determined 10 mg manganese/day to be safe. They chose an adequate and safe intake of manganese to be 2 to 5 mg/day for adults (NRC 1989).

Sixteen cases of manganese toxicity from drinking contaminated water were reported in a study by Kawamura et al. (1941). The symptoms included lethargy, increased muscle tonus, tremor, and mental disturbances. Children were affected less than the elderly. The drinking water was estimated to contain at least 28 mg manganese/L, which would be equivalent to an intake of 0.8 mg/kg/day (56 mg/day) for a 70-kg adult drinking 2 L of water/day.

Kondakis et al. (1989) conducted an epidemiological study in three areas of northwestern Greece containing maximum manganese concentrations of 14.6, 252.6 and 2300 μg/L in drinking water. Mean concentrations of manganese in hair samples were 3.51, 4.49 and 10.99 μg/g dry weight from the areas with low, medium, and high manganese concentrations, respectively, in drinking water. The concentration in whole blood was the same for all three areas. The individuals in the study were given a neurological examination designed to test for the presence and severity of 33 different symptoms associated with manganese central nervous system toxicity. The combined average scores for both sexes were 2.7, 3.9, and 5.2 for the low, medium, and high concentrations, respectively. Although this effect was not large, the score for the high concentration was significantly higher than the score recorded for the low concentration. The experiment was criticized for the small numbers of individuals tested, the lack of scatter data, and the lack of dietary data. Nevertheless, the experiment established an uncertainty about extrapolating dietary risk factors to drinking water without considering the possibility of differential absorption (EPA 1995).

In addition to the central nervous system effects, an iron-responsive anemia is commonly found with orally-induced manganese toxicity (Keen and Leach 1988).

3.1.3.2 Animal

A number of studies have shown that biochemical changes occur in the brains of rodents following the administration of about 1 mg/mL manganese dichloride tetrahydrate in drinking water (Lai et al. 1981, Leung et al. 1981; see Sect. 3.1.2.2 for further discussion). Various forms of manganese in the diet of mice affect biogenic amine levels in the brain. Mice were fed 2 g manganese/kg in the form of $MnCl_2 \cdot 4H_2O$, $Mn(CH_3COO)_2 \cdot 4H_2O$, $MnCO_3$, or MnO_2 for 12 months (Komura and Sakamoto 1992). Manganese dioxide feeding resulted in lowered dopamine levels in the corpus striatum, hypothalamus, and midbrain. Accumulation of manganese in the brain correlated with both reduced dopamine levels in the hypothalamus and suppression of motor activity in the manganese acetate group.

A study of more relevance to humans was conducted by Gupta et al. (1980). Neurological symptoms, including muscular weakness and rigidity of the lower limbs, were seen in a group of 4 rhesus monkeys after 18 months treatment with 6.9 mg manganese/kg/day (given as manganese dichloride tetrahydrate). Degenerated neurons in the substantia nigra and scanty neuromelanin granules in pigmented cells were reported upon histological analysis.

Lambs on a high manganese diet developed a reduction in hemoglobin. This observation is consistent with the anemia seen in humans and indicates that large amounts of manganese can interfere with intestinal iron absorption (Stokinger 1981).

3.1.4 Developmental and Reproductive Toxicity

3.1.4.1 Human

Information on developmental and reproductive toxicity of manganese in humans following oral exposure was unavailable.

3.1.4.2 Animal

Groups of four adult male rhesus monkeys were given daily doses of 0 or 25 mg manganese chloride tetrahydrate/kg (6.94 mg manganese/kg) by oral gavage for 18 months. The testes of the treated monkeys exhibited interstitial edema and degeneration of the seminiferous tubules (Murthy et al. 1980, EPA 1989).

Other studies measured the effect of manganese chloride on various brain enzyme activities. Rats were exposed to 0, 1, or 10 mg/mL in the drinking water from conception onwards. Both Na-K-ATPase and Mg-ATPase activities increased in most brain regions in treated rats as compared to controls between postnatal days 5 and 20 but were decreased by day 60. These transient enzyme changes occurred despite a dose-dependent increase in brain manganese levels (Lai et al. 1991). No differences were observed for brain monoamine oxidase activity (Leung et al. 1993).

Pregnant Long-Evans rats were fed diets containing 0, 400, 1100, or 3550 ppm manganese from day 2 of gestation. The F_1 offspring were fed the same diet until they were up to 225 days old. Decreased serum testosterone was observed in 100-day-old offspring exposed to 400 ppm manganese. Decreased fertility was seen upon mating the offspring receiving the 3550 ppm dose (Laskey et al. 1982).

To determine the effect of excess aluminum on manganese deficiency in developing mice, dams were fed manganese deficient diets with or without high aluminum throughout gestation and lactation. Offspring exposed to manganese deficient diets had growth retardation and reduced forelimb and hindlimb grip strength as compared to controls on postnatal day 24. These effects were exacerbated by high aluminum (Golub et al. 1991).

3.1.5 Reference Dose

3.1.5.1 Subchronic: drinking water

ORAL RfD_s: 0.005 mg/kg/day (EPA 1994)

UNCERTAINTY FACTOR: 1
NOAEL: 0.005 mg/kg/day

Subchronic: diet

ORAL RfD_s: 0.14 mg/kg/day (EPA 1994)
UNCERTAINTY FACTOR: 1

PRINCIPAL STUDIES: The same studies and comments apply for both the subchronic and chronic RfD derivations. Section 3.1.5.2 provides further discussion.

3.1.5.2 Chronic: drinking water

ORAL RfD_c: 0.005 mg/kg/day (EPA 1995)
UNCERTAINTY FACTOR: 1
MODIFYING FACTOR: 1
NOAEL: 0.005 mg/kg/day
CONFIDENCE:
Study: Low-to-medium
Data Base: Medium-to-low
RfD: Medium-to-low

VERIFICATION DATE: 09/22/92

PRINCIPAL STUDY: Kondakis et al. 1989

Chronic: diet

ORAL RfD_c: 0.14 mg/kg/day (EPA 1995)
UNCERTAINTY FACTOR: 1
MODIFYING FACTOR: 1
NOAEL: 0.14 mg/kg/day
LOAEL: none
CONFIDENCE:
Study: High
Data Base: Medium
RfD: Medium

VERIFICATION DATE: 09/22/92

PRINCIPAL STUDIES: Schroeder et al. 1966, WHO 1973, NRC 1989

COMMENTS: Because of the greater bioavailability of manganese from water, a separate RfD for water was calculated. The major advantage of the Kondakis et al. (1989) study is that it examined a sensitive human subpopulation exposed for a lifetime; however, confidence is low in the study because of lack of data on concurrent dietary manganese. The dietary RfD is based on a composite of data from the three principal references. The uncertainty factor of 1 was applied because the information used to determine the RfD was taken from large adult human populations, and the most sensitive subpopulation was represented within the group. Humans exert an efficient homeostatic control over manganese. It is important to recognize that manganese is an essential human nutrient (EPA 1995). The most current IRIS records (EPA 1995) indicate that the RfDs are pending change.

3.2 INHALATION EXPOSURES

3.2.1 Acute Toxicity

3.2.1.1 Human

The inhalation of manganese oxide fumes, such as could be produced from welding, can result in chills, fever, sweating, nausea, and coughing. These influenza-like symptoms begin 4–12 hours after exposure and diminish after 24 hours. This "metal fume fever" usually causes no permanent damage unless exposure is continually repeated (Proctor et al. 1988).

3.2.1.2 Animal

Intratracheal injections of manganese oxides (particle size <3 μm) caused congestion, pulmonary edema, and histological changes in the lungs of young rats. The higher oxides were more toxic (Stokinger 1981).

Monkeys exposed to high concentrations of manganese in an aerosol exhibited alternating periods of sudden movement followed by torpor, nervousness, severe tremor, alternate flection and extension of the upper limbs, yawning, and cyanosis. The monkeys returned to normal 3 weeks after exposure, but more severe symptoms, including uncertain gait and paresis, appeared in 5 months (Stokinger 1981).

Groups of three male and female Sprague-Dawley rats were exposed 6 hours/day, 5 days/week for 2 weeks to 0, 43, 82, or 138 mg manganese/m^3 (given as manganese dioxide). Dose-related increases in the incidence and severity of pneumonitis and wet weight of the lungs were seen. Granulomas were seen in the 138 mg/m^3 exposure group (Shiotsuka 1984).

Several animal studies reviewed by EPA (1995) demonstrate probable immunosuppression following exposure to manganese tetroxide and streptococci, enterobacter, or klebsiella. In one such study, DC-1 mice were exposed to various levels of manganese tetroxide for 2 hours followed by exposure to *Streptococcus pyogenes* aerosol for 20 minutes. The incidence of mortality was related to the dose of manganese. Prior immunity to streptococci did not counteract the effects of manganese tetroxide inhalation and consequent streptococci infection (Adkins et al. 1980).

3.2.2 Subchronic Toxicity

3.2.2.1 Human

Most human studies on manganese toxicity are epidemiological studies on populations exposed to manganese compounds in dust particles. Individuals in these studies were exposed to manganese for less than one year to more than 20 years. The primary difference between subchronic and chronic central nervous system symptoms is the reversibility of the early subchronic symptoms.

An overlap exists between the inhalation and oral routes since manganese contained in larger particle sizes (greater than about 2.5 μm) is deposited in the tracheobronchial and extrathoracic regions and is cleared by the action of the cilia into the gastrointestinal tract. It is not surprising that the same central nervous system symptoms are seen with both routes (see Sect. 3.1.2.1). Respiratory system effects, nasal irritation, colds, bronchitis, and pneumonia are increased in exposed populations, and these symptoms can be seen following subchronic and chronic exposures (see Sect. 3.2.3 for individual experiments).

3.2.2.2 Animal

Dose-dependent hyperplasia of the peribronchial tissue, pulmonary emphysema and atelectasis, exudate in the bronchioles, and thickening of the alveolar wall were observed in rhesus monkeys exposed 22 hours/day for 10 months to manganese at concentrations of 0, 0.7 or 3.0 mg/m^3 (given as manganese dioxide dust) (Suzuki et al. 1978).

3.2.3 Chronic Toxicity

3.2.3.1 Human

A study was conducted by Roels et al. (1987) in which 141 males occupationally exposed to manganese dioxide, tetroxide, sulfate, carbonate, and nitrate were compared to a group of 104 males who were not occupationally exposed to these compounds. The groups were matched in background environmental factors, work load, and shift responsibilities. The duration of employment ranged from 1 to 19 years with a mean of 7.1 years. A higher frequency of coughs, dyspnea during exercise, episodes of acute bronchitis, and altered lung ventilatory parameters were found in the exposed group. Significant alterations were also found in visual reaction time, audioverbal short-term memory, eye-hand coordination, and hand steadiness in the exposed group. A LOAEL of 0.34 mg/m^3 was determined from these observations.

A more recent study by Roels et al. (1992) examined 92 male workers exposed to manganese dioxide dust in a battery plant. Exposure time ranged from 0.2–17.7 years (mean, 5.3 years) and exposure concentrations of respirable and total dust were 0.215 mg/m^3 and 0.948 mg/m^3, respectively. No differences were found in the manganese-exposed workers for respiratory or neurological symptoms, spirometric measurements, hormone levels, or calcium metabolism as compared to unexposed controls. However, visual reaction time, hand-eye coordination, and hand steadiness were significantly impaired.

A group of 60 welders from three separate plants who were exposed to manganese fumes were studied by Chandra et al. (1981). The mean concentrations of manganese were 0.31, 0.57 and 1.74 mg/m^3 measured in the air from plants 1, 2, and 3, respectively. Frequent colds, coughing, and fever were

reported by the individuals from plant 1; workers from all three plants reported insomnia. Signs of neurological effects measured by "brisk, deep reflexes" in the legs and/or arms were seen in 25, 50, and 45% of workers in plant 1, 2 and 3, respectively. Tremors were also observed in one worker in plant 1 and four workers in plant 2. Increased urinary manganese and serum calcium levels were also seen in workers from all plants. A LOAEL of 0.11 mg/m^3 was determined from the mean exposure at plant 1.

A similar study was reported by Iregren (1990) in which 15 workers from each of two Swedish foundries were studied for manganese exposure. The inhalation exposure concentration varied from 0.02 to 1.4 mg/m^3, and the time of exposure varied from 1 to 35 years. A reference group of two unexposed workers from the same geographic area was matched (age, type of work) to each exposed worker. Neurobehavioral function was evaluated by eight computerized tests from the Swedish Performance Evaluation System and two manual dexterity tests. Significant differences were found between the exposed and unexposed groups in simple reaction time and manual dexterity (finger tapping speed). A concentration-response relationship, however, could not be established. A LOAEL of 0.09 mg/m^3 was determined for the neurological effects.

Alloy workers with an average of 16.7 years of work in a ferromanganese and silicomanganese alloy facility were compared to matched controls for symptom reporting and on a series of nervous system function tests (Mergler et al. 1994). Respirable manganese levels in the alloy plant at stationary sampling sites averaged 0.122 mg/m^3. Alloy workers had significantly higher manganese blood levels than the control group (1.12 μg/100 mL vs 0.72 μg/100 mL). Symptoms reported more frequently for the alloy workers included fatigue, adverse emotional state, memory loss, attention difficulties, nightmares, sweating without physical exertion, difficulty maintaining an erection, and tinnitus. Overall the alloy workers also performed more poorly than the controls on motor function tests, optic spatial organization of movement, dynamic organization, cognitive flexibility, and olfactory perception threshold.

Respiratory effects, including an increased incidence of colds, bronchitis, and pneumonia, have been reported in at least four other human studies. It is believed unlikely that exposure to manganese is solely responsible for the increased respiratory symptoms. A decrease in resistance to infectious agents, possibly as a result of a weakened immune response, is probably a contributing factor (EPA 1995).

3.2.3.2 Animal

Groups of 4 female rhesus monkeys were exposed to 0 or 30 mg/m^3 manganese 6 hours/day, 5 days/week for 2 years. Significantly decreased dopamine concentrations were observed in the caudate and globus pallidus regions of the brains of treated monkeys. No behavioral abnormalities were noted during routine (cage side) observations. Neurobehavioral dysfunction was not specifically tested (Bird et al. 1984).

3.2.4 Developmental and Reproductive Toxicity

3.2.4.1 Human

The same population of male factory workers studied by Roels (see Sect. 3.2.3.1) was also studied by Lauwerys et al. (1985) for reproductive effects. The results of a fertility questionnaire indicated that fewer children were born to workers exposed to manganese dust between the ages of 16–25 and 26–35. The same LOAEL of 0.34 mg/m^3 was calculated for reproductive effects.

3.2.4.2 Animal

Decreased body weight and impaired neurobehavioral performance (balance and coordination) were seen in the offspring of female HA/ICR mice that were exposed to 48.9 mg manganese/m^3 7 hours/day for 5 days/week. Exposure was initiated 4 months prior to breeding and continued through day 18 of gestation. Similar neurobehavioral responses were obtained from offspring of unexposed mice which were fostered to manganese-exposed females during lactation (Massaro et al. 1980).

3.2.5 Reference Concentration/Dose

3.2.5.1 Subchronic

A subchronic RfC for manganese has not been derived (EPA 1994).

3.2.5.2 Chronic

INHALATION RfC: 0.00005 mg/m^3 (EPA 1995)
UNCERTAINTY FACTOR: 1000
MODIFYING FACTOR: 1
NOAEL: none
LOAEL: 0.05 mg/m^3
CONFIDENCE:
Study: Medium
Data Base: Medium
RfC: Medium

VERIFICATION DATE: 09/23/93

PRINCIPAL STUDIES: Roels et al. 1987, 1992

COMMENTS: The LOAEL was derived from an occupational-lifetime integrated respirable dust concentration of manganese dioxide expressed as mg manganese/m^3 × years. Effects were based on impairment of neurobehavioral function as a result of occupational exposure to manganese dust. The uncertainty factor accounts for the use of a LOAEL (10), the protection of sensitive individuals (10), and data base limitations reflecting both the less-than-chronic exposure time and the lack of developmental data, as well as potential but unquantified differences in the toxicity of different forms of manganese (10).

3.3 OTHER ROUTES OF EXPOSURE

3.3.1 Acute Toxicity

3.3.1.1 Human

Taylor and Price (1982) reported a clinical case of acute pancreatitis that resulted from hemodialysis of a patient with a solution contaminated with manganese. Symptoms, which appeared within one hour from the start of dialysis, included severe vomiting, epigastric pain, increased heart rate, and increased blood pressure. The dialysis was discontinued after 30 minutes. The dialysate was found to contain 715 μmol/L manganese sulfate. The diagnosis of acute pancreatitis was made the next day (day 2). The patient suffered from a high fever, persistent abdominal pain, weakness, and a drop in serum calcium from day 2 through day 4. A high leukocyte count persisted past day 14 after which it returned to normal. The serum manganese levels were found to be 4.55, 1.71, and 0.65 μmol/L on days 2, 3, and 6, respectively. The patient was discharged free from abdominal pain and on a normal diet 31 days after manganese exposure.

3.3.1.2 Animal

A number of experiments have indicated that manganese is considerably more toxic by injection. LD_{50} values of 121 and 255 mg/kg in mice were determined for manganese dichloride given by intraperitoneal and intramuscular injections, respectively. LD_{50} values for the tetrahydrate are 190 mg/kg for intraperitoneal injection in mice and 138 mg/kg for intraperitoneal injection in rats. The latter value can be compared to the LD_{50} of 1484 mg/kg for oral exposure in rats as discussed in Sect. 3.1.1.2 (Lewis and Sweet 1984).

Histological changes in the lungs of rats have been reported to occur within minutes after the injection of 40 mg/kg of manganese dioxide. An injection of manganese dioxide followed by a like injection of manganese dichloride resulted in severe congestion and pulmonary edema that was often fatal (Stokinger 1981).

Brain damage has been induced in rats by direct injection of manganese into the brain (Sloot et al. 1994). Intrastriatal injections of manganese chloride produced dose-dependent (0.05–0.8 μmol) dopamine depletion and time-dependent (0.4 μmol) calcium accumulation.

Sprague-Dawley or Osborne-Mendel rats injected intraperitoneally with 40 mg manganese/kg (given as manganese dichloride) became hyperglycemic within 2 hours. The increase in blood sugar was accompanied by a decrease in plasma insulin. Manganese was rapidly concentrated in the liver (45 minutes) and the pancreas (15 minutes). Blood sugar values returned to control levels within 8 hours after the injection (Baly et al. 1985).

Intravenous injection of manganese dichloride to male New Zealand white rabbits caused a dose-responsive decrease in mean arterial pressure (3–100 μM/kg), an increase in heart rate (0.3–100 μM/kg), and alterations in the electrocardiogram. These effects were not attenuated by coadministration of $CaCl_2$ (Lee 1993).

3.3.2 Subchronic Toxicity

3.3.2.1 Human

Information on the subchronic toxicity of manganese in humans by other routes of exposure was unavailable.

3.3.2.2 Animal

Intraperitoneal injections to mice of 5 mg manganese chloride/kg/day, 5 days/week, for 9 weeks did not alter the cholinergic muscarinic receptor density or the dissociation constant of ^{3}H-quinuclidinyl benzilate in the striatum, frontal cortex, or hippocampus brain regions (Villalobos et al. 1994).

3.3.3 Chronic Toxicity

Information on the chronic toxicity of manganese in humans or animals by other routes of exposure was unavailable.

3.3.4 Developmental Toxicity

3.3.4.1 Human

Information on the developmental toxicity of manganese in humans by other routes of exposure was unavailable.

3.3.4.2 Animals

Swiss mice were given doses of manganese (II) chloride tetrahydrate by subcutaneous injection at doses of 0, 2, 4, 8, or 16 mg/kg/day on gestation days 6–15. Maternal body weight gain and feed consumption were significantly reduced in the 8 and 16 mg/kg groups as compared to controls. An increase was observed in the number of late resorptions in the 4, 8, and 16 mg/kg groups; a reduction in fetal body weights and an increase in delayed ossification of the bones of the skull and sternebra were observed in fetuses from the 8 and 16 mg/kg groups (Sánchez et al. 1993).

3.4 TARGET ORGANS/CRITICAL EFFECTS

3.4.1 Oral Exposures

3.4.1.1 Primary target(s)

1.Central nervous system: Initial symptoms include headache, insomnia, disorientation, speech disturbances, memory loss, and acute anxiety. Prompt removal of the affected person from the manganese source usually results in reversal of most of these symptoms. Continued subchronic to chronic exposure can result in motor difficulties, tremors, difficulty walking, and exaggerated reflexes similar to Parkinsonism. These later stages of toxicity are apparently secondary effects and are not reversible although the manganese concentrations in the tissues decrease to normal levels upon removal from the manganese source.

2.Reproductive system: Chronic feeding studies in rats have indicated decreased fertility results from chronic manganese exposure. Similar subchronic studies in monkeys have shown degenerative changes in the seminiferous tubules.

3.4.1.2 Other targets

Blood: An iron-responsive anemia can occur with orally-induced manganese toxicity possibly due to an interference with intestinal iron absorption by excess manganese.

3.4.2 Inhalation Exposures

3.4.2.1 Primary target(s)

1.Central nervous system: The same symptoms are seen as with acute to chronic oral exposure (Sect. 3.4.1.1). Since individuals are occupationally exposed to dust containing manganese during mining and manufacturing and to metal fumes during welding, inhalation is by far the most common route of exposure for manganese toxicity.

2.Respiratory system: Subchronic to chronic symptoms include an increased incidence of colds, bronchitis, and pneumonia. Dyspnea during exercise, decreased vital capacity, and decreased forced expiratory vital capacity have also been reported.

3.Reproductive system: Decreased fertility has been seen in subchronic to chronic human inhalation studies.

3.4.2.2 Other targets

1.Pancreas: Manganese is known to concentrate in the pancreas and alter insulin production in rats. Acute pancreatitis has been reported in humans following accidental intravenous exposure.

2.Immune system: Evidence in animal studies suggests that acute manganese exposure by inhalation results in an immunosuppression. The observed increase in the incidence of respiratory infections with subchronic to chronic human exposure to manganese substantiates this observation.

4. CARCINOGENICITY

4.1 ORAL EXPOSURES

Information on the carcinogenicity of manganese by the oral route in humans or animals was unavailable.

4.2 INHALATION EXPOSURES

Information on the carcinogenicity of manganese by the inhalation route in humans or animals was unavailable.

4.3 OTHER ROUTES OF EXPOSURE

4.3.1 Human

Information on the carcinogenicity of manganese by other routes of exposure in humans was unavailable.

4.3.2 Animal

DBA/1 mice were injected subcutaneously or intraperitoneally with 0.1 mL of a 1% aqueous solution of manganese chloride twice weekly for 6 months. An increased number of lymphosarcomas developed in the treated animals compared with the controls. The tumor incidence/number of animals in the dose group was: 24/36, 16/39, and 16/66 for the subcutaneous, intraperitoneal, and water control groups, respectively. The tumors appeared earlier in the treated groups as well (DiPaolo 1964).

Groups of 10 male and 10 female each of strain A Strong mice were injected intraperitoneally with 0, 6, 15, or 30 mg/kg manganous sulfate 3 times/week for 7 weeks. The animals were sacrificed and examined for tumors after 30 weeks. An increase in the average number of pulmonary adenomas/mouse was apparent at the mid and high doses but the increase was significant only at the high dose (Stoner et al. 1976).

F344 rats and female Swiss mice were injected intramuscularly with manganese powder and manganese dioxide (10 mg each). The F344 rats were also injected with manganese^{2+} acetyl-acetonate. No differences were seen in tumor incidence between treated and control animals with manganese powder or manganese dioxide; however, there was a significant increase in injection site fibrosarcomas with the manganese^{2+} acetylacetonate (Furst 1978).

Witschi et al. (1981) injected female A/J mice intraperitoneally with 80 mg/kg methylcyclopentadienyl manganese tricarbonyl. Cell proliferation was produced in the lungs but no increase in tumor incidence was seen.

4.4 EPA WEIGHT-OF-EVIDENCE

Classification D—Not classifiable as to human carcinogenicity (EPA 1995)
Basis—Existing studies are inadequate to assess the carcinogenicity of manganese.

4.5 CARCINOGENICITY SLOPE FACTORS

No slope factors for carcinogenicity have been calculated.

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