FaxBack # 11628

UNITED STATES ENVIRONMENTAL PROTECTION AGENCY
WASHINGTON, D.C. 20460

JULY 12, 1991

EPA Region 5 Records Ctr.
275100

Citizen,

Thank you for your letter of September 24, 1990, requesting information on potassium permanganate. I am providing answers for your questions 3, 6, 7, 8, and 9, which raise issues handled by the Environmental Protection Agency's (EPA's) Office of Solid Waste. The remaining questions regard EPA's Office of Toxic Substances.

**3. How can these chemicals (potassium permanganate and manganese), used in the quantities that they are being used in the garment industry, be allowed to be dumped in sanitary landfills?** In general, materials may be disposed of in non-hazardous waste landfills if they are not specifically listed as hazardous waste and/or do not exhibit any hazardous characteristic regulated under 40 CFR 261.21-261.24 (ignitability, reactivity, corrosivity, or toxicity). Since spent permanganate materials are already reduced, they are not likely to be powerful oxidizers and, therefore, are not likely to exhibit a hazardous waste characteristic. Other manganese compounds are not oxidizers and probably may be disposed of in a municipal or industrial landfill.

**6. How can the Texas Water Commission say this chemical is exempt under CFR 261.4? The sludge from the wastewater treatment has a heavy concentration of manganese dioxide which, is a hazardous, toxic chemical. Can this sludge be dumped in a sanitary landfill?** The Texas Water Commission is referring to the fact that industrial discharges from an identifiable source ("point-source" discharges), such as those from a textile operation, are excluded from regulation as a solid or hazardous waste (as in 261.4(a)(2)) when they are regulated under Section 402 of the Clean Water Act (CWA). Such discharges are specifically excluded under Section 1004(27) of the Resource Conservation and Recovery Act (RCRA). This reflects the intent of Congress to avoid duplicating regulation of certain waste streams. Facilities that have point-source discharge permits under the CWA must meet specific criteria given to them by state or local authorities (an example of which may be the Texas Water Commission). These criteria are set to protect the environment, the treatment system in a publicly owned treatment works (POTW), or the health and safety of employees of POTWs.

Sludges from the treatment of these wastewaters at the discharging facility or at the POTW are subject to regulation as solid wastes. If these sludges do not exhibit a characteristic of hazardous waste as described in the answer to question 3, they may be disposed of in a non-hazardous waste landfill. Given that POTWs do not generally wish to be saddled with a hazardous waste disposal problem, they often require the discharging

industries to remove potentially hazardous constituents from their wastewaters. In that way, the POTW can more or less guarantee that its own treatment sludges will not exhibit a characteristic of hazardous waste.
You may note that potassium permanganate is used for wastewater treatment in several industrial sectors, since it is an effective oxidizing agent and less toxic than comparable chromium-based compounds.

**7. How can the Texas Water Commission state that the pumice stones contaminated with manganese dioxide are classified as a Class II waste?** The classification of manganese dioxide by the Texas Water Commission as a "Class II" waste is a matter of state law.

**8. How can the pumice stones contaminated with manganese dioxide be sold to nurseries for use in flower beds?** Pumice stones containing manganese compounds are sold to nurseries for use in flower beds as a commercial product. Apparently, manganese is an essential soil nutrient and is ubiquitous in the environment.

**9. Do all three conclusions from the Texas Water Commission Report make sense when you evaluate the documentation and the dates of the newspaper articles?** The first two conclusions concerning continued monitoring of facilities and the prevalence of using a stone-washed process for garment processing are under the purview of the Texas Water Commission. I can confirm their conclusion that industrial discharges are exempt under 40 CFR 261.4 (and under RCRA section 1004(27)), as discussed under question 6, above.

I hope that this information is useful. We appreciate your interest in the environment.

Sincerely yours,

Sylvia K. Lowrance, Director
Office of Solid Waste

# 7.0 HAZARD IDENTIFICATION

## 7.1 Human Effects

### 7.1.1 Case Reports

***General Population***

A number of investigators reported the toxicity of total parenteral (TPN) manganese in humans, especially on changes in brain MRI scans (Ejima et al., 1992; Fell et al., 1996; Mirowitz and Westrich, 1992). These studies emphasize the difference in the effect of oral and parenteral manganese. When administered parenterally, manganese bypasses the typical excretory mechanisms in the gastrointestinal tract and liver and accumulates in the brain (Mirowitz and Westrich, 1992).

In addition, there are a limited number of case reports describing the outcome of exposure following accidental or intentional ingestion of manganese from potassium permanganate, a strong oxidizing agent. Unspecified toxic effects were reported following ingestion of 2.4 mg/kg-day potassium permanganate (0.83 mg Mn/kg-day) by a woman of unknown age and health status. This information was reported in a 1933 French study cited in NIOSH (1984), and was not available for review. Dagli et al. (1973) described a case in which oral ingestion of a 300 mg dose of potassium permanganate (104 mg Mn) resulted in extensive damage to the distal stomach and pyloric stenosis. Mahomedy et al. (1975) described two cases of methemoglobinemia following ingestion of an unspecified amount of potassium permanganate which had been prescribed by African tribal healers. Development of methemoglobinemia likely reflects the chemical oxidation of heme iron.

Holzgraefe et al. (1986) reported neurological effects in an adult man who ingested approximately 1.8 mg/kg-day of potassium permanganate (0.62 mg Mn) for 4 weeks. A syndrome similar to Parkinson's disease developed after about 9 months. However, data in this study are reported to be insufficient to establish causation (U.S. EPA, 1993). Bleich et al. (1999) published a 14-year follow-up of this case report. Most of the symptoms originally noted (including rigor, muscle pain, hypersomnia, increased libido, sweating, fatigue, and anxiety) had improved, and the study authors noted that there appeared to be no evidence for progression of the parkinsonian syndrome as described by others (Huang et al., 1998).

Additional case reports suggest the potential for manganese toxicity following oral exposure, but are difficult to assess quantitatively. One report involved a 59-year-old male who was admitted to the hospital with classical symptoms of 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." No source of manganese exposure was identified for this individual. Exposure may have resulted from the use of large quantities of vitamin and mineral supplements for 4 to 5 years. No quantitative data were provided in this report.

Manganese intoxication was described in a 62 year-old male who received total parenteral nutrition that provided 2.2 mg of manganese (form not stated) daily for 23 months (Ejima et al., 1992). This level corresponds to a dose of approximately 0.023 mg Mn/kg-day for a 70 kg adult. The patient's whole blood manganese concentration was elevated. The patient exhibited dysarthria, mild rigidity, hypokinesia with masked face, a halting gait, and severely impaired postural reflexes, and the diagnosis of this condition was parkinsonism. 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 (U.S. EPA, 1993).

*Sensitive Populations*

Individuals with impaired liver function or bile flow may represent potentially sensitive subpopulations for manganese exposure. For example, Hauser et al. (1994) reported changes in brain MRI scans in liver failure patients which were identical to those observed in cases of manganese intoxication. The patients (n=3) examined exhibited bilateral signal hyperintensity in the globus palladi and substantia nigrae in T1-weighted MRI and increased blood manganese levels but had no history of increased exposure to manganese. Hauser et al. (1994) postulated that impaired elimination of normal dietary manganese could result in manganese intoxication. Devenyi et al. (1994) described a case study of an 8 year-old girl with Alagille's syndrome, an autosomal dominant disorder characterized by neonatal cholestasis, intrahepatic bile duct paucity, and end-stage liver disease. The patient exhibited a stable peripheral neuropathy, and for a period of 2 months exhibited episodic, dystonic posturing, and cramping of her hands and arms. Whole blood manganese level was elevated (27 μg/L, in contrast to a normal range of 4 to 14 μg/L), and cranial T1-weighted magnetic resonance imaging (MRI) revealed symmetric, hyperintense globus pallidi and subthalamic nuclei. These findings were interpreted as indications of manganese toxicity. Following liver transplantation, the patient's manganese levels returned to normal, her neurological symptoms improved, and MRI results appeared normal. The interpretation of this series of events was that: 1) progressive liver dysfunction resulted in inadequate excretion of manganese into the bile, 2) subsequent accumulation of manganese resulted in neurotoxicity, and 3) liver transplantation restored biliary excretion and alleviated the symptoms.

Manganese has been identified as a possible etiologic agent in the occurrence of neurological symptoms associated with hepatic encephalopathy (a brain disorder associated with chronic liver damage). Medical evidence supporting an etiologic role has been summarized by Layrargues et al. (1998). Patients with chronic liver disorders such as cirrhosis experience a high incidence of extrapyramidal symptoms resembling those observed in cases of occupational manganism. Manganese concentration increases in the blood and brain of patients with chronic liver disease and these changes are accompanied by pallidal hyperintensity on T1-weighted MRI. Autopsy data from ten patients who died in hepatic coma indicate that manganese levels are 2- to 7-fold higher in the globus pallidus of cirrhotic patients when compared to the general population. Liver transplantation normalizes the pallidal MR signals and results in the disappearance of extrapyramidal symptoms. Conversely, transjugular intrahepatic portosystemic shunting (a procedure which increases the systemic availability of manganese) intensifies the pallidal MR signal and results in deterioration of neurological function.

### 7.1.2 Short-term Studies

*General Population*

Kawamura et al. (1941) reported health effects resulting from the ingestion of manganese-contaminated well water by 25 individuals. The source of contamination was identified as leachate from approximately 400 dry cell batteries buried near the drinking water well. Chemical analysis also revealed high levels of zinc in the well water. The length of exposure to manganese was estimated to be 2 to 3 months. The concentration of manganese in the well was approximately 14 mg Mn/L (as $Mn_3O_4$) when analyzed 7 weeks after the first case appeared. This level corresponds to a dose of approximately 28 mg Mn/day (assuming a daily water intake of 2 L), or 0.5 mg Mn/kg-day (for a 60 kg adult). When reanalyzed 1 month later, the manganese concentration had decreased by about 50%. Based on these measurements, retrospective extrapolation suggests that the initial exposure level may have been 28 mg Mn/L or higher. Assuming a daily water intake of 2 L, and an additional manganese intake from food of at least 2 mg/day, this represents a dose of at least 58 mg Mn/day. This intake of manganese is about 10 to 20 times the level considered to be safe and adequate by the Food and Nutrition Board of the National Research Council (NRC, 1989). Assuming a body weight of 60 kg for an adult, this intake level corresponds to a dose of 0.93 mg Mn/kg-day from drinking water. No information on dietary intake was available.

Health effects reported by Kawamura et al. (1941) included lethargy, increased muscle tonus, tremor and mental disturbances. Out of 25 people examined, 15 had symptoms. Five cases were considered severe, 2 cases were categorized as moderate and 8 cases were described as mild. The most severe symptoms were observed in the elderly. Younger people were less affected, and symptoms of intoxication were absent in young children (age 1 to 6 years). Three deaths occurred, including one from suicide. Upon autopsy, the concentration of manganese in the brain of one person was found to be 2 to 3 times higher than concentrations measured in two control autopsies. Extreme macroscopic and microscopic changes were seen in the brain tissue, especially in the globus pallidus. The authors also reported elevated levels of zinc in the well water, but concluded that the zinc appeared to have no relation to the observed symptoms or tissue pathology. This conclusion was largely based on the observation of morphological changes in the corpus striatum which are characteristic of manganese poisoning, but are not a feature of zinc poisoning.

While toxicity in the Kawamura et al. (1941) study is attributed to manganese, several aspects of the observed health effects are inconsistent with traits of manganism observed in humans following chronic inhalation exposure. Inconsistencies include the rapid onset of symptoms and rapid progression of the disease. Two adults who came to tend the members of one family developed symptoms within 2 to 3 weeks. The course of the disease was very rapid, progressing in one case from initial symptoms to death in 3 days. Some survivors recovered prior to significant decreases in the manganese concentration of the well water which resulted when the batteries that caused the contamination were removed from the site. This pattern contrasts with the longer latency period and irreversible damage caused by inhalation exposure to manganese.

These observations may represent differences in the pharmacokinetics of ingested versus inhaled manganese, but there is little information to support this conclusion. Although these individuals were clearly exposed to high levels of manganese, it is possible that additional factors contributed to the observed effects (U.S. EPA, 1993; ATSDR 2000).

***Sensitive Populations***

Study data for sensitive populations were not identified in the materials reviewed for preparation of this document.

### 7.1.3 Long-Term and Epidemiological Studies

***General Populations***

Kondakis et al. (1989) conducted an epidemiologic study of manganese in drinking water in northwest Greece. Three areas with different levels of manganese in the drinking water supply were chosen for this study. Area A had manganese concentrations of 3.6 to 14.6 μg/L, Area B had concentrations of 81.6 to 252.6 μg/L, and Area C had concentrations of 1,800 to 2,300 μg/L. The total population in the study areas ranged from 3,200 to 4,350 people. The study included only individuals over the age of 50 drawn from a random sample of 10% of all households. The sample sizes were 62, 49, and 77 for areas A, B, and C, respectively. The study authors reported that "all areas were similar with respect to social and dietary characteristics," but few details were provided. Kondakis et al. (1989) determined whole blood and hair manganese concentrations in samples collected from study participants. The mean concentration of manganese in hair was 3.51, 4.49 and 10.99 μg/g dry weight for areas A, B and C, respectively. Concentrations in hair differed significantly between areas C and A ($p < 0.001$). No significant differences in whole blood manganese levels were observed among the three areas. However, manganese concentration in blood is not considered to be a reliable indicator of manganese exposure (U.S. EPA, 1993).

Kondakis et al. (1989) also administered a neurological examination which evaluated the presence and severity of 33 symptoms (e.g., weakness/fatigue, gait disturbances, tremors, dystonia) in all subjects. The results of the neurological examination were expressed as a composite score. A higher neurological score indicated an increased frequency and/or severity of the 33 evaluated symptoms. Results for the three geographic areas are summarized in Table 7-1. Mean scores for both sexes combined were 2.7 (range 0–21) for Area A; 3.9 (range 0–43) for Area B; and 5.2 (range 0–29) for Area C. The authors indicated that the difference in mean scores for Area C versus Area A was statistically significant (Mann-Whitney Test, $z = 3.16$, $p = 0.002$, for both sexes combined), suggesting neurologic impairment in people living in Area C. In a subsequent analysis, logistic regression indicated a significant difference between areas A and C when both age and sex were taken into account (Kondakis, 1990).

**Table 7-1. Mean Neurological Scores of Residents in Three Areas of Northwest Greece with Different Levels of Manganese in Drinking Water (range is given in parentheses).**

| Subject | Area A (3.6–14.6 μg Mn/L) | Area B (81.6–252.6 μg Mn/L) | Area C (1,800–2,300 μg Mn/L) |
|---|---|---|---|
| Males | 2.4 (0–21) | 1.6 (0–6) | 4.9 (0–29) |
| Females | 3.0 (0–18) | 5.7 (0–43) | 5.5 (0–21) |
| Both | 2.7 (0–21) | 3.9 (0–43) | 5.2 (0–29) |

Source: Kondakis et al. (1989)

Limitations to the Kondakis study have been noted by ATSDR (2000). These include: 1) lack of clearly detailed descriptions of neurological signs and symptoms that reportedly increased following manganese exposure, and 2) failure to describe procedures for avoiding bias when evaluating subjective neurological scoring parameters. An additional shortcoming of this study is the lack of quantitative exposure data (U.S. EPA, 1996a). The individuals examined by Kondakis et al. (1989) also consumed manganese in their diet. The initial estimate of dietary intake was 10 to 15 mg/day based on high intake of vegetables (Kondakis, 1990). This figure was subsequently revised to an estimate of 5 to 6 mg Mn/day (Kondakis, 1993), but data were not provided to substantiate this estimate. Lack of dietary intake and water consumption data prevents determination of a quantitative dose-response relationship for manganese toxicity in this study. Nevertheless, this study raises concern for adverse neurological effects at estimated doses that are not far from the range of essentiality (U.S. EPA, 1996a).

Although conclusive evidence is lacking, some investigators have linked increased intake of manganese with violent behavior. Gottschalk et al. (1991) found significant increases in the level of manganese in the hair of convicted felons ($1.62 \pm 0.173$ ppm in prisoners compared with $0.35 \pm 0.020$ ppm in controls). The study authors suggested 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." The number of potential variables indicates that caution should be exercised in interpretation of these data.

Results from studies of an Aboriginal population in Groote Eylandt have been cited as additional evidence for a relationship between elevated manganese exposure, violent behavior, and adverse health effects. The soil on this Australian island is exceptionally high in manganese (40,000 to 50,000 mg/kg), and the fruits and vegetables grown in the region are reported to contain elevated concentrations of manganese. High alcohol intake, anemia, and a diet deficient in zinc and several vitamins (Florence and Stauber, 1989) may contribute to increased uptake and retention of manganese. The proportion of arrests in this native population is the highest in Australia, and high incidences of stillbirths and congenital malformations, as well as a high occurrence of Parkinson-like neurobehavioral syndrome, have been observed (Cawte and Florence, 1989; Kilburn, 1987). Clinical symptoms consistent with manganese intoxication are

present in about 1% of the inhabitants. Quantitative data on oral intake have not been reported, but elevated concentrations of manganese have been determined in the blood and hair of the Aborigines (Stauber et al., 1987). However, Stauber et al. (1987) did not find a correlation between hair levels of manganese and the severity of neurological symptoms in individuals.

A study of the neurologic status of the Aborigines in Groote Eylandt identified two general syndromes. One syndrome is characterized by muscle atrophy and weakness, while the other is characterized by ataxia and oculomotor disturbances (Kilburn, 1987). Although an association of adverse health effects with elevated manganese exposure is suggested by these observations, the small population of Groote Eylandt and the difficulty in defining an appropriate control population have prevented the identification of statistically significant trends (U.S. EPA, 1993).

Several of the studies above utilized hair analysis as a method for estimating exposure to manganese. ATSDR (2000) has outlined several potential limitations to the use of hair analysis. The normal cycle of hair growth and loss restricts its usefulness to a period of a few months following exposure. External contamination of hair by dye, bleaching agents, or other materials may result in values which are not representative of absorbed doses. The affinity of manganese for pigmented tissue may result in variation of manganese concentration with hair color.

Goldsmith et al. (1990) investigated a Parkinson's disease cluster within southern Israel. The prevalence of the disease was increased among persons 50 to 59 years old, suggesting an early onset of the disease. Well water and soils in the region reportedly contained high levels of manganese, although no quantitative data were provided. In addition, the manganese-containing fungicide Maneb was commonly used in the area. However, several factors limit the use of this study for evaluation of the human health effects of excess manganese exposure. Lack of environmental concentration data prevented reliable estimation of exposure rates. Potentially confounding factors included the high levels of aluminum, iron, and other metals in the soil and water, and the use of the herbicide paraquat in the area (ATSDR, 2000). Paraquat is structurally related to *N*-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP), a piperidine derivative which causes irreversible symptoms of parkinsonism in humans.

Vierrege et al. (1995) investigated the neurological impact of chronic manganese exposure via drinking water in a cross-sectional study of two proband cohorts in rural northern Germany. The study population was drawn from the county Herzogtum Lauernburg in the northernmost province of Germany. This region is characterized by agricultural and forestry activities but no steel or mining industry. Many of the residents of this area draw their drinking water from wells, and by law, the well water is routinely monitored for chemicals and bacteria. A survey was conducted in 1991 and was combined with a cross-sectional investigation of a randomly selected group of right-handed residents aged 40 years or older who had used their wells as the primarily source of drinking water for a minimum of 10 years (range 10 to 40 years). Complete documentation of manganese monitoring results for six years prior to the investigation was required for study eligibility. Participants were assigned to two groups on the basis of manganese concentration in their well water. Group A included individuals who continually ingested well

water containing between 0.300 and 2.160 mg Mn/L. Group B included individuals whose well water manganese concentration had never exceeded 0.050 mg/L. Detailed information on medical history, employment history, diet, alcohol consumption, drug use and smoking was collected by interview. Individuals in Group A were matched to individuals in Group B with respect to age, sex, nutritional habits, and drug intake. Criteria for exclusion from the study included history of employment in the steel industry, adherence to dietary restrictions, history of CNS-relevant drug use, diabetes mellitus, history of stroke, or treatment for psychiatric disorders. Conditions that could affect performance on the neurological assessment tests (neurorthopedic impairment of hand-finger function or poor vision) were also grounds for exclusion from the study.

A total of 164 eligible subjects was identified. Of these, 49 subjects were excluded for failure to meet the health or water monitoring criteria. Group A included 41 subjects (21 male and 20 female) with a mean age (± standard deviation) of 57.5 ± 10.3 years (range 41 to 84 years). Group B included 74 subjects with a mean age of 56.9 ± 11.8 years (range 41 to 86) years. No dietary differences were evident between the two groups. Neurological status was assessed by experienced personnel blinded to the group status of the subjects. Each participant was evaluated for neurotoxicological symptoms by use of a modified German version of a standardized symptoms list. Signs of parkinsonism were evaluated by the Columbia University Rating Scale (CURS). Fine motor ability (each hand) was assessed using a conventional apparatus ("Motorische Leistungsserie," MLS) and application of aiming, steadiness, line pursuit, and tapping tests. Manganese status was evaluated by determination of manganese in blood. The concentration of manganese in hair or nails was not determined.

The results of neurological evaluations are summarized in Table 7-2. There were no significant differences between groups for the mean item scores on the standardized symptoms list or the CURS. MLS test results were obtained for 36 group A subjects (18 male and 18 female, mean age 56.4 ± 8.4 years, range 41 to 72 years) and 67 Group B subjects (35 men and 32 women, mean age 55.1 ± 9.9 years, range 41 to 72 years). Results of participants older than 72 years were not included in the statistical analysis of MLS data because normative information from the general population have an upper age limit of 72 years. No significant differences were observed between groups for any test when results were standardized to age-corrected values. Mean blood manganese concentrations were 8.5 ± 2.3 μg/L and 7.7 ± 2.0 μg/L for groups A and B, respectively. The blood manganese values did not differ significantly and both fell within the normal range for the general (non-occupationally exposed) population. Separate analyses for possible confounding factors did not reveal differences in clinical or instrumental test outcomes related to high or low consumption of alcohol, mineral water, coffee, tea, tobacco, vegetables, or fruit. Where cases of parkinsonism (n = 3) were encountered in this study, they occurred in the low exposure group (Group B) and were considered to be typical Parkinson's disease and thus unrelated to manganese exposure. The authors of this study concluded that there was no evidence of an association between consumption of high concentrations of manganese in well water and neurological impairment (including those suggestive of parkinsonism).

**Table 7-2. Mean Neurological Scores of Residents in Germany Exposed to Different Levels of Manganese in Well Water.**

| Assessment | Measure | Exposure Group | |
|---|---|---|---|
| | | Group A (High) | Group B (Low) |
| Neurotoxicological Symptom Questionnaire | Item Number | 3.2 ± 3.0[a] | 3.9 ± 3.1 |
| CURS Parkinsonism | Item Number | 1.2 ± 1.0 | 1.7 ± 2.0 |
| MLS Aiming | Duration (sec) | 104.8 ± 9.1[b] | 102.9 ± 10.0 |
| MLS Steadiness | Errors (number) | 103.9 ± 103.9 | 103.1 ± 7.9 |
| | Duration of errors (sec) | 100.8 ± 10.6 | 100.2 ± 10.5 |
| MLS Line Pursuit | Errors (number) | 106.4 ± 7.6 | 106.6 ± 8.0 |
| | Duration of errors (sec) | 102.3 ± 8.1 | 103.1 ± 10.6 |
| | Total duration (sec) | 104.3 ± 12.6 | 100.7 ± 15.5 |
| MLS Tapping | Rate (number) | 103.1 ± 7.2 | 103.9 ± 10.5 |

[a] Mean ± standard deviation
[b] MLS test results are for right hand

Three potential limitations related to the ecologic design of this investigation were noted by Vieregge et al. (1995). First, the investigators could not control for possible migration of subjects with manganese-induced neurological disorders from the study area prior to the investigation. However, Vieregge et al. (1995) stated on the basis of inquiries and general experience in the region that a migration effect was unlikely to be significant. Second, although possible confounding by several dietary items or groups was evaluated and found to be non-evident, confounding effects of nutrition (particularly in subjects working outside their home residence) could not be completely excluded. Finally, blood manganese levels are thought to primarily reflect current body burden of manganese rather than exposure.

Iwami et al. (1994) reported that the incidence of motor neuron disease (MND) in a small town in Japan was positively correlated with a significantly increased manganese concentration in local rice and a low magnesium concentration in the drinking water. This study, however, did not provide good estimates of overall exposure to manganese in either the control population or the population with MND.

Adverse neurological effects (decreased performance in school and in neurobehavioral exams of the WHO core test battery) were reported in 11- to 13-year-old children who were exposed to excess manganese through ingestion of well water and from wheat fertilized with sewage water (He et al. 1994; Zhang et al. 1995). The exposed group consisted of 92 children pair-matched to 92 controls from a nearby area. The groups were matched for age, sex, grade, family income level, and parental education level; further, both groups lived on farms. The average manganese concentration of the drinking water of the exposed group was 0.241 mg/L compared to the control level of 0.04 mg/L. Although the study authors had drinking water data from a 3-year period, it was not clear how long the children were exposed prior to the study. Further, the exposure data were not well-characterized; therefore it was not possible to establish a cause-effect link between ingestion of excess manganese and preclinical neurological effects in children.

***Sensitive Populations***

Study data for sensitive populations were not identified in the materials reviewed for preparation of this document.

### 7.1.4 Beneficial Effects

Manganese is a naturally-occurring element that is required for normal physiological functioning in all animal species (U.S. EPA, 1996a). Manganese plays a role in bone mineralization, metabolic regulation, protein and energy metabolism, protection of cells from oxidative stress, and synthesis of mucopolysaccharides (ATSDR, 2000). Many of these roles are achieved by participation of manganese as a catalytic or regulatory factor for enzymes, including hydrolases, dehydrogenases, kinases, decarboxylases and transferases. In addition, manganese is a structural component of the metalloenzymes mitochondrial superoxide dismutase, pyruvate carboxylase, and liver arginase. Additional information on the biochemical and nutritional roles of manganese in human health is available in Wedler (1994) and Keen et al. (1999). At present, the optimal levels of oral manganese exposure have not been well defined for humans (Greger, 1999).

Overt signs of manganese deficiency have been demonstrated in multiple animal species (Keen et al., 1999). Biochemical effects observed in manganese-deficient animals include alterations in carbohydrate, protein, and lipid metabolism. Physiological outcomes associated with deficiency include impaired growth (Smith, 1944), skeletal abnormalities (Amdur et al., 1944; Strause et al., 1986), impaired reproductive function in females, and testicular degeneration in males (Boyer et al., 1942). The molecular basis for these effects has not been established with certainty, but may be related to the participation of manganese in numerous enzymatic reactions. In addition, the effect of manganese deficiency on mitochondrial superoxide dismutase activity has functional consequences. Manganese-deficient rats experience more oxidation of mitochondrial membranes of the heart and more formation of conjugated dienes than manganese-adequate rats (Malecki and Greger, 1996). In another study, Gong and Amemiya (1996) observed ultrastructural changes suggestive of oxidative damage in the retinas,-of rats fed a manganese-deficient diet for 12 to 30 months

Manganese is ubiquitous in human foods, and outright manganese deficiency has not been observed in the general population. However, observations reported by Doisy (1973) and Friedman et al. (1987) indicate that manganese is an essential element for humans. Doisy (1973) reported a decreased level of clotting proteins, decreased serum cholesterol, reddening of black hair, retarded growth of hair and nails, and scaly dermatitis in a subject inadvertently deprived of manganese. Friedman et al. (1987) administered a manganese-deficient diet to seven men for 39 days. Five of the seven subjects exhibited dermatitis at the end of the manganese-deficient period. The development of dermatitis was attributed to decreased activity of manganese-requiring enzymes that are required for skin maintenance. The symptoms cleared rapidly when manganese was restored to the diet.

## 7.2 Animal Studies

This section presents the results of manganese toxicity studies in animals. The first four subsections provide study results by duration of exposure. In general, acute studies are those which address exposure durations of 24 hours or less. Short-term studies have exposure durations greater than 24 hours but less than approximately 90 days. The exposure duration of subchronic studies is typically 90 days, and chronic studies are those in which exposure is longer than 90 days. Some studies may fall into more than one exposure category since they measure impacts over several exposure periods. The discussion of acute, short-term, subchronic and chronic studies summarizes observed toxicological effects on all body systems. The remaining subsections of Section 7.2 provide toxicological data related to specific organ systems and types of endpoints, including neurotoxicity, developmental and reproductive toxicity, and carcinogenicity.

### 7.2.1 Acute Toxicity

***Oral Exposure***

$LD_{50}$ values determined for selected manganese compounds are summarized in Table 7-3. Oral $LD_{50}$ values among the water soluble manganese compounds ranged from 400 to 475 mg Mn/kg for manganese chloride, and from 379 to 810 mg Mn/kg for potassium permanganate. An $LD_{50}$ of 836 mg Mn/kg was reported for manganese acetate.

Age may be a factor in susceptibility to acute manganese toxicity. Kostial et al. (1978) found that $MnCl_2$ produced the greatest oral toxicity in the youngest and oldest groups. Roth and Adleman (1975) proposed that the increased susceptibility of older rats may result from a decrease in adaptive responsiveness, which is characteristic of the aging process. Increased susceptibility of younger rats may reflect high intestinal absorption and body retention of manganese.

**Table 7-3. $LD_{50}$ Values for Manganese Compounds.**

| Compound | Species | Route | $LD_{50}$ (mg Mn/kg) | Reference |
|---|---|---|---|---|
| Manganese acetate | rat | oral | 836 | Smyth et al. (1969) |
| Manganese chloride | rat | oral | 425 | Shigan and Vitvickaja (1971) |
| | rat | oral | 475 | Kostial et al. (1978) |
| | rat | oral | 410 | Holbrook et al. (1975) |
| | mouse | oral | 450 | Shigan and Vitvickaja (1971) |
| | guinea pig | oral | 400 | Shigan and Vitvickaja (1971) |
| | rat | i.p. | 38 | Franz (1962); Holbrook et al. (1975) |
| | mouse | i.p. | 56 | Franz (1962); Holbrook et al. (1975) |
| | mouse | i.v. | 16 | Larsen and Grant (1997) |
| Manganese dioxide | rat | oral | 2,197 | Holbrook et al. (1975) |
| Manganese sulfate | mouse | i.p. | 44 | Bienvenu et al. (1963) |
| Manganese sulfate, tetrahydrate | mouse | i.p. | 64 | Yamamoto and Suzuki (1969) |
| Manganese nitrate | mouse | i.p. | 56 | Yamamoto and Suzuki (1969) |
| Methylcyclo-pentadienyl manganese tricarbonyl (MMT) | rat | oral | 10 | Hanzlik et al. (1980) |
| | rat | oral | 12 | Hinderer (1979) |
| | rat | oral | 12 | Hysell et al. (1974) |
| | mouse | oral | 48 | Hinderer (1979) |
| Potassium permanganate | mouse | oral | 750 | Shigan and Vitvickaja (1971) |
| | rat | oral | 379 | Smyth et al. (1969) |
| | rat | oral | 750 | Shigan and Vitvickaja (1971) |
| | guinea pig | oral | 810 | Shigan and Vitvickaja (1971) |

i.p. = intraperitoneal
i.v. = intravenous

*Parenteral Exposure*

Manganese compounds administered by parenteral routes generally result in mortality at lower doses. $LD_{50}$ values for the intraperitoneal route ranged from 14 to 64 mg Mn/kg. Franz (1962) and Bienvenu et al. (1963) conducted comparative intraperitoneal toxicity studies, and found that manganese is less toxic than many other metals. Jonderko (1965) found increased serum calcium and decreased inorganic phosphorous in rabbits exposed intramuscularly to 3.5 mg Mn/kg. Details on the compound and the duration of exposure were not available.

Baxter et al. (1965) measured physiological parameters in manganese-treated rats weighing 100 to 550 g. Measurements were made 1 to 72 hours after subcutaneous administration of 5 to 150 mg of manganese as $MnCl_2$ in saline. Levels of hemoglobin, hematocrit, and mean corpuscular volume were significantly increased in rats receiving 150 mg Mn/kg. A measurable response in these parameters occurred at 50 mg Mn/kg, while the peak increase in these parameters occurred at 12 and 18 hours after dosing. The maximum response occurred at 170 to 300 mg Mn/kg. Necrotic changes were noted in hepatic tissue 18 hours after a single dose of 170 mg Mn/kg.

Pancreatic endocrine function is affected by acute manganese exposure. Baly et al. (1985) injected rats intraperitoneally with 40 mg Mn/kg. Manganese injection resulted in a decrease in plasma insulin levels, an increase in plasma glucose levels, and a transitory increase in glucagon concentration.

Larsen and Grant (1997) administered a single intravenous dose of 150, 200, 300, or 400 μmol/kg manganese chloride in saline to male mice (5/group). These doses correspond to 8.2, 11, 16, and 22 mg Mn/kg, respectively. These study authors reported an $LD_{50}$ value of 300 μmol/kg (16 mg Mn/kg).

### 7.2.2 Short-Term Studies

*Oral Exposure*

Matrone et al. (1959) orally administered 2,000 ppm manganese as $MnSO_4 \cdot H_2O$ to 6-month-old anemic rabbits for 6 weeks. The investigators also administered 125 ppm Mn as $MnSO_4 \cdot H_2O$ to anemic newborn pigs for 27 days. In each case, the investigators observed decreased hemoglobin content in the blood of treated animals. Hemoglobin depression in baby pigs fed up to 2,000 ppm manganese was overcome by a dietary supplement of 400 ppm iron.

Kimura et al. (1978) provided rats with diets supplemented with 564 mg/kg of manganese as $MnCl_2$ for 3 weeks. Assuming a food consumption factor of 0.05 above the dietary background, this corresponds to a daily dose of 28 mg Mn/kg-day. The study authors reported that brain serotonin levels were decreased in manganese-treated rats. Monoamine oxidase activity was unchanged, but L-amino-acid decarboxylase activity in the brain was decreased by manganese

treatment. Histopathological analysis of the brain was not conducted. Blood serotonin levels were increased in treated rats, and this change was accompanied by decreased blood pressure.

Shukla et al. (1978) administered a dose of 16 mg $MnCl_2 \cdot 4H_2O$/kg (4.4 mg Mn/kg) in drinking water (dose calculated by investigators) to rats for 30 days and evaluated the effect on hepatic enzyme activity. Treated rats revealed significantly decreased succinic dehydrogenase, alcohol dehydrogenase, and β-amylase activity when compared with controls. In contrast, manganese exposure resulted in significantly increased activities of monoamine oxidase (MAO), adenosine triphosphatase, arginase, glutamate-pyruvate transaminase (= alanine aminotransferase, or ALT), ribonuclease, glucose-6-phosphatase, and α-amylase activity in the livers of treated rats.

Hietanen et al. (1981) also studied the effect of manganese on hepatic and extrahepatic enzyme activities. Male Wistar rats were exposed to 0.5% Mn (as $MnCl_2$) in the drinking water for 1, 4, or 6 weeks. Assuming an average body weight of 0.35 kg and average water consumption of 0.049 L/day (U.S. EPA, 1986d), this corresponds to an exposure of 0.7 mg Mn/kg-day. Changes in the activity of several enzymes, including aryl hydrocarbon hydroxylase, ethoxycoumarin *O*-deethylase, and epoxide hydrase, were observed at 1 week but not at 6 weeks. Enzyme activities were increased in the liver, and decreased in the intestines and kidney.

In a 14-day oral exposure study, NTP (1993) administered diets containing 0, 3,130, 6,250, 12,500, 25,000, or 50,000 ppm manganese sulfate monohydrate to F344 rats (5/sex/dose). All rats survived the exposure period. Statistically significant differences in manganese-treated rats included reduced body weight gain (57% decrease) and final body weight (13% decrease) in the high-dose males when compared to the control group. Decreased leukocyte and neutrophil counts and reduced liver weight were observed in high-dose males and females. The high-dose groups also exhibited diarrhea during the second week of the study. Manganese concentrations in the livers of animals receiving the 50,000 ppm diet were more than twice those of the controls. The NOAEL and LOAEL values based on decreased weight gain (males) and hematological changes were approximately 650 and 1,300 mg Mn/kg-day, respectively.

NTP (1993) also administered diets containing 0, 3,130, 6,250, 12,500, 25,000, or 50,000 ppm manganese sulfate monohydrate to $B6C3F_1$ mice (5/sex/dose) for 14 days. However, study animals were poorly randomized at the beginning of the study, and no effects clearly attributable to manganese exposure were identified.

***Parenteral Exposure***

Singh et al. (1974; 1975) administered 6 mg Mn/kg-day (as $MnSO_4 \cdot 4H_2O$) intraperitoneally to male IRTC rats for 25 days. Histopathological analysis of the livers revealed mild congestion of central veins and sinusoids, and some focal necrosis in treated animals.

Scheuhammer and Cherian (1983) reported toxic effects in the pancreas resulting from intraperitoneally injected manganese. The exposure duration was 30 days. Adverse effects included a pancreatitis-like reaction. The authors suggested that this reaction was potentiated by

the presence of manganese in the peritoneal cavity, and would not occur as readily with manganese administered by the oral route.

Khandelwal et al. (1984) administered 6 mg Mn/kg-day (as $MnCl_2 \cdot 4H_2O$) intraperitoneally to male IRTC rats for 28 days. Activity of succinic dehydrogenase and cytochrome oxidase in liver tissue were decreased after 28 days of manganese treatment.

Khan et al. (1997) administered 16 mg/kg-day $MnCl_2 \cdot 4H_2O$ in saline intravenously to male beagle dogs (3/group). Treatment duration was up to 4 hours/day for 4 days. Two of the three dosed animals were in moribund condition, and were sacrificed for ethical reasons (one on day 3 and one on day 4). The third treated dog died on day 4. Symptoms prior to death included vomiting, diarrhea, tremors, lethargy, reduced food intake, reduced blood pressure with reflex tachycardia, and severe hepatotoxicity.

### 7.2.3 Subchronic Studies

***Oral Exposure***

Mitochondria-rich organs, such as the liver and pancreas, are hypothesized to be most affected by excess manganese exposure. Wassermann and Wassermann (1977) reported ultrastructural changes of the liver cells in rats exposed to 200 mg/L of manganese chloride in their drinking water for 10 weeks. Assuming water consumption of 0.049 L/day and an average body weight of 0.35 kg (U.S. EPA, 1986d), this level of exposure corresponds to an average daily dose of approximately 12 mg Mn/kg-day. Increased metabolic activity was inferred from an increased amount of rough endoplasmic reticulum, the occurrence of multiple rough endoplasmic cisternae and prominent Golgi apparatus, and large Golgi vesicles filled with osmiophilic particles in the biliary area of the liver cell. The authors attributed this apparent increase in metabolic activity to biochemical processes related to the nutritional requirement for manganese, and homeostatic processes triggered by increased exposure. They noted that other observed liver effects, including the presence of glycogenosomes in the biliary area, groups of collagen fibers in the Disse's spaces, and degenerative changes in some centrilobular liver cells, may either be direct toxic phenomena or secondary responses to the effect exerted by manganese on other target tissues. ATSDR (2000) evaluated these data and designated 12 mg Mn/kg-day as the NOAEL in this study.

Carter et al. (1980) exposed young, iron-deficient rats to 400 to 3,550 ppm Mn as $Mn_3O_4$ for 32 weeks (route not specified). Manganese treatment resulted in decreased hemoglobin levels.

Leung et al. (1982) administered 1,000, 10,000, or 20,000 mg $MnCl_2 \cdot 4H_2O$/L in drinking water to female Wistar rats. Exposure was initiated at conception by administration of manganese-containing drinking water to the dams, and continued through age 60 days. The estimated doses were 38.9, 389, and 778 mg Mn/kg-day (U.S. EPA, 1993). Treated rats exhibited liver necrosis and ultrastructural alterations that resembled human cholestasis. A LOAEL of 38.9 mg Mn/kg-day was identified in this study based on hepatic necrosis.

In a 13-week study, NTP (1993) administered diets containing 0, 1,600, 3,130, 6,250, 12,500, or 25,000 mg/kg manganese sulfate monohydrate above basal levels to F344 rats (10/sex/dose). The concentration of manganese in the control diets was approximately 92 mg/kg. Mean daily intake of manganese sulfate monohydrate ranged from 98 mg/kg-day (32 mg Mn/kg-day) for the low-dose to 1,669 mg/kg-day (542 mg Mn/kg-day) for the high-dose males. For females, the range was 114 mg/kg-day (37 mg Mn/kg-day) for the low-dose group and 1,911 mg/kg-day (621 mg Mn/kg-day) for the high-dose group. No rats died during the study, and no clinical or histopathology findings were attributed to manganese exposure. Females receiving diets with ≥6,250 mg/kg manganese sulfate experienced decreased body weight gain. Absolute and relative liver weights were decreased in males receiving diets with ≥1,600 mg/kg, and in females in the highest dose group only. Hematological effects were also reported. All groups of exposed males exhibited a significantly increased neutrophil count. Lymphocyte counts were decreased in males receiving ≥6,250 mg/kg in the diet and females in the three highest dose groups. The low dose of 1,600 mg/kg (about 32 mg Mn/kg-day) was identified as the LOAEL for this study, based on effects on liver weight and neutrophil counts in male rats.

In a concurrent 13-week study, NTP (1993) administered diets containing 0, 3,130, 6,250, 12,500, 25,000, or 50,000 mg/kg manganese sulfate monohydrate above basal levels to $B6C3F_1$ mice (10/sex/dose). The concentration of manganese in the control diets was approximately 92 mg/kg. Mean daily intake of manganese sulfate monohydrate ranged from 328 mg/kg-day (107 mg Mn/kg-day) for the low-dose to 8,450 mg/kg-day (2,746 mg Mn/kg-day) for the high-dose group. No deaths were attributed to manganese exposure. All groups of male mice and female mice in the highest dose group exhibited significantly decreased body weight gain. Relative and absolute liver weights were decreased in males in the highest dose group. Both sexes receiving the 50,000 mg Mn/kg diet exhibited decreased hematocrit and hemoglobin concentration. The NTP report suggests that these findings may indicate microcytic anemia, which may have resulted from a sequestration or deficiency of iron. Males receiving ≥25,000 ppm also exhibited significantly lower leukocyte counts, although this finding was of questionable relevance to manganese exposure. No clinical findings were attributed to manganese exposure. The LOAEL for this study was 3,130 mg/kg-day (107 mg Mn/kg-day), based on significantly decreased body weight gain in male mice.

Komura and Sakamoto (1991) supplemented mouse diets with different chemical forms of manganese. Male mice (8/group) were exposed either to a control diet containing 130 mg Mn/kg, or a diet supplemented with an additional 2,000 mg Mn/kg as $MnCl_2 \cdot 4H_2O$, $Mn(CH_3COO)_2 \cdot 4H_2O$, $MnCO_3$, or $MnO_2$. Assuming an average food consumption of 13% of body weight, the average daily dose from the control diet was approximately 17 mg Mn/kg-day, while the average daily dose from the manganese enriched diet was 276 mg Mn/kg-day. The duration of treatment was 100 days. The mice were tested for spontaneous motor activity after 30 days. Blood and tissues were analyzed at the termination of the experiment. No significant difference in food intake among groups was seen. Body weight gain and red and white blood cell count was decreased in groups that received $Mn(CH_3COO)_2 \cdot 4H_2O$ or $MnCl_2$. Motor activity was reduced in the $MnCO_3$ group. Tissue manganese concentrations in groups receiving supplemental

manganese was 2 to 3 times that of controls. A LOAEL of 276 mg Mn/kg-day was identified in this study based on decreased weight gain and hematological effects.

***Parenteral Exposure***

Suzuki et al. (1975) administered 250, 500, or 1,000 mg of $MnO_2$ in saline to monkeys (*Macaca mullata*) by subcutaneous injection. Injections were given once a week for 9 weeks. The study authors reported a body weight of 4 kg for monkeys used in the study. Estimated time-averaged doses correspond to 5.6, 11, and 23 mg Mn/kg-day. At autopsy, manganese-treated monkeys had irregular arrangement of hepatic cords and lymphocytic infiltration.

### 7.2.4 Neurotoxicity

Occupational studies of miners, industrial workers, and agricultural workers have established injury to the central nervous system as the chief health effect associated with inhalation exposure to manganese. High level exposure by this pathway typically results in a suite of neurological effects collectively termed manganism. Chronic manganism associated with inhalation exposure is characterized by an extrapyramidal syndrome with symptoms that are somewhat similar to those observed in Parkinson's disease. One characteristic difference is the "cock-walk"of the manganism patient, in which the patient walks on his toes with his spine erect and elbows flexed. Further, manganism patients do not often exhibit the "resting tremor" that Parkinson's patients do, and they have a propensity for losing their balance and falling backwards. The clinical course of manganism occurs in three phases: an initial phase of subjective and nonspecific symptoms; an intermediate phase of evolving neurological symptoms related to speech, dexterity, facial expression, and movement; and an established phase characterized by persistent, often irreversible neurological deficits (Chang, 1996). While MRI scans of the brains of humans and non-human primates exposed to excess manganese indicate that the metal deposits in the globus pallidus and to a lesser extent in the substantia nigra, degenerative lesions are limited to the globus pallidus (Calne et al. 1994). An important question in the evaluation of health effects associated with manganese in drinking water is whether similar neurotoxicological effects occur following exposure by the oral route.

***Oral Exposure***

Table 7-4 summarizes studies of the neurotoxic effects of manganese exposure. A single study exists for evaluation of manganese exposure in primates by the oral route. Gupta et al. (1980) administered 25 mg $MnCl_2 \bullet 4H_2O$/kg orally to four male rhesus monkeys daily for 18 months. This level is equivalent to an average daily dose of 6.9 mg Mn/kg-day. Animals were maintained on monkey pellets, two bananas/day, and tap water. The monkeys developed muscular weakness and rigidity of the lower limbs. Histological analysis revealed degenerated neurons in the substantia nigra and scanty neuromelanin granules in some of the pigmented cells.

Bonilla and Diez-Ewald (1974) noted that chronic exposure of rats to manganese chloride produces a marked decrease in brain biogenic amines, particularly dopamine.

Singh et al. (1979) administered manganese (16 mg/kg in a 10% sucrose solution) alone or in combination with ethanol to groups of 20 male albino rats for 30 days. Exposure to manganese alone led to a 72% increase in manganese concentration in the brain (3.13 μg/g dry weight versus 1.82 μg/g for controls). This outcome was not altered by ethanol exposure. There were no morphologic changes in the brain tissue of any group. Significant alterations in activity were reported for several brain enzymes. Manganese exposure resulted in significant increases in monoamine oxidase ($p < 0.001$), adenosine triphosphatase ($p < 0.001$), ribonuclease ($p < 0.001$), and glutamate-oxaloacetate transaminase (= aspartate aminotransferase, or AST; $p < 0.001$). Significant decreases were observed for succinic dehydrogenase ($p < 0.02$ and deoxyribonuclease ($p < 0.001$). Concurrent exposure to ethanol resulted in a synergistic effect with some enzymes and an antagonistic effect with others. No mechanism was proposed to explain the pattern observed in the presence of ethanol.

Chandra et al. (1979) evaluated the neurological effects of manganese in mice exposed from birth. Neonatal mice were initially exposed by nursing from dams given 5 mg/mL $MnCl_2$ in their drinking water. After weaning at 25 days, the mice received manganese in their drinking water. Average exposures to manganese were determined to be 0.030 mg Mn/day for 60 days, 0.036 mg Mn/day through the 90$^{th}$ day, 0.075 mg Mn/day through the 120$^{th}$ day and 0.090 mg Mn/day for the interval between 150 and 180 days. Assuming a body weight of 0.03 kg at adulthood, the average daily dose at the termination of the experiment was approximately 3 mg Mn/kg-day. Elevated levels of striatal dopamine, norepinephrine, and homovanillic acid were observed at 60 and 90 days of age, with a concomitant increase in spontaneous locomotor activity. Exposure past 90 days did not influence motor activity. Chandra et al. (1979) proposed that the hyperactivity observed in these mice was an early behavioral effect of excess manganese exposure that resulted from elevated dopamine and norepinephrine levels. The study authors further suggested that the observed hyperactivity may be comparable to the psychomotor excitement observed in the early stages of human manganism.

Gray and Laskey (1980) found that dietary exposure to 1,100 mg/kg manganese (as $Mn_3O_4$) in rats for 2 months produced only reduced reactive locomotor activity. Assuming a body weight of 0.35 kg, this level of exposure corresponds to an average daily dose of 55 mg Mn/kg-day. Deskin et al. (1980) studied neurochemical alteration induced by manganese chloride in neonatal CD rats. Rats were intubated with daily doses of 1, 10, or 20 mg Mn/kg-day from birth to 24 days old. Neurochemical components were subsequently analyzed in the hypothalamus and corpus striatum. Administration of 10 and 20 mg Mn/kg-day resulted in significantly elevated manganese concentrations in both regions, but neurochemical alterations were observed only in the hypothalamus. These alterations included a decrease in dopamine concentration and turnover. The highest dose of manganese also resulted in a significant decrease in hypothalamic tyrosine hydroxylase activity, and an increase in monoamine oxidase activity. Visible signs of toxicity were not observed in any group.

Deskin et al. (1981) intubated rats with daily doses of 10, 15 or 20 mg $MnCl_2 \cdot 4H_2O$/kg from birth to 24 days old. The authors reported a significant elevation of serotonin levels in the hypothalamus, but not the striatum, following exposure to 20 mg Mn/kg.

**Table 7-4. Neurological Effects of Oral Exposure to Manganese.**

| Species | Compound | Route | Dose | Duration | CNS Effects | | | Reference |
|---|---|---|---|---|---|---|---|---|
| | | | | | Behavioral | Histological | Biochemical | |
| Mouse | $MnCl_2$ | drinking water | 3 µg $MnCl_2$/mL | 6 months | + | NS | + | Chandra et al. (1979) |
| Mouse | $MnCl_2$ | diet | 1% $MnCl_2$ (1 month), 4% $MnCl_2$ (5 months) | 6 months | NS | NS | + | Gianutsos and Murray (1982) |
| Mouse | $MnO_2$ | diet | 1 mg $MnO_2$/g | 7.5 months | - | NS | NS | Morganti et al. (1985) |
| Rat | $MnCl_2$ | drinking water | 5 mg $MnCl_2$/mL | 7 months | NS | NS | + | Bonilla and Diez-Ewald (1974) |
| Rat | $MnCl_2$ | gavage | 1, 10, 20 mg Mn/kg-day | Birth–24 days old | NS | NS | + | Deskin et al. (1980) |
| Rat | $MnCl_2 \bullet 4H_2O$ | gavage | 10, 15, 20 mg Mn/kg-day | Birth–24 days old | NS | NS | + | Deskin et al. (1981) |
| Rat | $MnCl_2 \bullet 4H_2O$ | drinking water | 1 mg $MnCl_2 \bullet 4H_2O$/mL | 12 months | + | NS | + | Chandra and Shukla (1981) |
| Rat | $MnCl_2 \bullet 4H_2O$ | drinking water | 1 mg $MnCl_2 \bullet 4H_2O$/mL | 28 months | NS | NS | + | Leung et al. (1981) |
| Rat | $MnCl_2 \bullet 4H_2O$ | drinking water | 1 mg $MnCl_2 \bullet 4H_2O$/mL | over 2 years | NS | NS | + | Lai et al. (1981) |
| Rat | $MnCl_2 \bullet 4H_2O$ | drinking water | 1 mg $MnCl_2 \bullet 4H_2O$/mL | 4 months | NS | - | + | Lai et al. (1982a) |

**Table 7-4 (continued)**

| Species | Compound | Route | Dose | Duration | CNS Effects | | | Reference |
|---|---|---|---|---|---|---|---|---|
| | | | | | Behavioral | Histological | Biochemical | |
| Rat | $MnCl_2$ | gavage | 150 mg Mn/kg | 42 days | + | NS | + | Kristensson et al. (1986) |
| Rat | $MnCl_2 \bullet 4H_2O$ | drinking water | 1 mg $MnCl_2 \bullet 4H_2O$/mL | 65 weeks | + | NS | NS | Nachtman et al. (1986) |
| Rat | $MnCl_2 \bullet 4H_2O$ | drinking water | 4,360 mg Mn/L | 60–265 days | NS | NS | + | Eriksson et al. (1987) |
| Rat | $MnCl_2$ | gavage | 25, 50 mg $MnCl_2 \bullet 4H_2O$ /kg-day | 14 or 21 days | NS | NS | + | Kontur and Fechter (1988) |
| Rat | $MnCl_2 \bullet 4H_2O$ | gavage | 0.357 Mn mg/kg-day | 30 days | + | NS | NS | Oner and Senturk (1995) |
| Rat | Not specified | 10% sucrose | 16 Mn mg/kg | 30 days | NS | NS | + | Singh et al. (1979) |
| Monkey | $MnCl_2 \bullet 4H_2O$ | diet | 25 mg $MnCl_2 \bullet 4H_2O$/kg | 18 months | + | + | NS | Gupta et al. (1980) |

Notes: NS = Not studied
Source: U.S. EPA, 1993

Chandra and Shukla (1981) exposed male albino rats to 1,000 mg/L $MnCl_2 \cdot 4H_2O$ (436 mg Mn/L) in drinking water. Assuming water consumption of 0.049 L/day and an average adult body weight of 0.35 kg, this level of exposure corresponds to an average daily dose of 61 mg Mn/kg-day. Levels of catecholamines, homovanillic acid, manganese, and the activity of monoamine oxidase were determined in the corpus striatum at time intervals up to 360 days. The investigators found initial increases in dopamine, norepinephrine, and homovanillic acid levels. This initial increase was followed by a period of normal levels. After 300 days, a decrease in all levels was observed. These changes were not correlated with the tissue concentration of manganese. The authors suggested that the decreased locomotor activity observed during later periods of manganese exposure may be related to lowered dopamine and norepinephrine levels in the brain, and that this stage of chronic toxicity may correspond to the later neurologic phase of motor dyskinesia in humans. Ali et al. (1981) conducted concurrent behavioral studies, and found an initial increase in spontaneous locomotor activity followed by a decrease during later periods of manganese exposure.

Lai et al. (1981) exposed female Wistar rats to 1,000 mg/L $MnCl_2 \cdot 4H_20$ (280 mg Mn/L) in drinking water. Exposure was initiated at mating. Pups were exposed *in utero* by administration of manganese in drinking water to dams via maternal milk during nursing, and by inclusion in drinking water after weaning. Groups of rats were exposed to manganese for over 2 years and were either 2 months or 24 to 28 months of age at examination. Assuming a body weight of 0.35 kg and water consumption of 0.049 L/day, the average daily dose for rats at adulthood was approximately 39 mg/kg-day. The brains were dissected and analyzed for activity of glutamic acid decarboxylase (GAD), choline acetyltransferase (ChAT), and acetylcholinesterase (AChE). GAD, ChAT, and AChE are neurochemical markers for the GABA and cholinergic systems, and had previously been implicated in manganese toxicity (Sitaramayya et al., 1974; Bonilla, 1978a, b). Adverse effects of chronic manganese exposure on the activity of GAD, ChAT, or AChE were not apparent in 2-month-old rats. The study authors reported that lifetime exposure to manganese produced effects that counteracted age-related decreases in GAD, ChAT, and AChE.

Leung et al. (1981) analyzed the same groups of rats used by Lai et al. (1981) for monoamine oxidase (MAO) activity. MAO is a key enzyme in oxidative degradation of neurotransmitter amines. The only effect observed following exposure of 2-month-old rats to manganese was a small decrease in the neurotransmitter serotonin in the cerebellum. No significant differences were observed in manganese-treated 24- to 28-month-old rats.

Lai et al. (1982a) examined the effects of manganese exposure on male Wistar rats. The rats were initially exposed to manganese *in utero*. Following weaning, the rats were exposed to 1,000 mg $MnCl_2 \cdot 4H_2O$/L (280 mg Mn/L) in drinking water for either 70 to 90 days or 100 to 120 days after birth. Assuming an adult weight of 0.35 kg, and water consumption of 0.049 L/day, this level corresponds to a dose of approximately 39 mg/kg-day. Levels of dopamine, noradrenaline, serotonin, and choline were determined. A significant decrease was seen in the uptake of dopamine by synaptosomes isolated from the hypothalamus, striatum and midbrain in 70- to 90-day-old rats. No effect was observed in the 100- to 120-day-old rats. Choline levels

were higher in 70- to 90-day-old-exposed rats and lower in 100- to 120-day-old-exposed rats when compared with controls. The authors suggested that this finding may reflect involvement of both the dopaminergic and cholinergic systems in manganese toxicity. They concluded that, although the rat may not serve as an ideal model for understanding the neurotoxic effects of manganese, neurochemical effects are discernible when analyses are made at the appropriate period.

Lai et al. (1982b) investigated the effect of manganese exposure on the developmental profile of acetylcholinesterase activity in different regions of the brain. Female Wistar rats were exposed to manganese chloride tetrahydrate provided in drinking water at a concentration of 1,000 mg/L. Exposure was initiated at conception. Male offspring were weaned onto drinking water containing 1,000 mg/L manganese chloride tetrahydrate and exposed for up to 60 days. Enzyme activity in the cerebral cortex, striatum, midbrain, pons and medulla, hypothalamus, and cerebellum was determined at 5, 12, 20, 30, and 60 days after birth. The developmental profile of the enzyme differed in the various regions. Activity was detected earlier in the more caudal regions, except in the cerebellum where there was no increase. Exposure to manganese from conception did not influence the developmental profile of acetylcholinesterase activity.

Gianutsos and Murray (1982) studied changes in the concentrations of dopamine and GABA in mice exposed to $MnCl_2$ in the diet. A 1% concentration of $MnCl_2$ was administered in the diet to an unspecified number of male CD-1 mice for 1 month. This level of exposure corresponds to 568 mg Mn/kg-day. The concentration was increased to 4% for an additional 5 months. During this period, the average daily dose was 2,272 mg Mn/kg-day. Dopamine content in the striatum and in the olfactory tubule at 6 months was reduced compared with controls ($p < 0.05$). GABA content of the striatum was increased ($p < 0.05$). Apparent increases in the substantia nigra area and a decrease in the cerebellum were not statistically significant. No changes in neurotransmitter levels were observed when assays were conducted after 1–2 months of exposure.

Morganti et al. (1985) conducted a behavioral study using male ICR strain Swiss mice. The mice were fed powdered Charles River's RMH 300 diet that contained 1,000 mg $MnO_2$/kg. This dietary concentration corresponds to approximately 632 mg Mn/kg. The mice consumed 5 g of food daily. Assuming a body weight of 0.03 kg (U.S. EPA, 1986d), this level of exposure corresponds to an average daily dose of 105 mg/kg-day. Neurobehavioral evaluation began after 16 weeks of feeding and continued at 2-week intervals for 30 weeks. The endpoints evaluated were open field and exploratory behavior, passive avoidance learning, and rotarod performance (a measurement of balance and coordination). Multivariate analysis of variance (2 treatments and 8 samples by week of exposure) was used to test for intergroup differences. No significant behavioral differences were apparent in any treatment group. In contrast, Morganti et al. (1985) observed significant effects in mice exposed to manganese by inhalation for 7 hours/day, 5 days/week, at levels greater than 50 mg Mn/$m^3$. The duration of exposure was 16 to 32 weeks. This level of inhalation exposure was considered by the authors to be comparable to the oral exposure.

Ali et al. (1985) studied the effect of dietary protein on manganese neurotoxicity. Rats received either a normal diet (21% casein) or a low protein diet (10% casein). Half of each dietary group served as a control while the other half received $MnCl_2 \bullet 4H_2O$ (3,000 mg Mn/L) in the drinking water for 90 days. Assuming an adult body weight of 0.35 kg and water consumption of 0.049 L/day, this corresponds to an average daily dose of 420 mg/kg-day. The low-protein diet was associated with decreased levels of brain dopamine (DA), norepinephrine (NE), and serotonin. Manganese exposure resulted in a marked increase in DA and NE levels, which were more pronounced in the low-protein group. A significant decrease in serotonin levels following manganese exposure occurred only in the low-protein group. Weaned $F_1$ pups of treated rats exhibited the same pattern of effects. The study authors concluded that protein deficiency can increase vulnerability of rats to the neurotoxic effects of manganese.

Nachtman et al. (1986) studied the behavioral effects of chronic manganese exposure. Male Sprague-Dawley rats were administered 0 or 1 mg $MnCl_2 \bullet 4H_2O$/mL in drinking water for 65 weeks. Assuming a body weight of 0.35 kg and water consumption of 0.049 L/day, this corresponds to an average daily dose of 39 mg Mn/kg-day. The treatment did not result in any change in body weight. The manganese-exposed rats exhibited a significant increase in locomotor activity during weeks 5 to 7. However, the effects were transient, and by 8 weeks the activities had returned to control levels. Treated rats examined at 14 and 29 weeks were found to be more responsive to the effects of *d*-amphetamine (a locomotor stimulant that works primarily by releasing dopamine) than were controls. There was no difference between manganese-treated rats and controls at 41 or 65 weeks. The investigators concluded that manganese exposure may result in a transient increase in dopaminergic function, as evidenced by increased spontaneous and *d*-amphetamine-stimulated locomotor activity.

Kristensson et al. (1986) studied the effect of manganese on the developing nervous system of young rats. Starting at 3 days of age, Sprague-Dawley rats received a daily dose of 150 mg Mn/kg-day (as $MnCl_2$) by gavage. The treatment continued until the rats reached 44 days of age. At days 15 to 22 there was a large but transient increase (7- to 40-fold) of manganese in the brain, and the rats displayed a rigid and unsteady gait. By 44 days, the rats appeared normal and brain manganese levels had declined to approximately 3 times the control level. Histological analysis revealed no abnormalities in the brains of manganese-exposed rats. Axonal growth and the axon-myelin relation were normal. A second group of rats was treated for 15 days. At this time point, half the rats were sacrificed and half were maintained untreated until sacrifice at 60 days of age. The rats were subsequently analyzed for brain content of dopamine and its metabolites, including 2,4-dihydroxyphenylacetic acid and homovanillic acid (HVA), and serotonin and its major metabolite 5-hydroxyindolacetic acid. Only HVA levels in the hypothalamus and striatum were affected by manganese treatment. Significantly decreased HVA levels were seen at the 15-day sacrifice. Similar decreases in rats treated for 15 days and allowed to recover until 60 days of age were not observed. The investigators concluded that divalent manganese has a very low degree of toxicity for the developing nervous system in rats, but that longer-term exposure to more active manganese compounds may cause severe damage to certain neurologic pathways. In addition, the investigators emphasized that rodents may not be

appropriate for comparison with primates. Unpublished studies, where monkeys exposed to manganese oxide developed severe motor disturbances, were cited as the basis for this conclusion.

Eriksson et al. (1987) studied the effect of long-term manganese exposure on biogenic amine levels in rat brain. Starting at 20 days of age, groups of male Sprague-Dawley rats were provided with drinking water containing 10 g/L manganese chloride ($MnCl_2 \bullet 4H_20$) for 60, 100, 165, or 265 days. This concentration corresponds to 2,777 mg Mn/L. Assuming an adult body weight of 0.35 kg and water consumption of 0.049 L/day, this level of exposure results in an average daily dose of approximately 390 mg Mn/kg-day. There were no clinical signs of toxicity. Following 60 days of exposure, manganese concentration in the striatum was estimated to be 1.3 to 2.0 mg/kg, in contrast to control levels of 0.4 to 0.5 mg/kg. Levels of dopamine, 3,4-dihydroxyphenylacetic acid, homovanillic acid, serotonin and 5-hydroxyindoleacetic acid were determined in discrete regions of the caudate-putamen. Rats exposed for 60 and 165 days showed significantly increased levels of dopamine (DA) and 3,4-dihydroxyphenylacetic acid, but these alterations were not seen in rats exposed for 100 or 265 days. This suggests an increased synthesis and turnover of dopamine that is reversible, even with continuous manganese exposure. This study identifies a LOAEL of 390 mg Mn/kg-day based on increased levels of dopamine at 60 days.

Kontur and Fechter (1988) intubated neonatal Long-Evans rats daily with 0, 25, or 50 mg/kg-day manganese chloride ($MnCl_2 \bullet 4H_20$) for 14 or 21 days. These doses correspond to 6.9 and 13.9 mg Mn/kg-day. The level of manganese in the brain was increased at both 14 and 21 days, but was greater at 14 days. Monoamine and metabolite levels were not altered in any brain region by manganese treatment. The study authors suggested that the different results reported by different laboratories may be attributable to species or strain differences, the dosing regimen or vehicle, the route of administration, or the time points chosen for testing. These data suggest a NOAEL of 6.9 mg Mn/kg-day for this study, based on the absence of effect on monoamine levels.

These collective studies suggest that preclinical neurological effects are possible in the human following oral exposure; however, there are dissimilarities in the spectrum of responses between rodent and primate models of toxicity that preclude a determination of the oral dose range that might be expected to induce these preclinical effects. Further, conflicting data concerning responses in humans and confounding factors in the limited human epidemiological studies prevent determination of any dose-response effect in humans exposed to manganese excesses via ingestion.

***Parenteral Exposure***

Although deficiencies exist in experimental design (U.S. EPA, 1984), primate studies by parenteral routes of exposure have reported extrapyramidal signs and histologic lesions similar to those described in humans. Mella (1924) treated four rhesus monkeys with $MnCl_2$ for 18 months. Two monkeys served as controls. The treated monkeys received gradually increasing doses of $MnCl_2$ by intraperitoneal injection on alternate days. The doses started at 5 mg and reached a maximum of 25 mg per injection. The monkeys exhibited uncontrolled, involuntary movements

(chorea) followed by rigidity, disturbances of motility, fine hand tremors, and finally, contracture of the hands. Histological changes were reported in the putamen, the caudate, and the globus pallidus.

Suzuki et al. (1975) exposed monkeys subcutaneously to 39.5, 79.0 or 158.0 mg Mn/kg as $MnO_2$ once a week for 9 weeks and found the latency of neurologic signs (tremors, excitability, choreiform movement, loss of equilibrium, and contracture of hands) inversely related to cumulative dose. Signs appeared earlier when higher doses were administered, but the severity of symptoms was not completely dose-related. The estimated daily doses in this experiment were 5.6, 11, and 23 mg Mn/kg-day.

Olanow et al. (1996) reported damage to the globus pallidus and substantia nigra in monkeys that were dosed intravenously with doses as low as 4.4 mg Mn/kg/week (for 7 weeks). The brain damage was accompanied by neuromuscular toxicity including bradykinesia, rigidity, facial grimacing, and abnormal posturing of the limbs. Newland and Weiss (1992) administered repeated daily intravenous doses of manganese to Cebus monkeys so that the monkeys received cumulative doses of 5 or 10 mg/kg for 450 days. The dosings were separated by at least one week. The authors observed that single intravenous doses of 5 or 10 mg Mn/kg-day resulted in a significant increase in the number of incomplete responses of dosed monkeys to a spring-loaded test device that measured physical exertion through a rowing motion. The increase in incomplete responses occurred within a few days after dosing began. Further, action tremor was observed in the monkeys who had received cumulative doses of 40 mg/kg or higher; however, dystonia was never observed.

Eriksson et al. (1992) subcutaneously injected two monkeys with 0.4 g doses of $MnO_2$ (0.253 g Mn) in water. Eleven doses were administered over 4 months, followed by a final dose at 12 months. Both animals developed an unsteady gait and exhibited hypoactive behavior. PET scans indicated that degeneration of dopaminergic nerve endings occurred following Mn intoxication.

Additional studies have examined the neurotoxic effects of manganese administered by parenteral routes in non-primate species. Mustafa and Chandra (1971) and Chandra (1972) reported paralysis of the hind limbs in rabbits administered 169 mg Mn/kg (as $MnO_2$) intratracheally. The paralysis developed after a period of 18 to 24 months. Examination of the of affected animals brains showed widespread neuronal loss and neuronal degeneration in the cerebral cortex, caudate nucleus, putamen, substantia nigra and cerebellar cortex. These findings are reminiscent of the characteristic histopathologic and neurologic consequences of manganism found in exposed workers (U.S. EPA, 1993). A marked decrease in brain catecholamine levels and related enzyme activity was also noted.

Histopathologic evaluations of exposed rats by Chandra and Srivastava (1970), Chandra et al. (1979) and Shukla and Chandra (1976) found scattered neuronal degeneration in the cerebral and cerebellar cortex. Daily intraperitoneal administration of 2 to 4 mg Mn/kg for $\leq$120 days appeared to be the threshold for the appearance of microscopic lesions. These studies also

demonstrated an association between the maximum number of degenerated neurons and maximum manganese concentration in the brain.

Scheuhammer (1983) treated male Sprague-Dawley rats intraperitoneally for 30 days with either 3.0 mg Mn/kg or an equal volume of 0.9% NaCl. Assuming an average adult body weight of 0.35 kg, this treatment corresponds to an average daily dose of 8.6 mg Mn/kg-day. Following sacrifice, the pancreas was removed, fixed in 10% buffered formalin, and subsequently processed for light microscopy. Significant pathological changes were observed in pancreatic tissue from manganese-exposed rats. The changes were characterized by a pancreatitis-like reaction consisting of expanded interacinar spaces, a thickened connective tissue capsule with invaginations of fibrotic connective tissue septa extending into the body of the gland, the presence of an inflammatory infiltrate of neutrophils, lymphocytes, macrophages, and the separation of groups of acini from the body of the pancreas with occasional destruction of acinar cells. Other peritoneal organs did not exhibit pathological changes. This study suggests that intraperitoneally injected Mn(II) exerts a selective toxicity on pancreatic tissue. Therefore, the study author cautioned against use of intraperitoneal injection as the route of administration for chronic Mn neurotoxicity studies.

Brouillet et al. (1993) administered 0, 0.5, 1, or 2 μmol of $MnCl_2$ in deionized water to male rats by a single intrastriatal injection. Assuming a body weight of 0.35 kg for an adult rat, these doses correspond to 0, 0.077, 0.171, and 0.314 mg Mn/kg. Each treatment group contained 9 to 10 rats. The lowest dose produced a significant reduction in dopamine, but had no effect on the other neurochemical markers examined. Doses of 0.171 and 0.314 mg Mn/kg produced a reduction in dopamine levels, changes in neurochemical markers, and indications of impaired oxidative metabolism.

### 7.2.5 Developmental/Reproductive Toxicity

***Developmental Studies***

Studies are limited regarding developmental toxicity in humans following oral exposures to manganese. Kilburn (1987) reported an increased incidence in birth defects and stillbirths in a small population of indigenous peoples in Groote Eylandt, Australia. Although the area was rich in manganese deposits and ingestion of excess amounts of the metal was suspected, the study suffered from a lack of exposure data, small sample sizes, and no suitable control group. Further, inhalation exposure to manganese could not be ruled out. Studies by He et al. (1994) and Zhang et al. (1995) suggest that oral exposures to excess manganese can possibly result in increased neurological deficits measured as poorer performance in school and on standardized neurobehavioral exams. These studies also suffer from a lack of adequate exposure data and the potential presence of confounding factors, such as exposure to other potential neurotoxicants and possible inhalation exposure to manganese.

Developmental studies conducted in animals are summarized in Table 7-5. These studies suggest that manganese is a potential developmental toxicant, but additional studies that are better controlled are necessary in order to determine how potent it is.

Several studies have reported developmental effects in animal models following oral administration of manganese. Järvinen and Ahlström (1975) exposed female rats to 4, 24, 54, 154, 504, or 1,004 mg Mn/kg (as manganese sulfate heptahydrate) in the diet for 8 weeks after weaning and during pregnancy. No signs of embryotoxicity or fetotoxicity were observed. Increases in the whole body content of manganese in fetuses and in liver manganese content of the dams were reported at dietary levels above 154 mg Mn/kg. No increase in liver manganese content was observed in non-pregnant females. Chandra and Shukla (1978) administered bolus doses of 1 mg Mn/kg-day to neonatal rats for 60 days. Neuronal degeneration and increased monoamine oxidase were reported on days 15 and 30 of the study, but no clinical or behavioral signs of manganese neurotoxicity were reported.

Several studies have measured changes in brain chemistry in neonatal rats following oral exposure to manganese. Deskin et al. (1980, 1981) dosed rat pups via gavage with $MnCl_2$ in 5% sucrose for 24 days starting on the first postnatal day. The administered doses in the earlier study were 0, 1, 10, and 20 mg Mn/kg-day. Decreased dopamine levels in the hypothalamus were reported at the two highest doses, and decreased tyrosine hydroxylase levels and increased monoamine oxidase activity (perhaps due to increased levels of the enzyme) were reported in the hypothalamus at the highest dose. No other changes in brain chemistry were reported in the hypothalamus, and no other brain section was affected. In the latter study, doses of 0, 10, 15, and 20 mg Mn/kg-day were administered. Hypothalamic serotonin was observed to be increased at the highest dose; the level of this transmitter was unaffected in the striatum. Lai et al. (1984) reported small decreases in choline acetyltransferase activity in the cerebellum and midbrain of 2-month-old rats that had been exposed to 40 mg Mn/kg-day from conception, throughout gestation, and throughout life. Other neuronal enzymes (e.g., glutamic acid decarboxylase, acetylcholinesterase) were unaffected.

Kristensson et al. (1986) dosed 3-day old male rat pups with 150 mg Mn/kg-day (in water) for 41 days. The authors reported a transient ataxia (days 15-22), which was resolved by the end of the dosing period, in the pups. Manganese levels in the blood and brain (brain levels were increased 7-40 fold) were elevated significantly over controls in 15- and 20-day old pups; brain levels had decreased to approximately 3-fold over control levels in 43-day old pups. Homovanillic acid (metabolite of dopamine) concentrations were decreased in the striatum and hypothalamus, but not in other brain regions; no other monoamines or their metabolites were affected.

**Table 7-5. Developmental Effects of Exposure to Manganese.**

| Compound | Species | Route | Dose (mg Mn/kg-day) | Effect | Reference |
|---|---|---|---|---|---|
| $MnSO_4 \bullet 7H_20$ | Rat (female) | Oral (diet) | 0<br>4<br>24<br>54<br>154<br>504<br>1,004 | Increased manganese concentration in fetus and maternal liver; no indications of embryo- or fetotoxicity | Järvinen and Ahlström (1975) |
| $MnCl_2$ | Rat | Bolus (in water) | 1 | Neuronal degeneration; increased monoamine oxidase; no indications (clinical or behavioral) of neurotoxicity | Chandra and Shukla (1978) |
| $MnCl_2$ | Rat | Oral (gavage) | 0<br>1<br>10<br>20 | Decreased dopamine; decreased tyrosine hydroxylase; increased monoamine oxidase activity (all changes in hypothalamus only) | Deskin et al. (1980) |
| $Mn_3O_4$ | Mouse (Male) | Oral (diet) | 1,050 | Decreased preputial gland, seminal vesicle, and testes growth | Gray and Laskey (1980) |
| $MnCl_2$ | Rat | Oral (gavage) | 0<br>10<br>15<br>20 | Increased hypothalamic serotonin | Deskin et al. (1981) |
| $Mn_3O_4$ | Rat | Oral (diet) | 0<br>350<br>1,050<br>3,500 | Decreased serum testosterone; decreased sperm count; decreased testes weight; prevented normal decrease in serum FSH | Laskey et al. (1982) |
| $MnCl_2$ | Rat | Oral (drinking water) | 240 | Delayed air righting reflex; delayed age of eye opening; delayed development of auditory startle | Ali et al. (1983) |
| $Mn_3O_4$ | Rat | Oral (drinking water) | 40 | Decreased chloline acetyltransferase activity in cerebellum and midbrain | Lai et al. (1984) |
| $MnCl_2$ | Rat | Oral (drinking water) | 0<br>68<br>136<br>232 | Decreased water consumption and decrease in weight gain in two highest dose groups; no changes in catecholamine or startle response in the exposed pups | Kontur and Fechter (1985) |

**Table 7-5. Developmental Effects of Exposure to Manganese (continued).**

| Compound | Species | Route | Dose (mg Mn/kg-day) | Effect | Reference |
|---|---|---|---|---|---|
| $Mn_3O_4$ | Rat | Oral (gavage) | 0<br>71<br>214 | Decreased serum testosterone following 7 days of hCG induction | Laskey et al. (1985) |
| $MnCl_2$ | Rat (male) | Oral (drinking water) | 150 | Transient ataxia; decreased striatal and hypothalamic homovanillic acid concentrations | Kristensson et al. (1986) |
| $MnCl_2 \bullet 4H_20$ | Mouse | Subcutaneous injection | 0<br>0.56<br>1.1<br>2.2<br>4.4 | Decreased weight gain/food consumption; increased late resorptions; reduced fetal body weight; increased incidence of morphological defects | Sanchez et al. (1993) |
| $MnCl_2$ | Rat (female)<br>Rabbit (female) | Oral (gavage) | 0<br>11<br>22<br>33 | Delayed skeletal and internal organ development and increased external malformations in rat pups delivered by Caesarean section. No effects in rabbit | Szakmáry et al. (1995) |
| $MnCl_2$ | Mouse | Subcutaneous injection | 50 | Late resorptions; postimplantation loss; skeletal anomalies; reduced fetal body weight | Colomina et al. (1995) |
| $MnCl_2$ | Rat | Intravenous | 0<br>$0.27 \times 10^{-3}$<br>$1.1 \times 10^{-3}$<br>$2.2 \times 10^{-3}$ | Increased incidence of skeletal malformations including angulated or irregularly shaped clavicle, femur, fibula, humerus, ilium, radius, scapula, tibia, and/or ulna | Treinen and Blazak (1995) |
| $MnCl_2$ | Mouse | Intravenous | 0.3<br>1.6 | Increased fetal weight at low dose; decreased fetal weight at high dose; fetal skeletal abnormalities at high dose | Grant et al. (1997) |
| $MnCl_2$ | Rat | Oral (drinking water) | 0<br>350<br>1,420 | Thinning of cerebral cortex; absence of convincing brain histopathological or behavioral evidence from perinatal manganese exposure on the brain | Pappas et al. (1997) |
| $MnCl_2$ | Rat | Oral (drinking water) | 11<br>22 | Decreased body weight gain; increased response to auditory stimulus | Dorman et al. (2000) |

A few studies have measured reproductive endpoints in the developing rodent. Manganese administered to pre-weanling male mice at a dose of 1,050 mg Mn/kg-day beginning on postnatal day 15 resulted in the decreased growth of reproductive organs (preputial gland, seminal vesicle, and testes) measured on days 58, 73, and 90 but did not affect body growth or liver or kidney weights (Gray and Laskey, 1980). Laskey et al. (1982) administered dietary manganese at doses of 0, 350, 1,050, and 3,500 mg Mn/kg-day to male and female rats fed a diet either adequate or deficient in iron. Males and females were mated during days 90-100 of the study; testes weights of male offspring fed the iron-deficient diet were decreased as compared to controls at day 40 at the highest two doses and at day 100 at the intermediate dose. While 40-day-old weanling rats did not exhibit any treatment-related hormonal changes, exposed rats showed a dose-related decrease in serum testosterone at 60-100 days of age (when age-related increases were expected), and no increase in serum luteinizing hormone was observed. The normal decrease in serum follicle stimulating hormone (FSH) from 60 to 100 days was prevented by manganese exposure. Epididymal sperm count was decreased by the treatment only when given with the iron-deficient diet.

In an additional study measuring the effects of manganese exposure on the developing reproductive system, Laskey et al. (1985) administered 0, 71, and 214 mg Mn (as $Mn_3O_4$)/kg-day via gavage to pre-weanling rats on postnatal days 1-21. The study authors measured serum levels of FSH, LH, and testosterone in the pups at 21 or 28 days of age. Manganese exposure did not affect endogenous or stimulated serum levels of FSH or LH, nor did it affect endogenous or acute human chorionic gonadotropin (hCG)-induced serum testosterone at 2 hours. Serum testosterone was decreased following 7 days of hCG induction, however. The delayed decrease in testosterone was hypothesized by the study authors to be a result of an unknown manganese-induced effect on the Leydig cell.

Ali et al. (1983) evaluated potential changes in developmental endpoints in rat pups after administering excess manganese in drinking water to pregnant dams fed a normal or low-protein diet. Manganese exposure was started 90 days prior to mating and continued throughout gestation and nursing. The offspring of dams who had ingested 240 mg Mn/kg-day exhibited delayed air righting reflexes. Significant delays in the age of eye opening and the development of auditory startle were reported in pups from dams ingesting protein-deficient diets. No decreases in body weight or brain weight were reported in the offspring of rats fed normal-protein diets.

Kontur and Fechter (1985) exposed pregnant Long-Evans rats to 0, 5,000, 10,000, or 20,000 mg/L of manganese chloride in drinking water throughout the gestation period. Rats in the 10,000 and 20,000 mg/L groups showed reduced water intake and a significant decrease in weight gain. A significant decrease in birth weight was observed in the 20,000 mg/L group. At one day of age, pups from the 10,000 and 20,000 mg/L groups had increased manganese levels in the forebrain, although there was no difference in the extent of accumulation between the two groups. The increased manganese levels were not associated with any changes in catecholamine function or startle response in the exposed pups. The authors concluded that manganese is not particularly toxic to developing rats, perhaps as a result of limited placental transfer.

The developmental effects of manganese have also been evaluated following parenteral administration. Sanchez et al. (1993) investigated the embryotoxic and teratogenic potential of manganese during organogenesis. Pregnant Swiss mice received daily subcutaneous injections of 0, 2, 4, 8 or 16 mg/kg-day of $MnCl_2 \cdot 4H_2O$ on days 6 to 15 of gestation. These doses correspond to 0, 0.56, 1.1, 2.2, or 4.4 mg Mn/kg-day, respectively. Dams were sacrificed on gestational day 18. Significant reductions in weight gain and food consumption were reported in dams receiving 8 mg/kg-day and above, and treatment-related deaths were reported at 16 mg/kg-day. A significant increase in the number of late resorptions was observed at doses of 4 mg/kg-day and higher, and reduced fetal body weight and an increased incidence of morphological defects were reported at doses of 2.2 mg Mn/kg-day and higher. No difference was seen in the incidence of individual or total malformations in treated groups when compared with controls. A NOAEL of 1.1 mg/kg-day was identified by the study authors for maternal toxicity. A NOAEL of 0.56 mg/kg-day was identified for embryo/fetal toxicity

Pappas et al. (1997) assessed behavioral, neurohistological, and neurochemical endpoints in rats exposed to manganese from conception to weaning. The investigators administered 0, 2,000, or 10,000 mg Mn/L as manganese chloride in drinking water to female rats (10/group) and their litters from conception until postnatal day (PND) 30. The average daily consumption of manganese during gestation was 350 and 1,420 mg/kg-day, respectively, for the two manganese treatment groups. No effects were observed on pregnancy or birth parameters and no physical abnormalities were evident in the offspring of treated dams. The findings reflect a lack of effects on reproductive capability. Fifty male pups from each treatment group were subsampled for behavioral tests (10 to 22 per group), histopathology (6 to 8 per group) and neurochemical analyses (6 to 8 per group). The rats exposed to 10,000 mg Mn/L showed a 2.5-fold increase in brain cortical Mn levels. They also experienced reduced weight gain during PND 9 to 32, and were hyperactive at PND 17. Behavioral tests were conducted on pups from all groups at PND 17, 90 or 95. No significant differences in performance were noted for the radial arm maze, elevated plus apparatus, or Morris water maze behavioral tests. Both doses resulted in thinning of the cerebral cortex. The observed thinning may have been a consequence of either perinatal malnutrition or a direct effect on cortical development. Brain monoamine levels and choline acetyltransferase activity were unaffected by manganese exposure. Tyrosine hydroxylase immunohistochemistry indicated that dopamine neurons of the substantia nigra were intact. Glial fibrillary acidic protein immunoreactivity, an indicator of neuronal damage, was not increased in cortex, caudate nucleus or hippocampus. The authors emphasized that the most noteworthy result of this study was the absence of convincing histopathological and behavioral evidence for persistent effects of perinatal manganese exposure on the brain.

Grant et al. (1997) failed to observe any effects of manganese exposure on weight gain, gross malformations, or skeletal malformations in the offspring of pregnant rats dosed via gavage with 22 mg Mn/kg-day on gestational days 6-17. Another study indicates a lack of persistent developmental effects from oral manganese exposure during gestation. Szakmáry et al. (1995) reported the developmental effects of manganese administered via gavage to pregnant rats throughout gestation and to pregnant rabbits through organogenesis (gestation day 6-20) at doses of 0, 11, 22, and 33 mg/kg-day. No developmental effects in the rabbit were observed. The

highest dose resulted in retardation of development of the skeleton and internal organs of the rat, as well as a significant increase in external malformations (e.g., clubfoot) in pups delivered by caesarean section. These effects, however, were not observed in 100-day-old offspring of dams that had been similarly dosed, indicating that the developmental effects were self-correcting. Manganese treatment did not affect the following endpoints in either the pup group that was surgically delivered or the group born live: ears, teeth, eyes, forward motion, clinging ability, body posture, correction reflex, or negative geotaxis reflex.

In a more recent study, Dorman et al. (2000) dosed neonatal CD rats with 11 or 22 mg Mn (in water)/kg-day for 21 days from birth to weaning. The high dose resulted in decreased body weight gain in the pups and affected brain neurochemistry. Manganese treatment induced a significant increase in the amplitude of response to an auditory stimulus but did not affect motor activity, performance in a passive avoidance task, or brain histopathology.

Colomina et al. (1995) conducted a study to determine which gestation day is most critical for developmental toxicity of manganese in mice. The investigators administered a 50 mg/kg dose of manganese chloride by subcutaneous injection once during the period between gestation days 9 and 12. Late resorptions, post-implantation loss, and skeletal anomalies increased in all treatment groups. Significant reductions in fetal body weight occurred following exposure on gestation day 9 or 10, indicating these days were most critical.

Treinen and Blazak (1995, abstract only) dosed female Sprague-Dawley rats (15/group) intravenously with 0, 5, 20, or 40 nmol/kg $MnCl_2$ on days 6 to 17 of gestation. These doses correspond to approximately 0, 0.27, 1.1, or 2.2 μg Mn/kg-day. Treatment resulted in an increased incidence of skeletal malformations (doses which elicited effects were not reported). The observed malformations included angulated or irregularly shaped clavicle, femur, fibula, humerus, ilium, radius, scapula, tibia, and/or ulna.

Grant et al. (1997) administered 6 or 30 μmol $MnCl_2$/kg-day to female mice (24/group) by intravenous injection on gestation days 6 to 17. These doses correspond to approximately 0.3 and 1.6 mg Mn/kg-day. The experiment was terminated on gestation day 20. No significant differences were noted in manganese-treated mice for number of corpora lutea, implantation sites, pre- or post-implantation losses, or number of viable fetuses per litter. Fetal weight was significantly increased ($p< 0.05$) at the lower dose, and significantly decreased ($p< 0.05$) at the 1.6 mg/kg-day dose. Skeletal abnormalities were noted in the fetuses of dams receiving the higher intravenous dose. In contrast, no increase in skeletal abnormalities was observed in the fetuses of mice administered 400 μmol of $MnCl_2$ (approximately 22 mg Mn/kg-day) by oral gavage daily from days 6 to 17 of gestation.

One *in vitro* developmental study was located. Hanna et al. (1996, abstract only) cultured two-stage mouse embryos in media containing varying concentrations of essential and non-essential minerals, including manganese. Embryos were incubated in culture media containing 0.05–200 μM manganese for 72 hours. Both essential and nonessential minerals were embryotoxic at relatively low doses.

### *Reproductive Studies*

Some inhalation data from occupational exposure studies suggest that male reproductive dysfunction is a primary endpoint of manganese toxicity. Toxicity is manifested in symptoms including loss of libido and impotence (U.S. EPA, 1996a). Some evidence indicates that the hypothalamus and pituitary are sites of manganese accumulation (see Section 6.2), suggesting disturbance of the hypothalamic-pituitary-gonadal axis hormones as a potential mechanism for reproductive effects. No human reproductive data for oral manganese exposure are available in the current literature. Reproductive studies in animals orally exposed to manganese are described below. Results of these studies are summarized in Table 7-6.

Chandra and colleagues consistently reported degenerative changes in the seminiferous tubules in the testes after parenteral exposure of rats and rabbits to manganese (Chandra, 1971; Shukla and Chandra, 1977; Imam and Chandra, 1975; Chandra et al., 1973, 1975). However, similar changes were not observed in subchronic or chronic studies in mice or rats (NTP, 1993).

Gray and Laskey (1980) exposed male mice to 1,100 mg Mn/kg as $Mn_3O_4$ in a casein diet from gestation day 15 to 90 days of age. Assuming a food consumption factor of 0.13 (U.S. EPA, 1986d), the estimated daily dose at the termination of the study would be approximately 143 mg/kg-day. Sexual development was retarded, as indicated by decreased weight of testes, seminal vesicles and preputial glands. Reproductive performance was not evaluated.

Laskey et al. (1982) exposed Long-Evans rats to 0, 400, 1,100 or 3,550 mg Mn/kg (as $Mn_3O_4$) in the diet from day 2 of mother's gestation to 224 days of age. Assuming a food consumption factor of 0.05 (U.S. EPA, 1986d), the average daily dose at the termination of the study was 0, 20, 55, or 177 mg Mn/kg-day. The investigators observed a dose-related decrease in serum testosterone concentration (without a concomitant increase in serum luteinizing hormone concentration), and reduced fertility at the highest dose. Testes weight, number of ovulations, resorption and preimplantation deaths, litter size, and fetal weights were unaffected by manganese exposure.

Laskey et al. (1985) conducted studies to assess the effect of manganese on hypothalamic, pituitary and testicular function. Long-Evans rat pups (8/litter) were dosed by gavage from day 1 to day 21 with a 50% sucrose solution containing particulate $Mn_3O_4$. The average daily dose of manganese was calculated to be 0, 71 or 214 mg Mn/kg-day. Assessments of the hypothalamic, pituitary, or testicular functions were determined by measuring the endogenous or stimulated serum concentrations of follicle-stimulating hormone, luteinizing hormone, and/or testosterone at 21 or 28 days of age. Body, testes, and seminal vesicles weight and tissue concentrations of Mn were also evaluated. Effects attributed to manganese included slight decreases in body and testes weights, and a reduction in serum testosterone. There was no indication of hypothalamic or pituitary dysfunction. The authors suggested that the decrease in testosterone level resulted from manganese-induced damage of Leydig cells.

**Table 7-6. Reproductive Effects of Exposure to Manganese.**

| Compound | Species | Route | Dose | Effect | Reference |
|---|---|---|---|---|---|
| $Mn_3O_4$ | Mouse | Oral (diet) | 143 mg Mn/kg-day | Decreased weight of testes, seminal vesicles and preputial glands after 90 days. | Gray and Laskey (1980) |
| $Mn_3O_4$ | Rat | Oral (diet) | 20 mg Mn/kg-day<br>55<br>177 | Dose-related decrease in serum testosterone concentration. Reduced fertility at 3550 ppm after 224 days. | Laskey et al. (1982) |
| $Mn_3O_4$ | Rat | Oral (gavage) | 71 mg Mn/kg-day<br>214 | Decreased body and testes weights. Reduction in serum testosterone. | Laskey et al. (1985) |
| $MnCl_2$ | Rat | i.p. | 8 mg/kg-day | Degenerative changes in approx. 50% of seminiferous tubules after 150 and 180 days. | Chandra (1971) |
| $MnCl_2 \bullet 4H_20$ | Rat | i.p. | 15 mg/kg-day | Increased Mn in testes; decreased nonprotein sulfhydryls and decreased activity of glucose-6-phosphate dehydrogenase and glutathione reductase after 15–45 days. | Shukla and Chandra (1977) |
| $MnCl_2 \bullet 4H_20$ | Rabbit | i.v. | 3.5 mg/kg | Inhibition of succinic dehydrogenase in seminiferous tubules after 5 days. Morphologic changes were not apparent. | Imam and Chandra (1975) |
| $MnSO_4$ | Rat | i.p. | 6 mg Mn/kg | Increased Mn in testes after 25–30 days. Degenerative changes in 10% of seminiferous tubules. | Chandra et al. (1975) |
| $MnO_2$ | Rabbit | i.t. | 250 mg/kg single dose | Destruction and calcification of the seminiferous tubules at 8 months. Infertile females. | Chandra et al. (1973) |

i.p. = intraperitoneal; i.v. = intravenous; i.t. = intratracheal

Studies exist, however, that report no adverse reproductive effects in female rats following oral manganese exposure. Pappas et al. (1997) dosed pregnant rats with up to 620 mg Mn/kg-day (as $MnCl_2$) throughout gestation. No treatment-related effects were reported in dam health, litter size, or sex ratios of the pups. The study did not include more extensive analysis of female reproductive organs. Grant et al. (1997) administered 22 mg Mn/kg-day (as $MnCl_2$) via gavage to pregnant dams on gestation days 6-17. No treatment-related effects were reported in dams as measured by mortality, clinical signs, food and water intake, or body weights.

### 7.2.6 Chronic Toxicity

NTP (1993) investigated the chronic toxicity of manganese in a 2-year oral exposure study. Concentrations of 0, 1,500, 5,000 or 15,000 mg/kg manganese sulfate monohydrate were administered in the diet to male and female F344 rats (70/sex). These dietary concentrations resulted in doses ranging from 30 to 331 mg Mn/kg-day for males, and 26 to 270 mg Mn/kg-day for females. Ten rats/group were sacrificed at 9 and 15 months. Survival of males in the high-dose group was significantly decreased starting at week 93 of the study, and death was attributed to advanced renal disease associated with manganese exposure. Food consumption was similar for all groups. However, by the end of the study, high-dose males exhibited a mean body weight that was 10% lower than controls. No clinical findings or effects on hematologic or clinical chemistry parameters were attributed to manganese exposure in any group. Tissue concentrations of manganese were elevated in the livers of mid- and high-dose males, concurrent with a decrease in hepatic iron concentrations. Renal disease in high-dose males was the only pathological effect noted. No increases in tumor incidence were attributed to manganese exposure.

The chronic oral toxicity of manganese was evaluated in mice in a concurrent study conducted by NTP (1993). Concentrations of 0, 1,500, 5,000, or 15,000 mg/kg manganese sulfate monohydrate were administered in the diet to $B6C3F_1$ mice (70/sex) in a 2-year oral exposure study. These dietary concentrations were reported to be equivalent to doses ranging from 63 mg Mn/kg-day to 722 mg Mn/kg-day for male mice, and from 77 mg Mn/kg-day to 905 mg Mn/kg-day for female mice. Interim sacrifices of 11 mice/group were made at 9 and 15 months. No clinical findings or effects on survival were observed in any group of mice. Mean body weights of males were not affected. Female mice had a dose-related decrease in mean body weight after week 37. The final mean body weights for the low-, mid- and high-dose females were 6%, 9% and 13% lower than controls, respectively. No differences were seen in food consumption for any group. No effects were reported on hematologic parameters. Tissue concentrations of manganese were significantly elevated in the livers of all exposed females, and in high-dose males. Elevated manganese concentration was associated with decreased hepatic iron.

### 7.2.7 Carcinogenicity

The carcinogenicity of ingested manganese was evaluated in concurrent 2-year oral exposure studies conducted in mice and rats by NTP (1993). An overview of these studies is provided below. No other studies of manganese carcinogenicity via the oral route were identified.

Groups of rats were exposed to dietary levels of manganese sulfate monohydrate that resulted in intakes ranging from 30 to 331 mg Mn/kg-day for males and 26 to 270 mg Mn/kg-day for females. At the termination of the study, no manganese-related increase in any tumor type was observed (NTP, 1993).

In a parallel study, NTP (1993) administered 0, 1,500, 5,000, and 15,000 mg/kg manganese sulfate monohydrate in the diet to $B6C3F_1$ mice (70/sex) for 2 years. These dietary concentrations resulted in intakes ranging from 63 to 722 mg Mn/kg-day for males and from 77 to 905 mg Mn/kg-day for females. The estimated manganese intake in the high-dose mice was approximately 107 times greater than the recommended dietary allowance. Incidence of thyroid follicular cell hyperplasia was significantly greater in high-dose male and female mice than in controls. The incidence of follicular cell adenomas is summarized in Table 7-7. In males, tumors were observed only at the highest dose (6% incidence). The highest incidence of tumors in females was also observed at the highest dose. No significant differences in tumor incidence relative to the controls were observed for either sex. The follicular cell tumors were seen only at the termination of the study (729 days), and their number was only slightly increased relative to the historical control range in female $B3C6F_1$ mice (0 to 9% historical range versus 10% tumor incidence in high-dose females). Hence, the relevance of these findings to human carcinogenesis is questionable. The issues of concern are: 1) the large intake of manganese required to elicit a response seen only at the end of the study, and 2) tumor frequencies that are not significantly different from historical controls. While NTP (1993) has concluded that the marginal increase in thyroid adenomas of the mice was equivocal evidence of carcinogenicity, others have questioned the relevance of these data to human carcinogenicity (U.S. EPA, 1993).

**Table 7-7. Follicular Cell Tumor Incidence in $B6C3F_1$ Mice.**

| | Concentration of $MnSO_4 \cdot H_2O$ in Diet | | | |
|---|---|---|---|---|
| **Sex** | **Control** | **Low** | **Medium** | **High** |
| Males | 0/50 | 0/49 | 0/51 | 3/50 |
| Females | 2/50 | 1/50 | 0/49 | 5/51 |

Source: NTP (1992)

Other studies reporting positive results for carcinogenicity are summarized in Table 7-8. Stoner et al. (1976) tested manganese sulfate in a mouse lung adenoma screening bioassay. These investigators exposed 6- to 8-week-old Strain A/Strong mice of both sexes (10/sex) to 6, 15 or 30 mg $MnSO_4$/kg via intraperitoneal injection. Doses were administered three times a week for a total of 21 injections. The cumulative doses were 132, 330 and 660 mg $MnSO_4$/kg. These doses corresponded to 42.9, 107.2 and 214.4 mg Mn/kg. Observation continued for 22 weeks after the dosing period, and the mice were sacrificed at 30 weeks. Table 7-9 summarizes the results of this study. The percentage of mice with tumors was elevated at the highest dose level, but the difference was not significant (Fisher Exact test) when compared with the vehicle controls. An apparent increase in the average number of pulmonary adenomas per mouse was noted both at the

**Table 7-8. Summary of Carcinogenicity Studies Reporting Positive Findings for Selected Manganese Compounds [a].**

| Compound | Species | Route | Dose | Duration (weeks intermit-tent) | Results | Reference |
|---|---|---|---|---|---|---|
| Manganese chloride | Mouse | i.p. | 0.1 mL of 1% | 26 | 41% - Lymphosarcomas | DiPaolo (1964) |
| | Mouse | s.c. | 0.1 mL of 1% | 26 | 67% - Lymphosarcomas | |
| | | | 0% (control) | | 24% - Lymphosarcomas | |
| Manganese sulfate | Mouse | i.p. | 660 mg/kg | 8 | 67% - Lung adenomas | Stoner et al. (1976) |
| | | | 0 mg/kg | | 31–37% - Lung ademomas | |
| Manganese acety-lacetonate (MAA) | Rat | i.m. | 1,200 mg/kg[b] | 26 | 40% (males) Fibrosarcomas 24% (females) Fibrosarcomas | Furst (1978) |
| | | | 0 mg/kg | | 4 % (control males and females) | |

i.p. = intraperitoneal; s.c. = subcutaneous; i.m. = intramuscular
[a] Source: U.S. EPA (1984)

**Table 7-9. Pulmonary Tumors in Strain A Mice Treated with Manganese Sulfate [a].**

| Total Dose | | | | | | |
|---|---|---|---|---|---|---|
| Group | mg $MnSO_4$/kg | mg Mn/kg | Mortality | Mice with Lung Tumors (%) | Average Number Tumors/Mouse [b] | Value [c] |
| Untreated control | 0 | 0 | 1/20 | 6/19 (31) | 0.28 ± 0.07 | NA |
| Solvent control (0.85% NaCl) | 0 | 0 | 1/20 | 7/19 (37) | 0.42 ± 0.10 | NA |
| Treated | 132 | 42.9 | 1/20 | 7/19 (37) | 0.47 ± 0.11 | NS |
| Treated | 330 | 107.2 | 0/20 | 7/20 (35) | 0.65 ± 0.15 | NS |
| Treated | 660 | 214.4 | 2/20 | 12/18 (67) | 1.20 ± 0.49 | 0.05[d] |
| 20 mg urethane [e] | 0 | 0 | 2/20 | 18/18 (100) | 21.6 ± 2.81 | NR |

[a] Source: Stoner et al. (1976)
[b] X ± S.E.
[c] Student t-test
[d] Fisher Exact Test p = 0.068
[e] Single intraperitoneal injection
NA = Not applicable; NS = Not significant; NR = Not reported

middle and high doses, but the increase was significant only at the high dose (660 mg $MnSO_4$/kg) (Student's t-test, $p < 0.5$). Although these study results are suggestive of carcinogenic activity, they do not conclusively meet the positive response criteria (increase in the mean number of tumors per mouse and an observable dose-response relationship) for the interpretation of lung tumor data in this mouse strain (Shimken and Stoner, 1975).

Furst (1978) injected F344 rats intramuscularly with manganese acetylacetonate and observed an increased incidence of fibrosarcomas at the injection site, but did not observe increased tumor incidence at other sites.

## 7.3 Other Key Data

### 7.3.1 Mutagenicity/Genotoxicity

*In Vivo Studies*

No studies or reports were identified which describe mutagenic or genotoxic effects in humans following oral exposure to manganese. Table 7-10 summarizes the results of the most

**Table 7-10. Genotoxicity of Manganese *In Vivo*.**

| Species (test system) | Compound | End Point | Route | Results | Reference |
|---|---|---|---|---|---|
| Nonmammalian systems: | | | | | |
| *Drosophila melanogaster* | $MnSO_4$ | Sex-linked recessive lethal | Feeding Injection | - | Valencia et al. (1985) |
| *Drosophila melanogaster* | $MnSO_4$ | Sex-linked recessive lethal | Feeding Injection | - | NTP (1993) |
| *Drosophila melanogaster* | $MnCl_2$ | Somatic mutation | Soaking larvae | - | Rasmuson (1985) |
| Mammalian systems: | | | | | |
| Albino rat (bone marrow cells) (spermatogonial cells) | $MnCl_2$ | Chromosomal aberrations | Oral | - | Dikshith and Chandra (1978) |
| Albino mouse | $MnSO_4$<br>$KMnO_4$ | Chromosomal aberrations<br>Chromosomal aberrations | Oral<br>Oral | +<br>+ | Joardar and Sharma (1990) |

recent *in vivo* mutagenicity and genotoxicity studies in animals. Results from additional studies are noted in the text below.

Studies of genotoxicity in animals have shown mixed results. The bone marrow cells of rats receiving a 50 mg/kg oral dose of manganese (as manganese chloride) showed an increased incidence of chromosomal aberrations (30.9%) compared with those of control animals (8.5%) (Mandzgaladze, 1966; Mandzgaladze and Vasakidze, 1966). However, Dikshith and Chandra (1978) administered repeated oral doses of manganese chloride (0.014 mg/kg-day) to male rats for 180 days and did not observe significant chromosomal damage in bone marrow or spermatogonial cells.

Joardar and Sharma (1990) administered oral doses of manganese sulfate (approximately 102, 202, and 610 mg/kg) and potassium permanganate (65, 130, and 380 mg/kg) to male Swiss albino mice for three weeks. Both compounds were clastogenic, with manganese sulfate being more potent. The frequencies of chromosomal aberrations in bone marrow cells and micronuclei were significantly increased by both salts. There was also a statistically significant, dose-dependent enhancement of sperm-head abnormalities. A LOAEL of 23 mg Mn/kg-day was identified for this effect by ATSDR (2000).

The divalent manganese ion (Mn II) interacts with DNA and chromosomes (Kennedy and Bryant, 1986; Yamaguchi et al., 1986). In cultured mammalian cells, both $MnCl_2$ and $KMnO_4$ produced chromosome aberrations, including breaks, exchanges and fragments (Umeda and Nishimura, 1979). DNA-strand breaks have also been induced by manganese in Chinese hamster ovary calls and human diploid fibroblasts (Hamilton-Koch et al., 1986; Snyder, 1988). Tests for induction of chromosomal aberrations and sister chromatid exchanges in cultured Chinese hamster ovary cells were positive for manganese sulfate monohydrate in the absence of S9 metabolic activation. In the presence of S9, only the sister chromatid exchange test was positive (NTP, 1993).

Tests for mutagenicity in *Drosophila melanogaster* have given negative results. Manganese sulfate monohydrate did not induce sex-linked recessive lethal mutations in germ cells of male *Drosophila* treated by feeding or injection (Valencia et al., 1985, as reported in NTP, 1993). Treatment of *D. melanogaster* with manganese chloride by soaking did not induce somatic mutation (Rasmuson, 1985).

***In Vitro Assays***

Table 7-11 summarizes the results of the most recent *in vitro* mutagenicity and genotoxicity studies. Additional results from early studies are included in the text below.

Manganese chloride was mutagenic in *Escherichia coli* (Demerec et al., 1951; Durham and Wyss, 1957; Zakour and Glickman, 1984), *Photobacterium fischeri* (Ulitzer and Barak, 1988) and *Serretia marcescens* (Kaplan, 1962). Both positive (Nishioka, 1975) and negative (Kanematsu et al., 1980) results have been reported for the *Bacillus subtilis* recombination assay. Positive (Pagano and Zeiger, 1992; Wong, 1988) and negative results (Wong, 1988) have also been reported for manganese chloride in the *Salmonella typhimurium* reversion assay. Assays in mammalian cell lines were positive for gene mutation in mouse lymphoma cells (Oberley et al., 1982) and enhancement of transformation in Syrian hamster embryo cells (Casto et al., 1979). An assay for DNA damage in human lymphocytes gave negative results with metabolic activation, and positive results without activation (De Meo et al., 1991).

Manganese sulfate gave positive results in the T4 bacteriophage mutation test (Orgel and Orgel, 1965), and the *B. subtilis* recombination assay with S9 activation (Nishioka, 1975). Pagano and Zeiger (1992) obtained positive results for mutagenicity in *S. typhimurium* strain TA97. In contrast, manganese sulfate monohydrate was not mutagenic in *S. typhimurium* strains TA98, TA100, TA1535, or TA1537, either with or without exogenous metabolic (S9) activation when assayed by Mortelmans et al. (1986). Results for strain TA97 were negative when assayed with S9 activation, and equivocal when assayed without metabolic activation. Assays in eukaryotic test systems were positive for mutagenicity in *S. cerevisiae* (Singh, 1984) and chromosomal aberrations in Chinese hamster ovary (CHO) cells (NTP, 1993). Manganese sulfate gave negative results when assayed for induction of sister chromatid exchange in CHO cells (NTP, 1993).

**Table 7-11. Genotoxicity of Manganese *In Vitro*.**

| Species (test system) | Compound | End Point | Strain | Results | | Reference |
|---|---|---|---|---|---|---|
| | | | | With S9 Activation | Without S9 Activation | |
| Prokaryotic organisms: | | | | | | |
| *Salmonella typhimurium* | $MnCl_2$ | Gene mutation | TA98<br>TA102<br>TA1535<br>TA1537 | -<br>-<br>-<br>- | -<br>-<br>-<br>+ | Wong (1988) |
| *Salmonella typhimurium* | $MnSO_4 \cdot H_2O$ | Gene mutation | TA97<br>TA98<br>TA100<br>TA1535<br>TA1537 | -<br>-<br>-<br>-<br>- | -/+<br>-<br>-<br>-<br>- | Mortelmans et al. (1986) |
| *Salmonella typhimurium* | $MnSO_4$ | Gene mutation | TA97 | ND | + | Pagano and Zeiger (1992) |
| *Salmonella typhimurium* | $MnCl_2$ | Gene mutation | TA100<br>TA102 | ND<br>ND | -<br>+ | DeMeo et al. (1991) |
| *Photobacterium fischeri* (bioluminescence test) | $MnCl_2$ | Gene mutation (restored luminescence) | Pf-13 (dark mutant) | ND | + | Ulitzur and Barak (1988) |
| *Escherichia coli* | $MnCl_2$ | Gene mutation | KMBL 3835 | ND | + | Zakour and Glickman (1984) |
| Bacteriophage (*E. coli lysis*) | $MnSO_4$ | Gene mutation | T4 | ND | + | Orgel and Orgel (1965) |
| *Bacillus subtilis* (recombination assay) | $MnCl_2$<br>$Mn(NO_3)_2$<br>$MnSO_4$<br>$Mn(CH_3COO)_2$<br>$KMnO_4$ | Inhibition of growth in recombination deficient mutant ($Rec^-$) compared to wild type ($Rec^+$) | M45 ($Rec^-$) | ND<br><br>+ | +<br>+<br><br>+<br>- | Nishioka (1975) |

**Table 7-11 (continued)**

| Species (test system) | Compound | End Point | Strain | Results | | Reference |
|---|---|---|---|---|---|---|
| | | | | With S9 Activation | Without S9 Activation | |
| *B. subtilis* (recombination assay) | $MnCl_2$<br>$Mn(NO_3)_2$<br>$Mn(CH_3COO)_2$ | Inhibition of growth in recombination deficient mutant ($Rec^-$) compared to wild type ($Rec^+$) | M45 ($Rec^-$) | ND<br>- | -<br>- | Kanematsu et al. (1980) |
| Eukaryotic organisms: | | | | | | |
| Fungi: *Saccharomyces cerevisiae* | $MnSO_4$ | Gene conversion, reverse mutation | D7 | ND | + | Singh (1984) |
| Mammalian cells: Mouse lymphoma cells | $MnCl_2$ | Gene mutation | L5178Y $TK_{+/-}$ | ND | + | Oberley et al. (1982) |
| Mammalian cells: Syrian hamster embryo cells | $MnCl_2$ | Enhancement of SA7 transformatio n | | ND | + | Casto et al. (1979) |
| Mammalian cells: Human lymphocytes (Single-cell gel assay) | $MnCl_2$ | DNA damage | | - | + | DeMeo et al. (1991) |
| Mammalian cells: Chinese hamster ovary cells | $MnSO_4$ | Chromosomal aberrations<br>Sister chromatid exchange | | -<br>+ | +<br>+ | NTP (1993) |

Notes:
- = negative results
+ = positive results
-/+ = equivocal results
ND = no data available
DNA = deoxyribonucleic acid
$MnSO_4 \cdot H_2O$ = manganese (II) sulfate monohydrate
$Mn(CH_3COO)_2$ = manganous acetate
$MnCl_2$ = manganous chloride
$Mn(NO_3)_2$ = manganous nitrate
$MnSO_4$ = manganous sulfate
Rec = recombination
Source: Modified from ATSDR (2000)

Comparatively little data are available that describes the genotoxic potential of other manganese compounds. Manganese oxide ($Mn_3O_4$) was not mutagenic in *S. typhimurium* or *S. cerevisiae* (Simmon and Ligon, 1977). Data obtained for manganese nitrate ($Mn(NO_3)_2$) in the *B. subtilis* recombination assay were inconsistent between studies (Nishioka, 1975; Kanematsu et al., 1980). Manganese acetate ($Mn(CH_3OO)_2$) was mutagenic in the *B. subtilis* recombination assay without exogenous metabolic activation, and gave negative results with activation (Nishioka, 1975; Kanematsu et al., 1980).

### 7.3.2 Immunotoxicity

Immunotoxicity and lymphoreticular effects do not appear to be significant outcomes of oral exposure to manganese. A single report describes effects in this category following oral exposure. NTP (1993) administered diets containing 0, 1,600, 3,130, 6,250, 12,500, or 25,000 mg/kg manganese sulfate monohydrate to F344 rats (10/sex/dose) in a 13-week study. Based on measured feed consumption, the study authors determined that the mean intake of manganese sulfate monohydrate ranged from 110 to 1,700 mg/kg-day (equal to about 36 to 553 mg Mn/kg-day) for males, and from 115 to 2,000 mg/kg-day (equal to about 37 to 621 mg Mn/kg-day) for females. Increased neutrophil counts were noted at 32 mg Mn/kg-day in male rats. Decreased leukocyte counts were noted at 155 mg Mn/kg-day in female rats.

Studies in animals exposed to manganese chloride by intraperitoneal or intramuscular injection suggest that manganese can affect several immunological cell types (ATSDR, 2000). Observed effects include stimulation of macrophage and natural killer cell activity in mice (Rogers et al., 1983; Smialowicz et al., 1985, 1987). Other effects include alteration of the responsiveness of lymphoid cells to mitogens and inhibited antibody production in response to a T-cell antigen (Hart, 1978; Lawrence, 1981; Srisuchart et al., 1987). The significance of these findings for human immune function is presently unknown.

### 7.3.3 Hormonal Disruption

No reports describing hormonal disruption associated with manganese exposure were located.

### 7.3.4 Physiological or Mechanistic Studies

***Biochemical and Physiological Role***

Manganese is a naturally-occurring element that is required for normal physiological functioning in all animal species (U.S. EPA, 1996a). It plays a role in bone mineralization, metabolic regulation, protein and energy metabolism, protection of cells from oxidative stress, and synthesis of mucopolysaccharides (ATSDR, 2000). Many of these roles are achieved by participation of manganese as a catalytic or regulatory factor for enzymes, including hydrolases, dehydrogenases, kinases, decarboxylases and transferases. In addition, manganese is a structural component of the metalloenzymes mitochondrial superoxide dismutase, pyruvate carboxylase, and

liver arginase. Studies conducted to determine the biochemical and nutritional roles of manganese in human health are reviewed in greater detail by Wedler (1994) and Keen et al. (1999).

The frequency of occurrence and consequences of manganese deficiency are issues of some debate (Keen et al., 1999). However, observations reported by Doisy (1973) and Friedman et al. (1987) suggest that manganese is an essential element for humans. Doisy (1973) reported decreased levels of clotting proteins, decreased serum cholesterol, reddening of black hair, retarded growth of hair and nails, and scaly dermatitis in a subject inadvertently deprived of manganese. Friedman et al. (1987) administered a manganese-deficient diet to seven men for 39 days. Five of the seven subjects exhibited dermatitis at the end of the manganese-deficient period. The development of dermatitis was attributed to decreased activity of manganese-requiring enzymes that are required for skin maintenance. The symptoms cleared rapidly when manganese was restored to the diet.

Manganese deficiency has been experimentally induced in multiple animal species. Outcomes associated with manganese deficiency in animals include impaired growth (Smith, 1944), skeletal abnormalities (Amdur et al., 1944; Strause et al., 1986), impaired reproductive function in females and testicular degeneration in males (Boyer et al., 1942), ataxia (Hurley et al., 1961), altered metabolism of carbohydrates (Baly et al., 1988; Hurley et al., 1984) and lipids (Abrams et al., 1976), and decreased cholesterol synthesis and excretion (Davis et al., 1990; Kawano et al., 1987). The biochemical basis for these effects has not been established with certainty, but it may be related to the participation of manganese in numerous enzymatic reactions.

Low serum manganese levels are associated with several disease states, including epilepsy, exocrine pancreatic insufficiency, multiple sclerosis, cataracts, and osteoporosis (Freeland-Graves and Llanes, 1994). In addition, the metabolic disorders phenylketonuria and maple syrup urine disease, genetic disorders of amino acid metabolism, are associated with poor manganese status (U.S. EPA, 1996a).

***Mechanisms of Neurotoxicity***

The central nervous system (CNS) has been identified as the major target of manganese toxicity (U.S. EPA, 1993; ATSDR, 2000). The blood-brain barrier (BBB) is a major regulator of the (CNS) milieu, and the rate and extent of manganese transfer across the BBB may be a determinant of manganese neurotoxicity (Aschner and Aschner, 1991). The mechanism by which manganese crosses the BBB to gain access to neuronal tissue has not been fully elucidated, but may be a function of binding to transferrin (Aschner and Aschner, 1991). In the portal circulation, manganese as Mn(II) initially binds to alpha-2-macroglobulin, and this complex cannot cross the BBB. The Mn(II)-alpha-2-macroglobulin complex is transported by the bloodstream to the liver (Tanaka, 1982), where a small fraction of the circulating Mn(II) may be oxidized to Mn(III). The iron-transporting protein transferrin has been shown to also bind Mn(III), and may be responsible for its transport into the brain. The observation that some of the regions of the brain that accumulate manganese (e.g., globus pallidus, striatum, and substantia

nigra) receive neuronal input from the transferrin-rich nucleus accumbens and the caudate-putamen supports this argument. Both of these regions are rich in transferrin receptors.

Additional evidence for the transferrin transport hypothesis was provided by an experiment in which rats were given a 6-hour intravenous administration of ferric-hydroxide dextran complex (Aschner and Aschner, 1990). The uptake of radiolabeled manganese into the brain was significantly ($p < 0.05$) inhibited following the administration of the iron complex as compared with rats administered iron-free dextran. It was concluded that iron homeostasis may play an important role in the regulation of manganese transport across the BBB, since both metals are transported by transferrin and may be competing for binding sites.

Once manganese has crossed the BBB, several neurotransmitter systems in the brain appear to be potential targets for manganese toxicity. The primary targets appear to be the monoamines, including dopamine, noradrenaline and serotonin (Neff et al., 1969; Mustafa and Chandra, 1971). The amino acid neurotransmitter γ-amino butyric acid (GABA) may also be affected (Gianutsos and Murray, 1982). Effects on neurotransmitters may be both specific and highly localized. Manganese neurotoxicity, for example, is reportedly associated with a selective depletion of dopamine in the striatum, a site of manganese accumulation (Neff et al., 1969; Bernheimer et al., 1973).

A resemblance exists between the symptoms of manganism and Parkinsonism, a condition characterized by loss of dopaminergic neurons in the substantia nigra and globus pallidus. In addition, several clinical features of manganism respond favorably to therapy with L-dopa in a manner similar to patients with Parkinson's disease (Mena et al., 1970) although long-term response of manganism patients to L-dopa has not been observed (ATSDR, 2000; Calne et al. 1994). However, despite some similarities in symptoms, a comparative study of a 52-year-old worker exposed to manganese in an ore crushing plant and a patient with Parkinson's disease did not reveal any similarity in neuropathology (Yamada et al., 1986). Barbeau (1984), Calne et al. (1994), and Pal et al. (1999) have summarized the similarities and differences between manganism and Parkinsonism. These researchers have noted that manganism characteristically occurs in phases of increasing severity and that sufferers exhibit dystonia (disordered tonicity of muscles), symptoms of extrapyramidal dysfunction such as bradykinesia (extreme slowness of movements and reflexes), monotonic speech, and an expressionless or even grimacing face. Although the altered gait and fine tremor are common to both Parkinsonism and manganism, the syndromes are different in that manganism patients sometimes have psychiatric disturbances early in the onset of the syndrome, have a tendency to fall backwards, do not have the Lewy bodies in the substantia nigra that are commonly found in Parkinson's patients. Further, fluorodopa positron emission tomography (PET) scans are normal in manganism patients but not in individuals with Parkinson's disease (ATSDR, 2000).

Mapping studies by Yamada et al. (1986) indicate that most of the neuronal degeneration attributed to manganese exposure lies close to monoamine cell bodies and pathways. Histopathology in manganese-exposed primates shows more widespread deposition of the metal, with intense signaling observed in both the globus pallidus and substantia nigra using MRI

(Newland and Weiss, 1992). Studies in humans indicate that excess manganese in the brain deposits primarily in the globus pallidus (Fell et al. 1996; Kafritsa et al. 1998; Ono et al. 1995) and damage to the human brain from manganese deposition may be limited to that region. In a study that supports these findings, the globus pallidus exhibited atrophy in an autopsy performed on a worker with inhalation-related manganese poisoning (Yamada et al., 1986).

Although there is consensus that the monoaminergic systems, particularly the dopaminergic system, are affected by excess exposure to manganese, the precise mechanism of action remains obscure. One hypothesis proposes that oxidation of dopamine plays a key role in manganese neurotoxicity. Manganese (III) has been shown to oxidize dopamine to its cyclized *O*-quinone (cDAoQ) (Archibald and Tyree, 1987). This irreversible process ultimately results in decreased dopamine levels. The formation of cDAoQ may subsequently initiate the generation of reactive oxygen species, leading to oxidative stress and cell death (Segura-Aguilar and Lind, 1989).

An alternative hypothesis for manganese toxicity proposes an effect on brain cytochrome P-450 activity. Liccione and Maines (1989) demonstrated a high sensitivity of rat striatal mitochondria to manganese-induced increases in cytochrome P-450 activity. These authors speculated that the increase in mixed function oxidase activity may trigger an increase in the formation of active oxygen species (e.g., superoxide anions) that exert a harmful effect on dopaminergic pathways.

Other mechanistic studies have identified tyrosine hydroxylase (TOH), the rate limiting enzyme in dopamine synthesis, as a potential target in manganese-induced neurochemical effects. Bonilla (1980) and Chandra and Shukla (1981) found that changes in TOH activity in the presence of manganese closely paralleled dopamine levels. Qato and Maines (1985) determined that alterations in the activity of TOH and other monooxygenases may be related to manganese-induced alterations in brain heme metabolism.

Manganese toxicity may be selectively associated with adverse effects on mitochondria. Maynard and Cotzias (1955) originally proposed the mitochondrion as the target organelle for manganese cytotoxicity, with adverse effects expressed primarily as disruption of Ca(II) homeostasis. Mn(II) preferentially accumulates in the mitochondria in regions of the brain associated with neurological symptoms and manganism. Once inside the mitochondria, Mn(II) disrupts oxidative phosphorylation. The fundamental role of mitochondrial energy metabolism in manganese neurotoxicity has been highlighted by the studies of Aschner and Aschner (1990) and Gavin et al. (1992), as cited in U.S. EPA (1996a) and ATSDR (2000).

The results of Brouillet et al. (1993) confirm that manganese impairs mitochondrial oxidative metabolism. In addition, their findings indicate that manganese neurotoxicity involves an *N*-methyl-D-aspartate receptor-mediated process similar to that observed for some other mitochondrial toxicants. Manganese may thus produce neuronal degeneration by an excitotoxic process secondary to its ability to disrupt oxidative energy metabolism.

### 7.3.5 Structure-Activity Relationship

Information on structure-activity relationships is not available for manganese.

## 7.4 Hazard Characterization

### 7.4.1 Synthesis and Evaluation of Major Noncancer Effects

Manganese is an ubiquitous element that is essential for normal physiological functioning in all animal species. The biochemical basis for this requirement is most likely the participation of manganese as a structural component or catalytic cofactor for many enzymes. The Adequate Intake levels for manganese range from 0.003 to 0.6 mg/day for infants from birth to 6 months, 0.6 mg/day for infants from 7 months to 1 year, 1.2 mg/day for children aged 1-3 years, 1.5 to 1.9 mg/day for children aged 4-13 years, and from 1.6 to 2.3 mg/day for adolescents and adults (Food and Nutrition Board, 2002). Although outright manganese deficiency has not been observed in the general population, sub-optimal intake may be of concern for some individuals.

In contrast to the beneficial effects of manganese as a nutrient, excess exposure to manganese may be associated with toxic effects. At present, the optimal level of oral exposure to manganese is not well defined (Greger, 1999).

Ingested manganese appears to be primarily absorbed in the Mn(II) form, and may compete with iron and cobalt for common absorption sites. Absorption varies among individuals and is also influenced by dietary factors. Absorption of 3 to 10% of ingested dietary manganese is considered to be representative of the general population (U.S. EPA, 1996a). Iron deficiency enhances the absorption of manganese in animals (U.S. EPA, 1984). Uptake of dietary manganese may be reduced in the presence of other dietary components such as calcium and phytate.

Once absorbed, manganese has the potential to accumulate in mitochondria-rich tissues, including liver, pancreas, and kidney. Lesser amounts accumulate in brain and bone. Manganese is efficiently removed from the blood by the liver and released into bile. Biliary secretion represents the major pathway for manganese transport to the intestine, and studies in humans indicate that manganese is primarily excreted in the feces. The rate of excretion responds efficiently to increased manganese intake. The rate of biliary secretion acts in concert with absorptive processes to establish homeostatic control of manganese levels in the body. As long as physiological systems are not overwhelmed, humans appear to exert efficient homeostatic control over manganese levels, so that levels in the body are kept relatively constant despite moderate variations in intake. Manganese is also reabsorbed in the intestine through enterohepatic circulation (Schroeder et al. 1966).

While it is apparent that exposure to excess manganese can result in increased tissue levels, the interrelationships between oral exposure levels, tissue accumulation, and health effects in humans are not completely understood. Epidemiological studies of workers exposed by

inhalation to manganese dusts and fumes have identified the central nervous system (CNS) as the primary target for chronic manganese toxicity by the inhalation route (U.S. EPA, 1993). Both Mn(III) and Mn(II) have been associated with the neurotoxic effects of manganese. While some researchers note the similarities in CNS effects occurring following manganese exposure and in Parkinson's disease (dystonia, rigidity, bradykinesia), there are significant differences in the two diseases. For example, manganism patients exhibit a less-frequent resting tremor than do Parkinson's patients, extrapyramidal symptoms including fixed expression or a facial grimace, active tremor (particularly in the upper body), a "cock-walk" in which the patient walks on the toes with the back stiff and the elbows flexed, a propensity to fall backwards (especially when pushed), and a failure to respond to dopaminomimetics (Barbeau, 1984; Calne et al., 1994; Pal et al., 1999).

Several investigators have proposed a link between elevated oral manganese intake by humans and neurological symptoms resembling manganism (Kawamura et al., 1941; Kilburn, 1987; Kondakis et al., 1989; Goldsmith et al., 1990). Results from these studies are described in detail in Section 7.1. In each case, the data from these studies were insufficient to establish that manganese was the causative factor (ATSDR, 2000). The evidence for a similar pattern of neurotoxicity in humans following oral exposure is therefore considered equivocal.

Numerous studies have investigated manganese neurotoxicity in rodent models. However, the utility of rodent studies for evaluating the potential neurotoxic effects of manganese in humans has been questioned. Although biochemical and behavioral evidence of neurological effects has been observed, signs of impaired motor function resembling those seen in humans are usually not detected. In particular, studies of rodents exposed to manganese by drinking water or food have been unable to produce the characteristic signs of extrapyramidal neurologic disease seen in humans. In contrast, chronic administration of manganese to monkeys by oral (one study) or parenteral routes (two studies) has resulted in neurological signs consistent with chronic manganism. The failure to reproduce these signs in rodent studies may result from differences in manganese accumulation and distribution between rodents and primates. The dietary requirement for manganese in rodents, for example, is estimated to be 100 times higher than in humans. In addition, neurotoxic effects in humans are associated with manganese accumulation in neuromelanin-rich regions of the brain, and the homologous regions in rats and mice lack this pigment. Although primates are likely to be better models of the neurological manifestations of manganese intoxication than rodent species, sufficient data from well-designed oral studies are not currently available.

An additional drawback to animal studies of manganese neurotoxicity is the inability to identify certain psychological or neurobehavioral signs. Overt neurological impairment in humans is often preceded by psychological symptoms such as irritability and emotional lability. Since accurate dose-response relationships based on neurobehavioral endpoints are generally not available from animal studies, neurochemical responses have been examined as alternative indicators of neurotoxicity. Such studies have been conducted on the assumption that since the toxic manifestations of chronic manganese exposure resemble Parkinsonism, altered biogenic amine metabolism in the CNS may be one of the underlying mechanisms. However the patterns

of neurochemical response reported following manganese exposure are not consistent among studies. Although manganese exposure is generally thought to result in decreased dopamine concentrations, some studies report increased or fluctuating levels. The effect of manganese on dopamine levels, for example, appears to be age-dependent. Neonatal rats and mice exposed to manganese from birth to 15 or 30 days of age have an increased levels of dopamine and norepinephrine in the brain (Chandra et al., 1979; Cotzias et al., 1976; Shukla et al., 1980). Further, temporal changes in dopamine neurochemistry have been observed with prolonged or continuous manganese treatment and it is not established how these time-related changes affect manganese-induced neurotoxicity.

Route of administration is also an issue of concern in evaluating the results of animal studies. Scheuhammer (1983), for example, determined that intraperitoneal injection is not the route of choice for studies of manganese exposure that are longer than 30 days in duration, especially for investigations of neurotoxicity. Intraperitoneally administered manganese appears to have a selectively toxic effect on the pancreas. This effect may make it difficult to distinguish between subtle neurochemical changes resulting directly from manganese exposure, and changes that are secondary to cellular damage in the pancreas. In addition, U.S. EPA (1984) noted that results from parenteral studies are of limited value in predicting the reproductive hazards of ingested manganese. At least one study exists, however, that shows the differential uptake and distribution of manganese administered via injection compared to oral dosing. Roels et al. (1997) investigated the uptake and distribution of manganese (as either $MnO_2$ or $MnCl_2$) in rats following intra peritoneal injection or gavage dosing. Manganese concentrations were not increased in the blood or brain following administration of 4 weekly doses of 1.22 mg Mn/kg of the dioxide via gavage; following i.p. dosing, manganese concentrations were significantly increased in the blood, striatum, cerebellum and cortex. Steady-state blood manganese concentrations were increased to similar levels by both gavage and i.p. dosing of $MnCl_2$. Gavage dosing of the dichloride significantly increased the cortex manganese concentrations, but not that of the other two regions. Intra peritoneal dosing of the compound increased the manganese levels in the striatum and cortex, but not the cerebellum. These data indicate that depending on the compound, injection administration of manganese results in higher blood and brain concentrations of the metal than does gavage administration.

Toxic effects of oral manganese exposure have also been reported in the hematopoietic, cardiovascular, reproductive, and digestive systems in animals. Hematological and biochemical outcomes vary depending on age and iron status, with young or iron-deficient animals more likely to exhibit adverse effects. Other effects observed following manganese exposure include reduced body weight and reduced liver weight. Animal studies suggest that manganese is not a potent developmental toxicant.

Infants have been identified as a potentially sensitive subpopulation for excess manganese exposure. This determination reflects evidence for higher levels of manganese retention in the brains of neonates than in adults, although the relationship between manganese accumulation in the neonatal brain and toxicity remains unclear (U.S. EPA, 1993). Additional concerns include evidence for greater extent of manganese transport across the blood-brain barrier, the high

concentration of manganese in some infant formulas, and evidence suggestive of a possible link between manganese exposure and learning disabilities. Although a causal relationship has not been established for elevated manganese intake and learning disabilities, a need for further research in this area has been noted (U.S. EPA, 1993).

Other potentially sensitive subpopulations for manganese exposure have been identified. In general, these are groups who may have greater potential for increased body burdens due to increased absorption or altered clearance mechanisms. The list includes pregnant women, elderly persons, iron- or calcium-deficient individuals, and individuals with impaired liver function.

### 7.4.2 Synthesis and Evaluation of Carcinogenic Effects

The carcinogenic potential of ingested manganese has not been systematically evaluated in epidemiological studies.

Data from animal studies are also limited. Currently, one of the few adequately designed investigations is the 2-year oral exposure study conducted by the National Toxicology Program (NTP, 1993). Groups of F344 rats (70/sex) were provided with diets containing 0, 1,500, 5,000, or 15,000 ppm manganese sulfate monohydrate. These dietary concentrations were reported to be equivalent to an intake ranging from 30 to 331 mg Mn/kg-day for males, and 26 to 270 mg Mn/kg-day for females. No increase in any tumor type could be attributed to manganese exposure.

In a concurrent study, $B6C3F_1$ mice were administered 0, 1,500, 5,000, or 15,000 mg/kg manganese sulfate monohydrate (NTP, 1993). These dietary concentrations were reported to be equivalent to an intake ranging from 63 to 722 mg Mn/kg-day for males and 77 to 905 mg Mn/kg-day for females. Compared to controls, the incidences of thyroid follicular cell hyperplasia were significantly greater in high-dose males and in females at all dose levels. The incidence of follicular cell adenomas in high-dose males (6%) was slightly greater than the range of historical incidence in NTP studies of follicular cell adenomas in male $B6C3F_1$ mice (0–4%). In high-dose females, the incidence of follicular cell adenomas (10%) was also slightly above the historical control range (0–9%). Follicular cell tumors were seen only at the termination of the study (729 days). NTP (1993) reported that the manganese intakes in the high-dose mice were 107 times greater than the recommended dietary level. While NTP (1993) concluded that these data provided "equivocal evidence of carcinogenic activity in mice," U.S. EPA (1993) questioned the relevance of these findings to human carcinogenesis. The basis for concern was 1) the large dose of manganese required to elicit a response observed only at the end of the study, and 2) tumor frequencies that were not statistically different from historical controls.

Three additional studies address the carcinogenicity of manganese. DiPaolo (1964) found that a larger percentage of DBA/1 mice exposed subcutaneously and intraperitoneally to manganese chloride developed lymphosarcomas when compared to controls. A comprehensive evaluation of these data was not possible, however, because they were published in an abstract form which lacked sufficient experimental detail. Stoner et al. (1976) found a higher frequency of

lung tumors in strain A/Strong mice administered manganese sulfate intraperitoneally as compared to controls. Although these results are suggestive of carcinogenic activity, they fail to meet the positive response criteria for the interpretation of lung tumor data in this strain of 1) an increase in the mean number of tumors per mouse, and 2) an observable dose-response relationship (Shimkin and Stoner, 1975). In the third study, Furst (1978) injected F344 rats intramuscularly with manganese acetylacetonate. An increased incidence of fibrosarcomas was observed at the injection site. Increased tumor incidence was not observed at other sites. When evaluated as a group, these studies do not provide convincing evidence for carcinogenicity of manganese.

Both negative and positive results have been obtained in assays for the genotoxic effects of manganese. Mutagenicity assays in multiple tester strains of *Salmonella typhimurium* gave predominately negative results for manganese sulfate monohydrate and manganese chloride when tested with or without exogenous metabolic activation by S9 fraction (Wong, 1988; DeMeo et al., 1991; Pagano and Zeiger, 1992; NTP, 1993). Neither compound induced mutations in *Drosophila melanogaster* as evaluated by sex-linked recessive lethal or somatic mutation assays (Rasmuson, 1985; Valencia et al., 1985; NTP, 1993). Dikshith and Chandra (1978) did not observe increased incidence of chromosomal aberrations in rat bone marrow or spermatogonial cells following oral administration of manganese chloride.

In addition to the negative results described above, positive results for manganese compounds have been obtained in some assays for genotoxicity. Manganese sulfate induced sister chromatid exchange and chromosomal aberrations *in vitro* in Chinese hamster ovary cells, and induced chromosomal aberrations *in vivo* in albino mice following oral administration (Joardar and Sharma, 1990). Manganese compounds also induced or enhanced mutation, transformation, chromosomal aberrations, and DNA damage in some assays conducted in mammalian cell lines (Casto et al., 1979; Oberly et al., 1982; DeMeo et al., 1991; NTP, 1993), bacteria (Orgel and Orgel, 1965; Nishioka, 1975; Zakour and Glickman, 1984), and yeast (Singh, 1984). Although these results suggest that manganese may have genotoxic potential, there are presently no epidemiological or unequivocal animal data to suggest that manganese is carcinogenic.

### 7.4.3 Mode of Action and Implications in Cancer Assessment

The molecular mechanisms responsible for the toxicity of manganese have not been identified with certainty. Most effort has focused on identification of mechanisms mediating the toxic effects observed in the central nervous system. Multiple researchers have proposed that elevated levels of Mn(II) and Mn(III) trigger the production of free radicals, reactive oxygen species, and other cytotoxic metabolites in brain tissue. Generation of these reactive species is hypothesized to occur via the oxidation or turnover of intracellular catecholamines, impacts on mitochondrial metabolism, or stimulation of cytochrome P-450 activity. Manganese may also influence transport systems, enzyme activity and receptor function in the brain and other organs. At the present time, there is no evidence to link these proposed mechanisms of action to carcinogenic potential.

### 7.4.4 Weight of Evidence Evaluation for Carcinogenicity

The weight of evidence for manganese carcinogenicity is currently rated as Group D (Not Classifiable) using the criteria of the U.S. EPA Guidelines for Carcinogen Risk Assessment (U.S. EPA, 1986a). The classification of Group D was verified on May 25, 1988 by the CRAVE Work Group of the U.S. EPA. The basis for this determination is the inadequacy of existing studies for assessment of manganese carcinogenicity (U.S. EPA, 1996a).

Manganese has not yet been evaluated using the criteria of the U.S. EPA Proposed Guidelines for Carcinogen Risk Assessment (U.S. EPA, 1996b). However, evaluation of currently available data suggests that the appropriate descriptor for manganese would be "inadequate data for an assessment of human carcinogenic potential." This descriptor is appropriate when the available information is judged to be inadequate to perform an assessment of human carcinogenic potential. It is applied when there are conflicting data on carcinogenicity or in situations where there is a paucity of data.

### 7.4.5 Sensitive Populations

Sensitive populations are defined as those which will exhibit an enhanced or altered response to a chemical when compared with most persons exposed to the same concentration of chemical in the environment. Factors that can contribute to this altered response include genetic composition, age, developmental stage, health status, substance use history, and nutritional status. These factors may alter the function of detoxification and excretory processes, or compromise the function of target organs. In general, the elderly with declining organ function and infants and children with developing organs are expected to be more sensitive to toxic substances than healthy adults.

### 7.4.6 Potential Childhood Sensitivity

Neonates have been identified as a potentially sensitive subpopulation for manganese exposure. This determination reflects observations in human (Zlotkin and Buchanan, 1986) and animal (Keen et al., 1986; Kostial et al., 1978; Rehnberg, et al. 1980) studies that suggest that neonates retain higher levels of administered manganese than adults.

In adults, manganese concentrations are retained within a narrow range by the ability of excretion systems to match the intake of this element (Fechter, 1999). The process responsible for manganese excretion is generally believed to require a significant time period to mature into the adult pattern, with adult patterns of excretion developing at about the time of weaning (Fechter, 1999). During this period of development, the young organism might be susceptible to manganese toxicity if exposed to high levels in the diet or via environmental contamination.

Data with respect to fetal accumulation are not numerous, but appear to consistently demonstrate that manganese is transported across the placenta to a limited extent (Fechter, 1999). When all available data are examined, it appears that the fetus is relatively protected from

manganese accumulation when maternal exposure occurs at relatively low doses. Under conditions of high maternal exposure, manganese accumulation also appears to be limited (Fechter, 1999). The mechanism underlying this lack of accumulation is unknown, but may reflect increased maternal excretion, limited uptake across the placenta, or fetal elimination.

The greatest concern for developmental susceptibility has been generated by data which suggest the existence of a period prior to weaning when the neonate is unable to eliminate manganese. Fechter (1999) reassessed data in the published literature and concluded that the available literature does not support a toxicokinetic basis for accumulation in the fetal or neonatal organism [relative to the adult organism], under conditions of excess exposure to manganese. While the available data indicate that manganese does reach brain tissue, currently available evidence does not support a clear regional distribution.

Kaur et al. (1980) found that younger neonates and 19-day fetuses were more susceptible to manganese toxicity than older rats. Studies with $^{54}Mn$ indicated that manganese was localized to the liver and brain in younger animals, and there was more manganese per unit weight in younger animals when compared with older animals.

Collipp et al. (1983) found that hair manganese levels in newborn infants increased significantly from birth (0.19 μg/g) to 6 weeks of age (0.885 μg/g) and 4 months of age (0.685 μg/g) when the infants were given formula. In contrast, there was no significant increase in babies who were breast-fed (0.330 μg/g at 4 months). These results were attributed to the difference in manganese content between infant formula and breast milk. Human breast milk is relatively low in manganese (7 to 15 μg/L), while levels in infant formulas are 3 to 100 times higher. Collipp et al. (1983) further reported that the level of manganese in the hair of learning disabled children (0.434 μg/g) was significantly increased in comparison to samples from normal children (0.268 μg/g).

There is at least one study reporting different responses in manganese-treated neonatal animals compared to treated adults (Dorman et al., 2000). Pups were administered $MnCl_2$ in water at 11 or 22 mg Mn/kg for 21 days by mouth and were dosed starting after birth, postnatal day 1 (PND 1), until weaning, PND 21. At PND 21, the effect of manganese treatment on motor activity, learning and memory (passive avoidance task), evoked sensory response (acoustic startle reflex), brain neurochemistry, and brain pathology was evaluated. Manganese treatment at the highest dose was associated with decreased body weight gain in pups, although the authors indicated absolute brain weight was not significantly altered. There were no statistically significant effects on motor activity or performance in the passive avoidance task. However, manganese treatment induced a significant increase in amplitude of the acoustic startle reflex. Significant increases in striatal DA and DOPAC concentrations were also observed in the high-dose treated neonates. No pathological lesions were observed in the treated pups. No effects on body weight or behavior were observed in treated adult animals in this study. The authors indicated that these results suggest that neonatal rats are at greater risk than adults for manganese-induced neurotoxicity when compared under similar exposure conditions. This study, along with evidence for increased absorption and reduced elimination in the neonate, suggests that

the very young may be more susceptible to the harmful effects of manganese exposure due to differences in toxicokinetics.

Other investigators have reported an association between elevated hair levels of manganese and learning disabilities in children (Barlow and Kapel, 1979; Pihl and Parkes, 1977). Although no causal relationship has been established for learning disabilities and manganese intake, further research in this area is warranted (U.S. EPA, 1993). The studies by He et al. (1994) and Zhang et al. (1995) reported increased manganese levels in hair of school-age children exposed to excess levels of manganese in drinking water and food stuffs. These studies conflict with the Kawamura et al. (1941) study which showed that children were not adversely affected by ingesting excess levels of manganese. The more recent studies differ in design, however, because they measured early preclinical neurological effects of manganese overexposure. The older studies did not have the sensitivity to measure such effects; this may explain why children were not previously identified as a sensitive population. None of the studies in children provide adequate exposure levels or properly control for confounding factors; therefore, they are not strong enough to indicate that children are more sensitive than adults. They do confirm the need for additional studies to investigate the possibility that children may be more susceptible than adults to the effects of manganese overexposure.

High levels of manganese in infant formulas may also be of concern since Lönnerdal et al. (1987) reported increased absorption and retention of manganese in neonatal animals. Manganese has also 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). Dieter et al. (1992) stated that "if there were a toxicological limit to manganese according to the principles of preventive health care, then it would have to be set at 0.2 mg/L of manganese in water for infants as a group at risk."

### 7.4.7 Other Potentially Sensitive Populations

U.S. EPA (1996a) has identified additional sensitive subpopulations for manganese exposure. In general, these are groups who may have greater potential for increased body burdens due to increased absorption or altered clearance mechanisms. The list includes pregnant women, elderly persons, iron- or calcium-deficient individuals, and individuals with impaired liver function.

# 8.0 DOSE-RESPONSE ASSESSMENT

## 8.1 Dose-Response for Noncancer Effects

### 8.1.1 RfD Determination

***Choice of Principal Study and Critical Effect***

Manganese is an essential trace element that is required for normal physiologic function in humans and animals. Excess exposure to manganese, particularly via the inhalation route, is associated with neurotoxicological symptoms that resemble parkinsonism. Thus, derivation of the RfD must consider issues of both essentiality and toxicity.

The RfD is not based on rodent studies, because rodents do not exhibit the same neurologic deficits that humans do following exposure to manganese. For example, manganese at high doses induces parkinson-like symptoms in humans and primates, but not in rodents. Because of the species difference in the response to manganese exposure, rodents are not good models for manganese toxicity studies. More details on this can be seen in IRIS (USEPA, 1996a).

The reference dose (RfD) is based on the extensive information available for the dietary intake of manganese by human populations (U.S. EPA, 1996a). Freeland-Graves et al. (1987) reviewed human studies and proposed an estimated safe and adequate daily dietary intake of 3.5 to 7 mg for adults. WHO (1973) reviewed data on adult diets and concluded on the basis of manganese balance studies that 2 to 3 mg/day is an adequate daily intake and 8 to 9 mg/day is "perfectly safe."

***Dose-Response Assessment and Method of Analysis***

The current RfD for manganese was derived from information gathered in dietary surveys of manganese exposure. In various surveys, manganese intakes of adults eating western-type and vegetarian diets ranged from 0.7 to 10.9 mg per day (Freeland-Graves, 1994; Gibson, 1994 as cited by Food and Nutrition Board, 2002). Depending on individual diets, a normal intake may be well over 10 mg per day, especially from a vegetarian diet Based on this information, the U.S. EPA (1996a) considers a dietary intake of 10 mg/day to be safe for a 70 kg adult. Thus, the resulting dose of 0.14 mg/kg-day represents a NOAEL for chronic human consumption of manganese in the diet (U.S. EPA, 1996a).

***Application of Uncertainty and Modifying Factors***

U.S. EPA (1996a) has recommended use of an uncertainty factor of 1 for derivation of the manganese RfD. This recommendation is based on the following considerations. Manganese is an essential trace element for human health. The information used to derive the RfD was collected from many large human populations consuming normal diets over an extended period of time. The available data suggest that as long as physiological systems are not overwhelmed,

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# Alternative Disinfectants and Oxidants Guidance Manual

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# 5. POTASSIUM PERMANGANATE

Potassium permanganate ($KMnO_4$) is used primarily to control taste and odors, remove color, control biological growth in treatment plants, and remove iron and manganese. In a secondary role, potassium permanganate may be useful in controlling the formation of THMs and other DBPs by oxidizing precursors and reducing the demand for other disinfectants (Hazen and Sawyer, 1992). The mechanism of reduced DBPs may be as simple as moving the point of chlorine application further downstream in the treatment train using potassium permanganate to control taste and odors, color, algae, etc. instead of chlorine. Although potassium permanganate has many potential uses as an oxidant, it is a poor disinfectant.

## 5.1 Potassium Permanganate Chemistry

### 5.1.1 Oxidation Potential

Potassium permanganate is highly reactive under conditions found in the water industry. It will oxidize a wide variety of inorganic and organic substances. Potassium permanganate (Mn 7+) is reduced to manganese dioxide ($MnO_2$) (Mn 4+) which precipitates out of solution (Hazen and Sawyer, 1992). All reactions are exothermic. Under acidic conditions the oxidation half-reactions are (CRC, 1990):

$$MnO_4^- + 4H^+ + 3e^- \quad MnO_2 + 2H_2O \qquad E^o = 1.68V$$

$$MnO_4^- + 8H^+ + 5e^- \quad Mn^{2+} + 4H_2O \qquad E^o = 1.51V$$

Under alkaline conditions, the half-reaction is (CRC, 1990):

$$MnO_4^- + 2H_2O + 3e^- \quad MnO_2 + 4OH^- \qquad E^o = 0.60V$$

Reaction rates for the oxidation of constituents found in natural waters are relatively fast and depend on temperature, pH, and dosage.

### 5.1.2 Ability To Form a Residual

It is not desirable to maintain a residual of $KMnO_4$ because of its tendency to give water a pink color.

## 5.2 Generation

Potassium permanganate is only supplied in dry form. A concentrated $KMnO_4$ solution (typically 1 to 4 percent) is generated on-site for water treatment applications; the solution is pink or purple in color. $KMnO_4$ has a bulk density of approximately 100 lb/ft$^3$ and its solubility in water is 6.4 g/mL at 20°C.

Depending on the amount of permanganate required, these solutions can be made up in batch modes, using dissolver/storage tanks with mixers and a metering pump for small feed systems. Larger systems will include a dry chemical feeder, storage hopper and dust collector configured to automatically supply permanganate to the solution dissolver/storage tank.

$KMnO_4$ solution is made up of dry crystalline permanganate solids added to make-up water and then stirred to obtain the desired permanganate concentration. The cost of $KMnO_4$ ranges from $1.50 to $2.00 per pound (1997 costs), depending on the quantity ordered. Shipment containers are typically buckets or drums. Potassium permanganate is supplied in various grades. Pure $KMnO_4$ is non-hygroscopic but technical grades will absorb some moisture and will have a tendency to cake together. For systems using dry chemical feeders, a free-flowing grade is available that contains anti-caking additives (Hazen and Sawyer, 1992).

Potassium permanganate is a strong oxidizer and should be carefully handled when preparing the feed solution. No byproducts are generated from making the solution. However, this dark purple/black crystalline solid can cause serious eye injury, is a skin and inhalation irritant, and can be fatal if swallowed. As such, special handling procedures include the use of safety goggles and a face shield, an MSA™/NIOSH approved dust mask, and wearing impervious gloves, coveralls, and boots to minimize skin contact.

# 5.3 Primary Uses and Points of Application

Although potassium permanganate can inactivate various bacteria and viruses, it is not used as a primary or secondary disinfectant when applied at commonly used treatment levels. Potassium permanganate levels that may be required to obtain primary or secondary disinfection could be cost prohibitive. However, potassium permanganate is used in drinking water treatment to achieve a variety of other purposes including:

- Oxidation of iron and manganese;
- Oxidation of taste and odor compound;
- Control of nuisance organisms; and
- Control of DBP formation.

## 5.3.1 Primary Uses

### *5.3.1.1 Iron and Manganese Oxidation*

A primary use of permanganate is iron and manganese removal. Permanganate will oxidize iron and manganese to convert ferrous (2+) iron into the ferric (3+) state and 2+ manganese to the 4+ state. The oxidized forms will precipitate as ferric hydroxide and manganese hydroxide (AWWA, 1991). The precise chemical composition of the precipitate will depend on the nature of the water, temperature, and pH.

The classic reactions for the oxidation of iron and manganese are:

$$3Fe^{2+} + KMnO_4 + 7H_2O \quad 3Fe(OH)_{3(s)} + MnO_{2(s)} + K^+ + 5H^+$$

$$3Mn^{2+} + 2KMnO_4 + 2H_2O \quad 5MnO_{2(s)} + 2K^+ + 4H^+$$

These reactions show that alkalinity is consumed through acid production at the rate of 1.49 mg/L as $CaCO_3$ per mg/L of $Fe^{+2}$ and 1.21 mg/L as $CaCO_3$ per mg/L of $Mn^{+2}$ oxidized. This consumption of alkalinity should be considered when permanganate treatment is used along with alum coagulation, which also requires alkalinity to form precipitates.

The potassium permanganate dose required for oxidation is 0.94 mg/mg iron and 1.92 mg/mg manganese (Culp/Wesner/Culp, 1986). In practice, the actual amount of potassium permanganate used has been found to be less than that indicated by stoichiometry. It is thought that this is because of the catalytic influence of $MnO_2$ on the reactions (O'Connell, 1978). The oxidation time ranges from 5 to 10 minutes, provided that the pH is over 7.0 (Kawamura, 1991).

#### 5.3.1.2 Oxidation of Taste and Odor Compounds

Potassium permanganate is used to remove taste and odor causing compounds. Lalezary et al. (1986) used permanganate to treat earthy-musty smelling compounds in drinking water. Doses of potassium permanganate used to treat taste and odor causing compounds range from 0.25 to 20 mg/L.

#### 5.3.1.3 Control of Nuisance Organisms

Asiatic Clams

Cameron et al. (1989) investigated the effectiveness of potassium permanganate to control the Asiatic clam in both the juvenile and adult phases. The adult Asiatic clam was found to be much more resistant to permanganate than the juvenile form. Potassium permanganate doses used to control the juvenile Asiatic clam range from 1.1 to 4.8 mg/L.

Zebra Mussels

Klerks and Fraleigh (1991) evaluated the effectiveness of permanganate against adult zebra mussels. Continuous potassium permanganate dosing of 0.5 to 2.5 mg/L proved to be the most effective.

#### 5.3.1.4 DBP Control

It is anticipated that potassium permanganate may play a role in disinfection and DBP control strategies in water treatment. Potassium permanganate could be used to oxidize organic precursors at the head of the treatment plant minimizing the formation of byproducts at the downstream disinfection stage of the plant (Hazen and Sawyer, 1992). Test results from a study conducted at two water treatment plants in North Carolina (Section 5.5.1) showed that pretreatment with permanganate reduced chloroform formation; however, the reduction was small at doses typically used at water

treatment plants. The study also indicated that pre-oxidation with permanganate had no net effect on the chlorine demand of the water (Singer et al., 1980).

## 5.3.2 Points of Application

In conventional treatment plants, potassium permanganate solution is added to the raw water intake, at the rapid mix tank in conjunction with coagulants, or at clarifiers upstream of filters. In direct filtration plants, this oxidant is typically added at the raw water intake to increase the contact time upstream of the filter units (Montgomery, 1985). In all cases, potassium permanganate is added prior to filtration.

Potassium permanganate solution is typically pumped from the concentrated solution tank to the injection point. If the injection point is a pipeline, a standard injection nozzle protruding midway into the pipe section is used. Injection nozzles can also be used to supply the solution to mixing chambers and clarifiers. Permanganate is a reactive, fast-acting oxidizer and does not require special mixing equipment at the point of injection to be effective.

### *5.3.2.1 Impact on Other Treatment Processes*

The use of potassium permanganate has little impact on other treatment processes at the water treatment facility. See Section 5.7 for permanganate operational considerations.

# 5.4 Pathogen Inactivation and Disinfection Efficacy

Potassium permanganate is an oxidizing agent widely used throughout the water industry. While it is not considered a primary disinfectant, potassium permanganate has an effect on the development of a disinfection strategy by serving as an alternative to pre-chlorination or other oxidants at locations in a treatment plant where chemical oxidation is desired for control of color, taste and odor, and algae.

## 5.4.1 Inactivation Mechanisms

The primary mode of pathogen inactivation by potassium permanganate is direct oxidation of cell material or specific enzyme destruction (Webber and Posselt, 1972). In the same fashion, the permanganate ion ($MnO_4^-$) attacks a wide range of microorganisms such as bacteria, fungi, viruses, and algae.

Application of potassium permanganate results in the precipitation of manganese dioxide. This mechanism represents an additional method for the removal of microorganisms from potable water (Cleasby et al., 1964). In colloidal form, the manganese dioxide precipitant has an outer layer of exposed OH groups. These groups are capable of adsorbing charged species and particles in addition to neutral molecules (Posselt et al., 1967). As the precipitant is formed, microorganisms can be adsorbed into the colloids and settled.

## 5.4.2 Environmental Effects

Inactivation efficiency depends upon the permanganate concentration, contact time, temperature, pH, and presence of other oxidizable material. Several of the key parameters are discussed below.

### *5.4.2.1 pH*

Alkaline conditions enhance the capability of potassium permanganate to oxidize organic matter; however, the opposite is true for its disinfecting power. Typically, potassium permanganate is a better biocide under acidic conditions than under alkaline conditions (Cleasby et al., 1964 and Wagner, 1951). Results from a study conducted in 1964 indicated that permanganate generally was a more effective biocide for E. coli at lower pHs, exhibiting more than a 2-log removal at a pH of 5.9 and a water temperature of both 0 and 20°C (Cleasby et al., 1964). In fact, Cleasby found that pH is the major factor affecting disinfection effectiveness with potassium permanganate. As such, natural waters with pH values of 5.9 or less would be conducive to potassium permanganate disinfection, particularly as a substitute for prechlorination. Moreover a study conducted at the University of Arizona found that potassium permanganate will inactivate *Legionella pneumophila* more rapidly at pH 6.0 than at pH 8.0 (Yahya et al., 1990a).

These results are consistent with earlier results concerning the effects of pH on commercial antiseptic performance (Hazen and Sawyer, 1992). In general, based on the limited results from these studies, disinfection effectiveness of potassium permanganate increases with decreasing pH.

### *5.4.2.2 Temperature*

Higher temperatures slightly enhance bactericidal action of potassium permanganate. The results from a study conducted on polio virus showed that oxidation deactivation is enhanced by higher temperatures (Lund, 1963). These results are consistent with results obtained for *E. coli.* inactivation (Cleasby et al., 1964).

### *5.4.2.3 Dissolved Organics and Inorganics*

The presence of oxidizable organics or inorganics in the water reduces the disinfection effectiveness of this disinfectant because some of the applied potassium permanganate will be consumed in the oxidation of organics and inorganics. Permanganate oxidizes a wide variety of inorganic and organic substances in the pH range of 4 to 9. Under typical water conditions, iron and manganese are oxidized and precipitated and most contaminants that cause odors and tastes, such as phenols and algae, are readily degraded by permanganate (Hazen and Sawyer, 1992).

## 5.4.3 Use as a Disinfectant

A number of investigations have been performed to determine the relative capability of potassium permanganate as a disinfectant. The following sections contain a description of the disinfection efficiency of potassium permanganate in regards to bacteria, virus, and protozoa inactivation.

#### 5.4.3.1 Bacteria Inactivation

High dosage rates were required to accomplish complete inactivation of bacteria in three studies. Early research showed that a dose of 2.5 mg/L was required for complete inactivation of coliform bacteria (Le Strat, 1944). In this study, water from the Marne River was dosed with potassium permanganate at concentrations of 0 to 2.5 mg/L. Following mixing, the samples were placed in a darkened room for 2 hours at a constant temperature of 19.8°C.

Banerjea (1950) investigated the disinfectant ability of potassium permanganate on several waterborne pathogenic microorganisms. The investigation studied *Vibrio cholerae*, *Salm. typhi*, and *Bact. flexner*. The results indicated that doses of 20 mg/L and contact times of 24 hours were necessary to deactivate these pathogens; however, even under these conditions the complete absence of *Salm. typhi* or *Bact. flexner* was not assured, even at a potassium permanganate concentration that turned the water an objectionable pink color.

Results from a study conducted in 1976 at the Las Vegas Valley Water District/Southern Nevada System of Lake Mead water showed that complete removal of coliform bacteria were accomplished at doses of 1, 2, 3, 4, 5, and 6 mg/L (Hazen and Sawyer, 1992). Contact times of 30 minutes were provided with doses of 1 and 2 mg/L, and 10 minutes contact times were provided for higher dosages in this study.

#### 5.4.3.2 Virus Inactivation

Potassium permanganate has been proven effective against certain viruses. A dose of 50 mg/L of potassium permanganate and a contact time of 2 hours was required for inactivation of poliovirus (strain MVA) (Hazen and Sawyer, 1992). A "potassium" permanganate dose of 5.0 mg/L and a contact time of 33 minutes was needed for 1-log inactivation of type 1 poliovirus (Yahya et al., 1990b). Tests showed a significantly higher inactivation rate at 23°C than at 7°C; however, there was no significant difference in activation rates at pH 6.0 and pH 8.0.

Potassium permanganate doses from 0.5 to 5 mg/L were capable of obtaining at least a 2 log inactivation of the surrogate virus, MS-2 bacteriophage with *E. coli* as the host bacterium (Yahya et al., 1989). Results showed that at pH 6.0 and 8.0, a 2-log inactivation occurred after a contact time of at least 52 minutes and a residual of 0.5 mg/L. At a residual of 5.0 mg/L, approximately 7 and 13 minutes were required for 2-log inactivation at pHs of 8.0 and 6.0, respectively. These results contradict the previously cited studies that potassium permanganate becomes more effective as the pH decreases.

#### 5.4.3.3 Protozoa Inactivation

No information pertaining to protozoa inactivation by potassium permanganate is available in the literature. However, based on the other disinfectants discussed in this report, protozoa are significantly more resistant than viruses; therefore, it is likely that the dosages and contact times required for protozoa inactivation would be impractical.

#### 5.4.3.4 CT Curves

Table 5-1 shows CT values for the inactivation of bacteriophage MS-2. These data have been provided as an indication of the potential of potassium permanganate. These values are somewhat inconsistent and do not include a safety factor and should not be used to establish CT requirements.

**Table 5-1. Potassium Permanganate CT Values for 2-log Inactivation of MS-2 Bacteriophage**

| Residual (mg/L) | pH 6.0[1] (mg min / L) | pH 8.0[1] (mg min / L) |
|---|---|---|
| 0.5 | 27.4 (a) | 26.1 (a) |
| 1.5 | 32.0 (a) | 50.9 (b) |
| 2 | - | 53.5 (c) |
| 5 | 63.8 (a) | 35.5 (c) |

Source: USEPA, 1990.
Note: [1] Letters indicate different experimental conditions.

A 1990 study investigated CT values for *Legionella pneumophila* inactivation. CT values for 99 percent (2-log) inactivation of *Legionella pneumophila* at pH 6.0 were determined to be 42.7 mg min/L at a dose of 1.0 mg/L (contact time 42.7 minutes) and 41.0 mg min/L at a dose of 5.0 mg/L (contact time 8.2 minutes) (Yahya et al., 1990a).

## 5.5 Disinfection Byproduct Formation

No literature is available that specifically addressed DBPs when using potassium permanganate. However, several studies have been conducted with water treatment plants that have replaced the pre-chlorination process with potassium permanganate and relocated the point of chlorine addition for post-treatment disinfection. Pretreatment with permanganate in combination with post-treatment chlorination will typically result in lower DBP concentrations than would otherwise occur from traditional pre-chlorination (Ficek and Boll, 1980; and Singer et al., 1980). Under this approach, potassium permanganate serves as a substitute for chlorine to achieve oxidation and may also reduce the concentration of natural organic matter (NOM). However, systems should evaluate the impact on CT values before moving the point of chlorination. The following subsections summarize the outcomes of two studies.

### 5.5.1 Chapel-Hill and Durham, North Carolina Water Treatment Plants

An investigation was conducted at the Chapel-Hill and Durham Water Treatment Plants to evaluate the effects of potassium permanganate pretreatment on trihalomethane formation (Singer et al., 1980). The Chapel-Hill Water Treatment Plant uses pre-chlorination prior to the rapid mix tank. At the Durham Water Treatment Plant, chlorine is not added until after the sedimentation basin prior to the filtration. Both are surface water treatment plants, treating water with low concentrations of

alkalinity. Both sources of water are known to have high trihalomethane formation potentials (Young and Singer, 1979).

Raw water samples taken from Chapel-Hill were found to contain relatively high turbidities, ranging from 46 to 110 NTU and total organic carbon (TOC) concentrations ranging from 5.6 to 8.9 mg/L. The Durham samples were coagulated then allowed to settle, which resulted in better water quality than the Chapel-Hill samples. Following settling, this sample had a turbidity of 6.4 NTU and a TOC of 2.9 mg/L. Sulfuric acid and sodium hydroxide were used to adjust the sample pH to either 6.5 or 10.3. These pH values were selected because they encompass the pH range typically found in surface water coagulation-filtration and lime-softening treatment plants.

Potassium permanganate doses of 2 and 5 mg/L were found to be totally consumed within 1 and 4 hours, respectively, by the Chapel-Hill samples. At doses of 2 and 5 mg/L, the potassium permanganate demand of the Durham samples after 4 hours were approximately 1.3 and 1.8 mg/L, respectively.

This difference in permanganate demands between the Chapel-Hill and Durham samples may be attributed to the water quality of the samples, in particular the TOC concentrations. TOC measurements before and after the application of permanganate were approximately equal; however, it is likely that the TOC after disinfection was at a higher oxidation state. Results of this study also showed that permanganate is more reactive as an oxidant at higher pH values.

Despite the high degree of permanganate consumption, the reaction of permanganate appears to have relatively little effect on chlorine demands. For example, consumption of 6 mg/L of permanganate resulted in a chlorine demand reduction of approximately 1 mg/L. This observation suggests that permanganate reacts with water impurities in a different manner, or at different sites, than chlorine. One other possible explanation is that permanganate oxidizes certain organic substances, thereby eliminating their chlorine demand and only partially oxidizing other organic substances making them more reactive to chlorine.

Both the Chapel-Hill and Durham samples were tested for their chloroform formation potential. This measurement is based on the amount of chloroform produced after seven days. The potential of the Durham sample was reduced by 30 and 40 percent at pH 6.5 and 10.3, respectively, as a result of the application of 10 mg/L of potassium permanganate for a period of 2 hours. Similar results were obtained for the Chapel-Hill samples; however, the results at pH 6.5 did not show a reduction in chloroform formation potential at low doses.

Two experiments were conducted on Chapel-Hill raw water to further explore the effects of low doses of permanganate. The results indicated that permanganate has no effect on chloroform production at doses up to 1 mg/L. At higher doses, chloroform formation potentials were reduced.

In summary, the key results obtained from the studies conducted at the Chapel-Hill and Durham Water treatment plants were:

- The reactivity of permanganate is a function of pH, permanganate dose, and raw water quality.
- Permanganate reduces chloroform formation potentials. The reduction in the chloroform formation potential is proportional to the amount of permanganate available after the initial demand is overcome. Doses up to 1 mg/L were found to have no effect on chloroform formation potentials.
- At pretreatment doses typically employed at water treatment plants, the effect of permanganate on the overall chloroform production is relatively small. If permanganate is to be used specifically to reduce trihalomethane formation, larger doses will be required. However, one advantage for using permanganate for pretreatment is that the point of application of chlorine can be shifted downstream of the sedimentation basins. This is likely to result in fewer trihalomethane compounds.

### 5.5.2 American Water Works Association Research Foundation TTHM Study

Another investigation examined the impacts of potassium permanganate addition on byproduct formation at four water treatment plants (Ficek and Boll, 1980). All were conventional plants using pre-chlorination in the treatment process. Plant design capacities ranged from 4.5 to 15 mgd. Process modifications were made at each plant to replace the pre-chlorination facilities with oxidation facilities for potassium permanganate addition. After the modifications were complete, an AWWARF research team conducted a study to determine the impact of potassium permanganate addition on total trihalomethane (TTHM) concentrations (George et al., 1990).

Prior to switching from pre-chlorination to pre-oxidation with potassium permanganate, average daily TTHM concentrations at all four plants were between 79 and 99 µg/L. The average TTHM concentration for all four plants was 92 µg/L. Following the conversion to potassium permanganate, three of the four plants experienced greater than 30 percent reduction in TTHM concentrations. In addition to TTHM reduction, potassium permanganate was found to oxidize taste and odor causing compounds, iron and manganese, organic and inorganic matter, and reduce algal growth. Results from the study also showed that the simultaneous application of potassium permanganate and chlorine can increase THM formation.

## 5.6 Status of Analytical Methods

The atomic adsorption spectrophotometry method for the measurement of manganese is the preferred method for measuring permanganate concentrations. Two colorimetric methods, persulfate and periodate are also available (Standard Methods, 1995).

## 5.7 Operational Considerations

In utilizing potassium permanganate in water treatment, caution should be taken to prevent overdosing, in which case, excess manganese will pass through the treatment plant. Proper dosing

should be maintained to ensure that all of the permanganate is reduced (i.e., forming $MnO_2$ solids) and removed from the plant upstream of, or within, the filters. If residual manganese is reduced downstream of the filters, the resulting solids can turn the finished water a brown/black color and precipitate in the homes of consumers on heat exchange surfaces such as hot water heaters and dishwashers.

Use of potassium permanganate can also be a source of manganese in the finished water, which is regulated in drinking water with a secondary maximum contaminant level of 0.05 mg/L. Under reducing conditions, the $MnO_2$ solids accumulated in filter backwash water and settling basins can be reduced to soluble $Mn^{2+}$ and pass through the filters thereby remaining in the finished water.

Also, under these conditions, soluble $Mn^{2+}$ in return water from settling basin dewatering facilities and filter backwash water recycled to the head of the plant are potential sources of manganese that will have to be treated and/or controlled to minimize finished water manganese levels (Singer, 1991).

Overdosing of permanganate in conventional plants is generally corrected by settling the excess $MnO_2$ solids in the settling basin. Removal of the excess permanganate can be monitored qualitatively by observing the disappearance of the pink color characteristic of permanganate. In plants that do not utilize flocculation and sedimentation processes permanganate dosing should be closely monitored (Montgomery, 1985).

In general, potassium permanganate does not interfere with other treatment processes or plant conditions. Permanganate can be added downstream of, or concurrently with, coagulant and filter polymer aids. Powdered activated carbon (PAC) and permanganate should not be added concurrently. PAC should be added downstream of permanganate because it may consume permanganate, rendering it unavailable for the oxidation of target organics. (Montgomery, 1985).

The space requirements for permanganate feed equipment vary depending on the type and size of feed system. Dry feed systems require about half the floor area of batch systems because batch systems typically have two dissolving tanks for redundancy. However, the head space requirements are greater for dry feed systems where the storage hopper and dust collector are stacked on top of the dry feeder (Kawamura, 1991). On-site storage of potassium permanganate also warrants some consideration. Per OSHA requirements, oxidants such as permanganate should be stored separate from organic chemicals such as polymers and activated carbon.

# 5.8 Summary

## 5.8.1 Advantages and Disadvantages of Potassium Permanganate Use

The following list highlights selected advantages and disadvantages of using potassium permanganate as a disinfection method for drinking water. Because of the wide variation of system

size, water quality, and dosages applied, some of these advantages and disadvantages may not apply to a particular system.

### Advantages

- Potassium permanganate oxidizes iron and manganese.
- Potassium permanganate oxidizes odor and taste-causing compounds.
- Potassium permanganate is easy to transport, store, and apply.
- Potassium permanganate is useful in controlling the formation of THMs and other DBPs.
- Potassium permanganate controls nuisance organisms.
- The use of potassium permanganate has little impact on other treatment processes at the water treatment facility.
- Potassium permanganate has been proven effective against certain viruses.

### Disadvantages

- Long contact time is required.
- Potassium permanganate has a tendency to give water a pink color.
- Potassium permanganate is toxic and irritating to skin and mucous membranes.
- No byproducts are generated when preparing the feed solution, however this dark purple/black crystalline solid can cause serious eye injury, is a skin and inhalation irritant, and can be fatal if swallowed. Over-dosing is dangerous and may cause health problems such as chemical jaundice and drop in blood pressure.

## 5.8.2 Summary Table

More research is needed regarding the disinfection properties and oxidation byproducts of permanganate in water treatment. Also, a CT credit needs to be assigned to permanganate if it is to be utilized as a disinfectant. However, given that alternative oxidants, such as ozone and chlorine dioxide, demonstrate much greater efficacy in microbial control, permanganate is not likely to be utilized as a primary oxidant for precursor control. Table 5-2 summarizes the information presented in this chapter regarding the use of potassium permanganate in the drinking water treatment process.

**Table 5-2. Summary of Potassium Permanganate Use**

| Consideration | Description |
|---|---|
| Generation | Product supplied in dry form in buckets, drums, and bulk. On-site generation of solution is required using chemical mixing and feed equipment. |
| Primary uses | Control of odor and taste, remove color, control biological growth, and remove iron and manganese. |
| Inactivation efficiency | Not a good disinfectant. Can serve better as an alternative to chlorine or other disinfectants where chemical oxidation is desired. |
| Byproduct formation | No literature was found that specifically addressed DBP formation from potassium permanganate oxidation. Pretreatment with permanganate in combination with post-treatment chlorination will typically result in lower DBP concentrations than would otherwise occur from traditional pre-chlorination. |
| Limitations | Not a good disinfectant; primarily used for pretreatment to minimize chlorine usage and byproduct formation. |
| Points of application | Conventional Treatment: raw water addition, rapid mix tank in conjunction with coagulants, clarifiers upstream of filters. Direct Filtration: raw water intake. In all cases permanganate should be added upstream of filters. |
| Special considerations | Caution should be taken to prevent overdosing. More research is needed to determine disinfection properties and oxidation byproducts. |

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**5. POTASSIUM PERMANGANATE ..... 5-1**

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EPA 541-R00-062
2000

# EPA Superfund
# Record of Decision Amendment:

# Avco Lycoming (Williamsport Division)
# OU 2
# Williamsport, PA
# 04/06/2000

zone within the same well. The TCE-contaminated air would be removed from the well and treated with VGAC. Recovery wells would be positioned at similar intervals as those used for a groundwater extraction and treatment system.

| | |
|---|---|
| Capital Cost | $333,900 |
| Annual O&M Costs | $118,000 |
| 30-year Present Worth | $1,760,000 |
| **Total Remediation Present Worth** | **$2,610,000** |

**Alternative 4:** **Potassium Permanganate Oxidation Process**

This technology would involve injecting a solution of potassium permanganate into the shallow aquifer to oxidize VOCs. An initial slug of potassium permanganate would be injected in approximately 50 to 70 locations. This initial slug would treat the initial mass of VOCs and help to remediate "pockets" of higher concentrations. Once the initial slug of potassium permanganate had been introduced to the subsurface, a series of approximately 200 passive injection wells would be installed for injection of potassium permanganate to treat groundwater flowing off-Facility.

| | |
|---|---|
| Capital Cost | $1,101,100 |
| Annual O&M Costs | $94,150 |
| 30-year Present Worth | $2,225,000 |
| **Total Remediation Present Worth** | **$3,065,000** |

**Alternative 5:** **Hydrogen Peroxide Oxidation Process**

This technology would inject a solution of hydrogen peroxide into the shallow aquifer to oxidize VOCs. An initial slug of hydrogen peroxide would be injected in approximately 50 to 70 locations. This initial slug would treat the initial mass of VOCs and help to remediate "pockets" of higher concentrations. Once the initial slug of hydrogen peroxide bad been introduced to the subsurface, a series of approximately 200 passive injection wells would be installed for injection of hydrogen peroxide to treat groundwater flowing off-Facility.

EPA R01-R90-049
1990

# EPA Superfund
# Record of Decision:

# Baird & McGuire
# OU 4
# Holbrook, MA
# 09/27/1990

Text:

(1) PERMITTING/PRE-DESIGN STUDIES, (2) GROUNDWATER EXTRACTION, (3) TREATMENT, AND (4) DELIVERY TO DISTRIBUTION SYSTEM. EACH COMPONENT IS DESCRIBED BELOW.

1. PERMITTING/PRE-DESIGN STUDIES

SINCE THE DONNA ROAD AQUIFER IS NOT PART OF THE BAIRD & MCGUIRE SITE, SECTION 121(E), WHICH WAIVES THE ADMINISTRATIVE PERMITTING REQUIREMENTS FOR REMEDIAL ACTIONS CONDUCTED ON-SITE IS NOT APPLICABLE, THEREFORE ALL NECESSARY FEDERAL, STATE AND LOCAL PERMITS MUST BE OBTAINED FOR THIS REMEDIAL ACTION. TWO PERMITS WHICH WILL BE CRITICAL TO THE TIMELY IMPLEMENTATION OF THIS REMEDY WILL BE A WATER WITHDRAWAL PERMIT AS REQUIRED BY THE MASSACHUSETTS WATER MANAGEMENT ACT AND A NEW SOURCE APPROVAL AS REQUIRED BY THE MASSACHUSETTS DEPARTMENT OF ENVIRONMENTAL PROTECTIONS (DEP) "GUIDELINES AND POLICIES FOR PUBLIC WATER SUPPLIES" DOCUMENT.

THE RANDOLPH-HOLBROOK JOINT WATER BOARD CURRENTLY HAS A WATER WITHDRAWAL PERMIT WHICH AUTHORIZES THEM TO WITHDRAW A TOTAL OF 3.27 MGD FROM THE FOLLOWING FOR POINTS: SOUTH STREET WELL NO. 1, DONNA ROAD WELLFIELD, RICHARDI RESERVOIR AND THE GREAT POND/UPPER RESERVOIR. THE JOINT WATER BOARD IS CURRENTLY OPERATING AT CLOSE TO THAT 3.27 MGD CAPACITY, THE ADDITION OF 0.31 MGD WILL PLACE THE JOINT BOARD OVER THEIR PERMITTED CAPACITY THUS REQUIRING A NEW PERMIT. ALSO UNDER THE MASSACHUSETTS WATER MANAGEMENT ACT THE ADDITION OF A NEW WELL CONSTITUTES A NEW WITHDRAWAL POINT AND REQUIRES A NEW PERMIT.

THE "GUIDELINES AND POLICIES FOR PUBLIC WATER SUPPLIES" GUIDE PROVIDES FOR A NINE-STEP PROCEDURE FOR SEEKING MA DEP APPROVAL OF A DRINKING WATER SOURCE. THE PROCESS IS A PHASED APPROACH WHICH INCLUDE EXPLORATION AND PRELIMINARY TESTING, A FIVE DAY PUMP TEST, AND A SUMMARY HYDROLOGIC REPORT.

ALTHOUGH ALL STUDIES AND HISTORICAL DATA INDICATE THE DONNA ROAD AQUIFER SHOULD BE ABLE TO MEET THE 0.31 MGD LOST DEMAND UNDER THE SOURCE APPROVAL PROCESS, DEP MAY LIMIT THE PUMPING OF THE WELLS BASED ON THE SAFE YIELD (THE MAXIMUM RATE AT WHICH THE SYSTEM CAN BE EXPECTED TO DELIVER WATER CONTINUALLY INDER A DEFINED SET OF DROUGHT CONDITIONS) OF THE AQUIFER. SHOULD THE DONNA ROAD AQUIFER BE UNABLE TO PROVIDE THE ENTIRE LOST DEMAND OF 0.31 MGD, ANY INCREMENTAL DIFFERENCE BETWEEN 0.31 MGD AND THE AMOUNT OF WATER THE DONNA ROAD AQUIFER PROVIDES WILL BE OBTAINED BY INCREASING THE DIVERSION OF THE FARM RIVER. IF HOWEVER, THE PRODUCTION OF GROUNDWATER FROM DONNA ROAD IS INSUFFICIENT TO SUPPORT THE BALANCE BETWEEN THE REMEDY SELECTION CRITERIA, EPA WILL REEXAMINE THE REMEDY. EPA ANTICIPATES THAT A WATER PRODUCTION FROM DONNA ROAD OF LESS THAN 0.21 MAY PROMPT SUCH A REEVALUATION.

GROUNDWATER EXTRACTION

THE EXTRACTION SYSTEM IS CONCEPTUALIZED AS TWO 12-INCH DIAMETER WELLS APPROXIMATELY 40 FEET DEEP, AND 800 TO 1,000 FEET APART, ALIGNED PERPENDICULAR TO GROUNDWATER FLOW. SUBMERSIBLE PUMPS LOCATED IN EACH WILL EXTRACT WATER AND PUMP IT DIRECTLY TO TREATMENT UNITS. IT IS ANTICIPATED THAT THE PUMPS WILL BE TURNED ON AND OFF BY PRESSURE/DEMAND. THE EXACT NUMBER AND LOCATION OF THE WELLS WILL BE REFINED DURING THE HYDROGEOLOGIC

INVESTIGATIONS NECESSARY FOR THE MADEP NEW SOURCE APPROVAL PROCESS.

TREATMENT

NATIONAL PRIMARY DRINKING WATER REGULATIONS (NPDWR) (40 CFR 141, SUBPART H) REQUIRE THAT PUBLIC WATER SYSTEMS SUPPLIED BY A GROUNDWATER SOURCE UNDER THE DIRECT INFLUENCE OF SURFACEWATER PROVIDE FILTRATION AND DISINFECTION TREATMENT PROCESSES, UNLESS THE SUPPLIER CAN DEMONSTRATE THAT THE RAW WATER SOURCE MEETS STRINGENT CRITERIA FOR BACTERIA AND OTHER MICROBIOLOGICAL CONTAMINANTS. THE FILTRATION TREATMENT STEPS PROPOSED FOR IRON AND MANAGAESE CONTROL AND THE SUBSEQUENT DISINFECTION STEP WILL SATISFY THE REQUIREMENTS OF 49 CFR 141, SUBPART H.

AS LEVELS OF IRON AND MANGANESE IN THE DONNA ROAD AQUIFER EXCEED FEDERAL DRINKING WATER STANDARDS, INCLUDED IN THIS ALTERNATIVE, PERMANGANATE TREATMENT SYSTEM. THE IRON AND MANGANESE TREATMENT SYSTEM CONSISTS OF ADDING POTASSIUM PERMANGANATE TO THE EXTRACTED WATER. THE POTASSIUM PERMANGANATE THEN CAUSES THE IRON AND MANGANESE TO PRECIPITATE OUT OF THE WATER. THE PROCESS IS THEN FOLLOWED BY GREENSAND FILTRATION. THE GREENSAND ACTS AS A FILTER TO FURTHER REMOVE PRECIPITATE.

ALTHOUGH THE TREATMENT METHOD IS WELL ESTABLISHED, A PILOT TEST WILL BE PERFORMED TO ASSURE ITS EFFECTIVENESS BEFORE DESIGN AND IMPLEMENTATION.

DISTRIBUTION SYSTEM

TREATED GROUNDWATER WILL BE PIPED TO THE CURRENT DISTRIBUTION SYSTEM WHICH IS WITHIN A FEW HUNDRED FEET OF THE RANDOLPH-HOLBROOK WATER DISTRIBUTION MAIN. NO MODIFICATIONS TO THE DISTRIBUTION SYSTEM ARE ANTICIPATED.

#DE
DECLARATION

THE SELECTED REMEDY IS PROTECTIVE OF HUMAN HEALTH AND THE ENVIRONMENT, ATTAINS FEDERAL AND STATE REQUIREMENTS THAT ARE APPLICABLE OR RELEVANT AND APPROPRIATE FOR THIS REMEDIAL ACTION AND IS COST-EFFECTIVE. THE SELECTED REMEDY UTILIZES PERMANENT SOLUTIONS AND ALTERNATIVE TREATMENT TECHNOLOGIES TO THE MAXIMUM EXTENT PRACTICABLE. THE STATUTORY PREFERENCE FOR REMEDIES THAT UTILIZE TREATMENT AS A PRINCIPLE ELEMENT TO REDUCE THE MOBILITY, TOXICITY, OR VOLUME OF HAZARDOUS SUBSTANCES IN NOT APPLICABLE.

JULIE BELAGA
REGIONAL ADMINISTRATOR, EPA REGION I DATE 09/27/90

ROD DECISION SUMMARY
BAIRD & MCGUIRE SITE/ALTERNATE WATER SUPPLY

#SNLD

I. SITE NAME, LOCATION AND DESCRIPTION

THE BAIRD & MCGUIRE SITE IS LOCATED ON SOUTH STREET IN NORTHWEST HOLBROOK, MASSACHUSETTS, APPROXIMATELY 14 MILES SOUTH OF BOSTON. THE TWENTY-ACRE SITE IS BOUNDED BY SOUTH STREET TO THE SOUTH AND WEST, NEAR ROAD TO THE NORTH, AND THE COCHATO RIVER TO THE EAST. APPROXIMATELY 2.5 MILES DOWNSTREAM FROM THE SITE, THE COCHATO RIVER FLOWS PAST A SLUICE GATE REGULATING THE DIVERSION OF RIVER WATER TO THE RICHARDI RESERVOIR, A WATER SUPPLY SOURCE FOR THE TOWNS OF HOLBROOK, RANDOLPH, AND BRAINTREE. THIS DIVERSION HAS BEEN CLOSED SINCE 1983.

EIGHT OF THE TWENTY ACRES HAVE BEEN OWNED BY THE BAIRD & MCGUIRE, INC. SINCE 1912, WHEN CHEMICAL MANUFACTURING OPERATIONS BEGAN. THE BAIRD & MCGUIRE PROPERTY ORIGINALLY INCLUDED A LABORATORY, STORAGE AND MIXING BUILDINGS, AN OFFICE BUILDING AND A TANK FARM.

FOR OVER 70 YEARS, BAIRD & MCGUIRE, INC. OPERATED A CHEMICAL MANUFACTURING AND BATCHING FACILITY ON THE PROPERTY. LATER ACTIVITIES INCLUDED MIXING, PACKAGING, STORING AND DISTRIBUTING VARIOUS PRODUCTS, INCLUDING HERBICIDES, PESTICIDES, DISINFECTANTS, SOAPS, FLOOR WAXES AND SOLVENTS. SOME OF THE RAW MATERIALS USED AT THE SITE WERE STORED IN THE TANK FARM AND PIPED TO THE LABORATORY OR MIXING BUILDINGS. OTHER RAW MATERIALS WERE STORED IN DRUMS ON-SITE. WASTE DISPOSAL METHODS AT THE SITE INCLUDED DIRECT DISCHARGE INTO THE SOIL, NEARBY BROOK AND WETLANDS, AND A FORMER GRAVEL PIT (NOW COVERED) IN THE EASTERN PORTION OF THE SITE. UNDERGROUND DISPOSAL SYSTEMS WERE ALSO USED TO DISPOSE OF WASTES.

THE BAIRD & MCGUIRE SITE INCLUDES A PORTION OF THE COCHATO RIVER SEDIMENTS. THIS AREA BEGINS AT APPROXIMATELY THE CENTER OF THE SITE FENCE ALONG THE COCHATO RIVER AND EXTENDS NORTH TO UNION STREET.

THE SOUTH STREET WELLFIELD, PART OF THE MUNICIPAL WATER SUPPLY FOR HOLBROOK, IS WITHIN 1,500 FEET OF THE BAIRD & MCGUIRE PROPERTY. THE LAST OPERATING WELL WAS SHUT DOWN IN 1982 DUE TO ORGANIC CONTAMINATION. STUDIES INDICATE THAT CONTAMINANTS USED OR STORED AT THE SITE WERE POSSIBLE SOURCES FOR CONTAMINATION OF THE WELL. IN DECEMBER 1982, THE BAIRD & MCGUIRE SITE WAS PLACED ON EPA'S PROPOSED NATIONAL PRIORITIES LIST (NPL).

A MORE COMPLETE DESCRIPTION OF THE SITE CAN BE FOUND IN THE FOCUSED FEASIBILITY STUDY AT PAGES 1-2 THROUGH 1-4.

#SHEA
II. SITE HISTORY AND ENFORCEMENT ACTIVITIES

A. LAND USE AND RESPONSE HISTORY

IN 1983, EPA CONDUCTED A REMOVAL ACTION AT THE SITE AFTER A WASTE LAGOON OVERFLOWED NEAR THE COCHATO RIVER AND SPREAD CONTAMINANTS INTO THE RIVER. EMERGENCY ACTIVITIES INCLUDED REMOVING APPROXIMATELY 1,000 CUBIC YARDS OF HEAVILY CONTAMINATED SOILS, CONSTRUCTION OF A GROUNDWATER INTERCEPTION/RECIRCULATION SYSTEM TO LIMIT CONTAMINATED GROUNDWATER FROM MIGRATING INTO THE RIVER, REGRADING THE CONTAMINATED WASTE DISPOSAL AREA AND COVERING IT WITH A TEMPORARY CLAY CAP. IN RESPONSE TO THE LAGOON OVERFLOW, THE TRI-TOWN WATER BOARD (HOLBROOK, RANDOLPH, AND BRAINTREE) CLOSED THE SLUICE GATE LOCATED APPROXIMATELY 2.5 MILES DOWNSTREAM FROM THE SITE THAT DIVERTED WATER TO THE RICHARDI RESERVOIR. TO DATE, THE SLUICE GATE REMAINS CLOSED.

A SECOND REMOVAL ACTION FOR THE SITE WAS INITIATED IN 1985 FOLLOWING THE DISCOVERY OF DIOXIN IN SITE SOILS. EPA CONDUCTED ADDITIONAL SAMPLING OF AIR, SOILS AND WATER, AND AN ADDITIONAL 5,600 FEET OF FENCE WAS INSTALLED AT THAT TIME.

ANOTHER MAJOR ACTIVITY CONDUCTED AT THE SITE BY EPA IN 1985 THROUGH 1987 WAS AN INITIAL REMEDIAL MEASURE (IRM). A NEW WATER MAIN WAS CONSTRUCTED ALONG SOUTH STREET TO REPLACE AN EXISTING MAIN THAT PASSED THROUGH THE BAIRD & MCGUIRE SITE. THE WATER MAIN PASSING THROUGH THE SITE WAS ABANDONED AND FILLED WITH CONCRETE. THE BAIRD & MCGUIRE LABORATORY AND MIXING BUILDINGS AND TANK FARM WERE DEMOLISHED AND REMOVED AS PART OF THE IRM, AND A TEMPORARY SYNTHETIC CAP WAS INSTALLED OVER THAT PORTION OF THE SITE. WOOD FROM THE DEMOLISHED BUILDINGS WAS SHREDDED AND PLACED INTO BARRELS AND CRATES THAT ARE CURRENTLY STORED ON-SITE IN THE STORAGE BUILDING.

A RECORD OF DECISION (ROD) FOR THE SITE, SIGNED IN 1986, DIVIDED THE CLEANUP OF THE BAIRD & MCGUIRE SITE INTO OPERABLE UNITS. AN OPERABLE UNIT IS A DISCRETE PART OF AN ENTIRE RESPONSE ACTION THAT DECREASES A RELEASE, A THREAT OF A RELEASE, OR A PATHWAY OF EXPOSURE. EPA DETERMINED IN THE 1986 ROD THAT OPERABLE UNITS ARE APPROPRIATE FOR THE OVERALL REMEDIATION OF THE BAIRD & MCGUIRE SITE. THE 1986 ROD SELECTED TWO MAJOR REMEDIAL COMPONENTS, EXTRACTION AND ON-SITE TREATMENT OF GROUNDWATER (OPERABLE UNIT #1), AND, ON-SITE EXCAVATION AND INCINERATION OF CONTAMINATED SOIL, MUCH OF WHICH IS CURRENTLY COVERED BY TEMPORARY CAPS (OPERABLE UNIT #2). IN ADDITION, THE DEMOLITION MATERIAL REMAINING FROM THE ORIGINAL BAIRD & MCGUIRE BUILDINGS WILL BE INCINERATED ON-SITE WHEN THE SOIL INCINERATION PORTION OF THE LONG-TERM REMEDIAL ACTION PROGRAM IS INITIATED.

EPA AND THE US ARMY CORPS OF ENGINEERS HAVE COMPLETED THE DESIGN OF THE ON-SITE GROUNDWATER EXTRACTION/TREATMENT/RECHARGE SYSTEM (OPERABLE UNIT #1), AND THE US ARMY CORPS OF ENGINEERS AWARDED THE CONSTRUCTION CONTRACT TO BARLETTA ENGINEERING CORPORATION IN FEBRUARY 1990. IN AUGUST 1989, A SERIES OF TESTS WAS CONDUCTED AT EPAS OFFICE OF RESEARCH AND DEVELOPMENT FACILITY IN ARKANSAS AID IN DETERMINING THE OPERATING PROCEDURES THAT WILL MOST EFFECTIVELY DESTROY SOIL CONTAMINANTS. PREPARATION OF THE INCINERATION SYSTEM SPECIFICATIONS IS CURRENTLY UNDERWAY, AND THE SOLICITATION OF BIDS IS EXPECTED TO TAKE PLACE DURING THE FALL OF 1990.

A SECOND ROD FOR OPERABLE UNIT #3, WHICH ADDRESSED COCHATO RIVER SEDIMENT CONTAMINATION, WAS SIGNED ON SEPTEMBER 14, 1989. THE DESIGN IS EXPECTED TO BEGIN IN THE FALL OF 1990.

THIS ROD IS FOR OPERABLE UNIT #4 AND ADDRESSES AN ALTERNATE WATER SUPPLY/REPLACEMENT OF LOST DEMAND WHICH RESULTED FROM THE CONTAMINATION AND SUBSEQUENT SHUTDOWN OF THE SOUTH STREET WELLS.

A MORE DETAILED DESCRIPTION OF THE SITE HISTORY CAN BE FOUND IN THE FOCUSED FEASIBILITY SEDIMENT STUDY AT PAGES 1-5 THROUGH 1-6.

B. ENFORCEMENT HISTORY

THE BAIRD & MCGUIRE FACILITY HAD A LENGTHY HISTORY OF VIOLATING ENVIRONMENTAL LAWS. FROM THE MID-1950S ON, THE COMPANY RECEIVED NUMEROUS CITATIONS FOR VIOLATIONS OF THE FEDERAL INSECTICIDE, FUNGICIDE, AND RODENTICIDE ACT. FURTHER, BOTH THE STATE AND THE LOCAL GOVERNMENTS TOOK LEGAL ACTIONS AGAINST THE COMPANY AT VARIOUS TIMES.

EPA INVOLVEMENT UNDER THE COMPREHENSIVE ENVIRONMENTAL RESPONSE, COMPENSATION, AND LIABILITY ACT (CERCLA) BEGAN IN MARCH 1983 WITH THE FIRST REMOVAL ACTION CONDUCTED AT THE SITE. BAIRD & MCGUIRE, INC. CEASED OPERATING SHORTLY THEREAFTER, AND THE COMPANY AND ITS OFFICERS TOOK THE POSITION THAT THEY DID NOT HAVE SUFFICIENT ASSETS TO PAY FOR THE REMEDIAL WORK NECESSARY AT THE SITE.

IN OCTOBER 1983, THE UNITED STATES OF AMERICA, ON BEHALF OF THE ADMINISTRATOR OF EPA, FILED A COST RECOVERY ACTION UNDER SECTIONS 104(A) AND (B) AND 107(A) OF CERCLA. THE COMPLAINT SOUGHT REIMBURSEMENT FOR COSTS INCURRED BY THE UNITED STATES IN REMEDYING SITE CONDITIONS FROM BAIRD & MCGUIRE, INC., BAIRD REALTY CO., INC. (SUBSEQUENTLY KNOW AS THE ANN E. REALTY TRUST, INC.), CAMERON M. BAIRD, AND GORDON M. BAIRD.

BAIRD & MCGUIRE, INC. OWNED AND OPERATED THE BAIRD & MCGUIRE FACILITY. BAIRD REALTY CO., INC. WAS A RECORD OWNER OF PART OF THE SITE. CAMERON BAIRD WAS THE PRESIDENT, TREASURER, AND CHIEF EXECUTIVE OF BAIRD & MCGUIRE, INC. GORDON M. BAIRD (CAMERON'S BROTHER) WAS THE CHAIRMAN OF THE BOARD OF BAIRD & MCGUIRE, INC.

THE GOVERNMENT CONTENDS THAT BOTH INDIVIDUALS EXERCISED CONTROL OVER THE COMPANY'S CONDUCT, ACTIVITIES AND OPERATIONS. THE DEFENDANTS TO THE LAWSUIT, AS LISTED ABOVE, ARE ALSO THE ONLY POTENTIALLY RESPONSIBLE PARTIES ("PRPS") IDENTIFIED TO DATE BY EPA.

THE PRPS MAINTAINED FROM EARLY ON IN DISCUSSIONS WITH EPA BOTH THAT THEY LACKED THE FINANCIAL ASSETS TO CONDUCT THE REMEDY AND THAT THEY WERE NOT LIABLE. THE PRPS PROVIDED SOME INFORMATION REGARDING THEIR FINANCES, AND THE UNITED STATES OBTAINED A LIEN ON A PARCEL OF PROPERTY OWNED BY THE ANN E. REALTY TRUST, INC. EPA SUBSEQUENTLY DETERMINED THAT THE PRPS WERE UNABLE AND UNWILLING TO IMPLEMENT THE FULL REMEDY AT THE SITE.

THE COST RECOVERY ACTION FILED IN 1983 WAS SETTLED ON AN "ABILITY TO PAY" BASIS IN 1987. THE CONSENT DECREE THAT WAS SIGNED BY ALL PARTIES IN SEPTEMBER 1987 INCLUDES THE FOLLOWING REQUIREMENTS OF THE DEFENDANTS:

* A CASH PAYMENT TO EPA OF $900,000, MADE IN TWO INSTALLMENTS;

* FULL EPA ACCESS TO THE SITE FOR THE PURPOSES OF IMPLEMENTING

RESPONSE ACTIONS;

* LIENS ON THE BAIRD & MCGUIRE PROPERTY, WHICH CONSISTS OF 2 LOTS OWNED BY THE ANN E. REALTY TRUST AND THE BAIRD & MCGUIRE LOT; AND

* RIGHTS TO INSURANCE POLICIES WHICH MAY PROVIDE COVERAGE FOR COSTS INCURRED IN RESPONSE TO THE RELEASE OR THREAT OF RELEASE OF HAZARDOUS SUBSTANCES FROM THE BAIRD & MCGUIRE PROPERTY.

PURSUANT TO THE BAIRD'S ASSIGNMENT TO EPA OF THEIR RIGHTS REGARDING INSURANCE POLICIES, EPA HAS NEGOTIATED WITH INSURERS OF BAIRD & MCGUIRE, INC FOR COST RECOVERY. TO DATE, NO SETTLEMENTS HAVE BEEN REACHED WITH THESE PARTIES.

THE PRPS HAVE HAD NO INVOLVEMENT IN THE FOCUSED FEASIBILITY STUDY (FFS) AND REMEDY SELECTION PROCESS FOR THIS OPERABLE UNIT. EPA NOTIFIED THE PUBLIC, INCLUDING THE PRPS, OF THE ISSUANCE OF THE PROPOSED PLAN, BUT RECEIVED NO PRP COMMENTS ON THE PROPOSED PLAN.

SPECIAL NOTICE HAS NOT BEEN ISSUED IN THIS CASE FOR THE EARLIER OPERABLE UNITS SINCE THE COST RECOVERY CASE, FILED IN 1983, WAS SETTLED WITH THE ONLY PRPS IN 1987.

## III. COMMUNITY RELATIONS

THROUGHOUT THE SITE'S HISTORY, COMMUNITY CONCERN AND INVOLVEMENT HAS BEEN HIGH. EPA HAS KEPT THE COMMUNITY AND OTHER INTERESTED PARTIES APPRISED OF THE SITE ACTIVITIES THROUGH BAIRD & MCGUIRE TASK FORCE MEETINGS, INFORMATIONAL MEETINGS, FACT SHEETS, PRESS RELEASES AND PUBLIC MEETINGS.

IN 1985, EPA RELEASED A COMMUNITY RELATIONS PLAN WHICH OUTLINES A PROGRAM TO ADDRESS COMMUNITY CONCERNS AND KEEP CITIZENS INFORMED ABOUT AND INVOLVED IN ACTIVITIES DURING REMEDIAL ACTIVITIES. THROUGHOUT 1985 AND 1986, EPA HELD A SERIES OF PUBLIC INFORMATIONAL MEETINGS TO DESCRIBE THE PLANS FOR AND RESULTS OF THE REMEDIAL INVESTIGATION, FEASIBILITY STUDY, AND OTHER ACTIONS TAKEN BY THE AGENCY AT THE SITE DURING THIS TIME.

IN MAY 1989, EPA MADE THE ADMINISTRATIVE RECORD AVAILABLE FOR PUBLIC REVIEW AT EPA'S OFFICES IN BOSTON AND AT THE HOLBROOK PUBLIC LIBRARY. THE ADMINISTRATIVE RECORD WAS UPDATED IN JUNE 1989 TO INCLUDE DOCUMENTS USED BY THE AGENCY FOR THE COCHATO RIVER SEDIMENT STUDY DECISION AND AGAIN IN JUNE 1990 FOR THE ALTERNATE WATER SUPPLY/LOST DEMAND STUDY. IN JUNE 1990 EPA PUBLISHED A NOTICE AND A BRIEF ANALYSIS OF THE PROPOSED PLAN FOR THIS OPERABLE UNIT IN THE PATRIOT LEADER ON JUNE 22, 1990 AND MADE THE PLAN AVAILABLE TO THE PUBLIC AT THE HOLBROOK PUBLIC LIBRARY.

ON JUNE 26, 1990, EPA HELD AN INFORMATIONAL MEETING TO DISCUSS THE ALTERNATIVES PRESENTED IN THE ALTERNATE WATER SUPPLY FOCUSED FEASIBILITY STUDY AND TO PRESENT THE AGENCY'S PROPOSED PLAN. ALSO DURING THIS MEETING, THE AGENCY ANSWERED QUESTIONS FROM THE PUBLIC. FROM JUNE 27, 1990 TO JULY 26, 1990, THE AGENCY HELD A 30 DAY PUBLIC COMMENT PERIOD TO ACCEPT PUBLIC COMMENT ON THE ALTERNATIVES PRESENTED IN THE FOCUSED FEASIBILITY STUDY, THE PROPOSED PLAN AND ON ANY OTHER DOCUMENTS PREVIOUSLY RELEASED TO THE PUBLIC. ON JULY 17, 1990, THE AGENCY HELD A PUBLIC

HEARING TO DISCUSS THE PROPOSED PLAN AND TO ACCEPT ANY ORAL COMMENTS. A TRANSCRIPT OF THIS MEETING, THE COMMENTS, AND THE AGENCY'S RESPONSE TO COMMENTS ARE INCLUDED IN THE ATTACHED RESPONSIVENESS SUMMARY.

#SROU

## IV. SCOPE AND ROLE OF OPERABLE UNIT OR RESPONSE ACTION

AS ANTICIPATED IN THE "FUTURE ACTION" SECTION OF THE 1986 ROD FOR THE SITE, AN ALTERNATE WATER SUPPLY FOCUSED FEASIBILITY STUDY WAS PERFORMED TO SELECT A POTENTIAL WATER SOURCE THAT COULD REPLACE THE LOST DEMAND WHICH OCCURRED WHEN THE SOUTH STREET WELLS WERE SHUT DOWN DUE TO POSSIBLE CONTAMINATION RESULTING FROM BAIRD & MCGUIRE INDUSTRIAL PRACTICES. THIS REMEDIAL ACTION WILL ADDRESS REPLACEMENT OF THAT LOST DEMAND.

#SSC

## V. SUMMARY OF SITE CHARACTERISTICS

THIS ROD DOES NOT ADDRESS SITE RELATED CONTAMINANTS, RATHER IT INVOLVES SELECTING AN ALTERNATE WATER SUPPLY TO REPLACE THE SOUTH STREET WELLS LOST DEMAND WHICH OCCURRED BECAUSE OF CONTAMINATION FROM BAIRD & MCGUIRE. THE 1986 AND 1989 RODS FOR OPERABLE UNITS #1, #2 AND #3 ADDRESSED ALL SOURCES OF CONTAMINATION FROM THE BAIRD & MCGUIRE SITE. A DESCRIPTION OF THOSE SITE CHARACTERISTICS CAN BE FOUND IN SECTION 5.20-5.21.5 OF THE REMEDIAL INVESTIGATION (RI) AND SECTION 5.4-5.42.5 OF THE ADDENDUM TO THE RI AND PAGES 1-12 THROUGH 1-17 OF THE COCHATO RIVER FOCUSED FEASIBILITY STUDY. NO FURTHER INVESTIGATION OF THE BAIRD & MCGUIRE SITE WAS DONE IN CONNECTION WITH THIS FOCUSED FEASIBILITY STUDY OR ROD.

#SSR

## VI. SUMMARY OF SITE RISKS

THE ALTERNATE WATER SUPPLY FFS STUDY AREA DIFFERS FROM THE RI AND RI ADDENDUM SITE STUDY AREA (OPERABLE UNITS #1 AND #2) AND THE FFS SEDIMENT STUDY AREA (OPERABLE UNIT #3). THE RISKS ASSOCIATED WITH EACH OF THESE OPERABLE UNITS WERE ADDRESSED IN THE 1986 AND 1989 RODS. RISKS ASSOCIATED WITH DRINKING OF THE GROUNDWATER IN THE SOUTH STREET WELL AREA, THE LOST DEMAND OF WHICH THIS ALTERNATE WATER SUPPLY WILL REPLACE, IS 4 X (10-3), OUTSIDE EPA'S RISK RANGE OF 1 X (10-4) TO 1 X (10-6). THE SOUTH STREET WELLS WERE CLOSED IN 1982 AND THEREFORE, NO ONE IS CURRENTLY DRINKING WATER.

A COMPLETE DESCRIPTION OF THE BAIRD & MCGUIRE SITE RISKS CAN BE FOUND IN THE 1987 FEASIBILITY STUDY AT PAGES 2-1 THROUGH 2-32 AND THE SEDIMENT FOCUSED FEASIBILITY STUDY AT PAGES 1-18 THROUGH 1-58.

AS THIS OPERABLE UNIT DOES NOT ADDRESS CONTAMINATION FROM THE BAIRD & MCGUIRE SITE, THERE WERE NO SITE RISKS ASSOCIATED WITH THIS FOURTH OPERABLE UNIT. THEREFORE NO RISK ASSESSMENT WAS PERFORMED IN CONNECTION WITH THIS STUDY.

#DSA

## VII. DEVELOPMENT AND SCREENING OF ALTERNATIVES

### A. STATUTORY REQUIREMENTS/RESPONSE OBJECTIVES

UNDER ITS LEGAL AUTHORITIES, EPA'S PRIMARY RESPONSIBILITY AT SUPERFUND SITES IS TO UNDERTAKE REMEDIAL ACTIONS THAT ARE PROTECTIVE OF HUMAN HEALTH AND THE ENVIRONMENT. IN ADDITION, SECTION 121 OF CERCLA ESTABLISHES SEVERAL OTHER STATUTORY REQUIREMENTS AND PREFERENCES, INCLUDING: A REQUIREMENT THAT EPA'S REMEDIAL ACTION, WHEN COMPLETE, MUST COMPLY WITH ALL FEDERAL AND MORE STRINGENT STATE ENVIRONMENTAL STANDARDS, REQUIREMENTS, CRITERIA OR LIMITATIONS, UNLESS A WAIVER IS INVOKED; A REQUIREMENT THAT EPA SELECT A REMEDIAL ACTION THAT IS COST-EFFECTIVE AND THAT UTILIZES PERMANENT SOLUTIONS AND ALTERNATIVE TREATMENT TECHNOLOGIES OR RESOURCE RECOVERY TECHNOLOGIES TO THE MAXIMUM EXTENT PRACTICABLE; AND A PREFERENCE FOR REMEDIES IN WHICH TREATMENT WHICH PERMANENTLY AND SIGNIFICANTLY REDUCES THE VOLUME, TOXICITY OR MOBILITY OF THE HAZARDOUS SUBSTANCES IS A PRINCIPAL ELEMENT OVER REMEDIES NOT INVOLVING SUCH TREATMENT. SECTION 121 ALSO PROVIDES THAT IF EPA SELECTS A REMEDY NOT APPROPRIATE FOR THE ABOVE PREFERENCES, EPA IS TO PUBLISH AN EXPLANATION AS TO WHY A REMEDIAL ACTION INVOLVING SUCH REDUCTION WAS NOT SELECTED. RESPONSE ALTERNATIVES WERE DEVELOPED TO BE CONSISTENT WITH THESE CONGRESSIONAL MANDATES.

BASED ON PRELIMINARY INFORMATION SUCH AS CONSTRAINTS OF THE PRESENT WATER SYSTEM AND KNOWN AVAILABLE WATER SOURCES, A REMEDIAL ACTION OBJECTIVE WAS DEVELOPED TO AID IN THE DEVELOPMENT AND SCREENING OF ALTERNATIVES. THE RESPONSE OBJECTIVE FOR OPERABLE UNIT #4 IS:

* TO IDENTIFY A CANDIDATE WATER SOURCE THAT WILL REPLACE THE 0.31 MILLION GALLONS PER DAY (MGD) LOST DEMAND IN AN ENVIRONMENTALLY SOUND, COST-EFFECTIVE MANNER WITHOUT PLACING ADDITIONAL STRESS ON THE GREAT POND RESERVOIR SYSTEM OR EXISTING WATER TREATMENT FACILITIES.

### B. TECHNOLOGY AND ALTERNATIVE DEVELOPMENT AND SCREENING

CERCLA AND THE NCP SET FORTH THE PROCESS BY WHICH REMEDIAL ACTIONS ARE EVALUATED AND SELECTED. IN ACCORDANCE WITH THESE REQUIREMENTS, A RANGE OF ALTERNATIVES WAS DEVELOPED FOR THE SITE.

AS DISCUSSED IN CHAPTER 3 OF THE FOCUSED FEASIBILITY STUDY, ALTERNATE WATER SUPPLY SOURCES WERE IDENTIFIED, ASSESSED AND SCREENED BASED ON IMPLEMENTABILITY, EFFECTIVENESS, AND COST (FIGURE 1 AND TABLES 1 AND 2). THE PURPOSE OF THE INITIAL SCREENING WAS TO NARROW THE NUMBER OF POTENTIAL REMEDIAL ACTIONS FOR FURTHER DETAILED ANALYSIS WHILE PRESERVING A RANGE OF OPTIONS. EACH ALTERNATIVE WAS THEN EVALUATED AND SCREENED IN CHAPTER 3 OF THE FEASIBILITY STUDY.

IN SUMMARY, OF THE L3 ALTERNATE WATER SUPPLY SOURCES SCREENED IN CHAPTER 3, THREE PLUS THE NO ACTION ALTERNATIVE WERE RETAINED FOR DETAILED ANALYSIS. TABLES 1 AND 2 IDENTIFY THE THREE ALTERNATIVES THAT WERE RETAINED THROUGH THE SCREENING PROCESS, AS WELL AS THOSE THAT WERE ELIMINATED FROM FURTHER CONSIDERATION.

#DOA

## VIII. DESCRIPTION OF ALTERNATIVES

THIS SECTION PROVIDES A NARRATIVE SUMMARY OF EACH ALTERNATIVE EVALUATED. A DETAILED TABULAR ASSESSMENT OF EACH ALTERNATIVE CAN BE FOUND IN TABLE 5-3 OF THE FOCUSED, FEASIBILITY STUDY.

### A. ALTERNATE WATER (AW) SUPPLY SOURCES

ALTERNATIVE NA: NO ACTION (AW-NA)

ANALYSIS OF THE NO ACTION ALTERNATIVE IS REQUIRED BY FEDERAL LAW AND IS INCLUDED FOR COMPARISON WITH OTHER ALTERNATIVES. IN THIS ALTERNATIVE, NO ALTERNATIVE WATER SUPPLY TO REPLACE THE LOST DEMAND WOULD BE DEVELOPED.

ESTIMATED FIVE-YEAR REVIEW COSTS: $ 0
ESTIMATED TOTAL COST (NPW): $ 0

ALTERNATIVE 1: REACTIVATION OF THE DONNA ROAD ACUIFER AW-1)

THIS ALTERNATIVE HAS BEEN CHOSEN AS EPA'S PREFERRED ALTERNATIVE FOR THE ALTERNATE WATER SUPPLY/REPLACEMENT OF LOST DEMAND. SEE PAGES 15 THROUGH 19 FOR A DISCUSSION OF THE SELECTED REMEDY.

ALTERNATIVE 2: INCREASED FARM RIVER DIVERSION AW-2)

IN THIS ALTERNATIVE, AN ADDITIONAL 0.31 MGD OF WATER WOULD BE DIVERTED FROM THE FARM RIVER INTO THE RICHARDI RESERVOIR TO REPLACE THE LOST DEMAND. THE FARM RIVER CURRENTLY PROVIDES AN UNDOCUMENTED VOLUME OF WATER TO THE RICHARDI RESERVOIR THROUGH A DIVERSION CHANNEL LOCATED AT THE NORTH END OF THE RESERVOIR. CURRENTLY, WATER DRAWN FROM THE RICHARDI RESERVOIR IS TREATED AND DISINFECTED AT THE RANDOLPH-HOLBROOK WATER TREATMENT FACILITY. THIS FACILITY OPERATES BEYOND CAPACITY AT TIMES, AND EXPANSION OF THE FACILITY WOULD BE NECESSARY IF THE FLOW FROM THE RESERVOIR AND, HENCE TO THE TREATMENT FACILITY, WERE INCREASED. THE RANDOLPH-HOLBROOK JOINT WATER BOARD IS PLANNING TO EXPAND THE CAPACITY OF THE WATER TREATMENT PLANT TO ADDRESS ITS CURRENT OVERLOAD SITUATION; IMPLEMENTATION OF THIS ALTERNATIVE WOULD BE POSSIBLE ONLY AFTER COMPLETION OF THE EXPANSION.

ADDITIONALLY, SINCE LEVELS OF IRON AND MANGANESE IN THE FARM RIVER EXCEED FEDERAL DRINKING WATER STANDARDS, INCLUDED IN THIS ALTERNATIVE IS A POTASSIUM PERMANGANATE TREATMENT SYSTEM TO BE INSTALLED AT THE RANDOLPH-HOLBROOK TREATMENT FACILITY. THIS IRON AND MANGANESE TREATMENT SYSTEM CONSISTS OF ADDING POTASSIUM PERMANGANATE TO THE EXTRACTED WATER; THE POTASSIUM PERMANGANATE CAUSES THE IRON AND MANGANESE TO PRECIPITATE (FORM A SOLID AND DROP OUT OF THE SOLUTION) OUT OF THE WATER. THE PROCESS IS THEN FOLLOWED BY GREENSAND FILTRATION. THE GREENSAND ACTS AS A FILTER TO FURTHER REMOVE PRECIPITATE. THE WATER WOULD THEN BE DISINFECTED AT THE RANDOLPH/HOLBROOK WATER TREATMENT PLANT. IMPLEMENTATION OF THIS ALTERNATIVE WOULD REQUIRE COMPLIANCE WITH THE MASSACHUSETTS WATER MANAGEMENT ACT (OBTAINING A WATER WITHDRAWAL PERMIT) AND OBTAINING A SOURCE APPROVAL UNDER THE DEP "GUIDELINES AND POLICIES FOR PUBLIC WATER SUPPLIES" DOCUMENT. (SEE SECTION X.A.L, PAGE 15, 16 FOR A DESCRIPTION OF THESE PROCESSES).

ESTIMATED TIME FOR DESIGN AND CONSTRUCTION: DEPENDENT UPON EXPANSION OF THE RANDOLPH-HOLBROOK TREATMENT FACILITY AND DEP PERMITS AND APPROVALS.

| | |
|---|---|
| ESTIMATED CAPITAL COST: | $306,000 |
| ESTIMATED O & M (PRESENT WORTH): | $68,100 |
| ESTIMATED TOTAL COST (PRESENT WORTH): | $374,000 |

ALTERNATIVE 3: DIVERSION OF COCHATO RIVER AW-3)

IN THIS ALTERNATIVE, THE DIVERSION OF THE COCHATO RIVER INTO THE RICHARDI RESERVOIR WOULD BE RE-ESTABLISHED. THE COCHATO RIVER IS CAPABLE OF SUPPLYING THE 0.31 MGD LOST DEMAND. WATER QUALITY IN THE COCHATO RIVER WAS EXTENSIVELY ANALYZED DURING THIS FFS AND DURING THE COCHATO RIVER SEDIMENT FFS. THE RESULTS OF THESE STUDIES INDICATED THAT, LIKE THE FARM RIVER AND THE DONNA ROAD AQUIFER, THE ONLY CONTAMINANTS WHICH EXCEED FEDERAL DRINKING WATER STANDARDS ARE IRON AND MANGANESE.

LIKE ALTERNATIVE AW-2, WATER FROM THE COCHATO RIVER WOULD BE CURRENTLY DRAWN FROM THE RICHARDI RESERVOIR IS TREATED AND DISINFECTED AT THE RANDOLPH-HOLBROOK WATER TREATMENT FACILITY. THIS FACILITY OPERATES BEYOND CAPACITY AT TIMES, AND EXPANSION OF THE FACILITY WOULD BE NECESSARY IF THE FLOW FROM THE RESERVOIR AND, HENCE TO THE TREATMENT FACILITY, WERE INCREASED. THE RANDOLPH-HOLBROOK JOINT WATER BOARD IS PLANNING TO EXPAND THE CAPACITY OF THE WATER TREATMENT PLANT TO ADDRESS THIS CURRENT OVERLOAD SITUATION; IMPLEMENTATION OF THIS ALTERNATIVE WOULD BE POSSIBLE ONLY AFTER COMPLETION OF THE EXPANSION.

ADDITIONALLY, SINCE LEVELS OF IRON AND MANGANESE IN THE COCHATO RIVER EXCEED FEDERAL DRINKING WATER STANDARDS, INCLUDED IN THIS ALTERNATIVE IS A POTASSIUM PERMANGANATE TREATMENT SYSTEM TO BE INSTALLED AT THE RANDOLPH-HOLBROOK TREATMENT-SYSTEM. THIS IRON AND MANGANESE TREATMENT SYSTEM CONSISTS OF ADDING POTASSIUM PERMANGANATE TO THE EXTRACTED WATER. THE POTASSIUM PERMANGANATE CAUSES THE IRON AND MANGANESE TO PRECIPITATE FROM THE WATER. THE PROCESS IS THEN FOLLOWED BY GREENSAND FILTRATION. THE GREENSAND ACTS AS A FILTER TO FURTHER REMOVE PRECIPITATE. THE WATER WOULD THEN BE TREATED AT THE RANDOLPH/HOLBROOK WATER TREATMENT FACILITY. IMPLEMENTATION OF THIS ALTERNATIVE WOULD REQUIRE COMPLIANCE WITH THE MASSACHUSETTS WATER MANAGEMENT ACT (OBTAINING A WATER WITHDRAWAL PERMIT) AND OBTAINING SOURCE APPROVAL UNDER DEP 1,GUIDELINES AND POLICIES FOR PUBLIC WATER SUPPLIES" DOCUMENT. (SEE SECTION X.A.L, PAGE 15, 16 FOR A DESCRIPTION OF THESE PROCESSES).

ESTIMATED TIME FOR DESIGN AND CONSTRUCTION: DEPENDENT UPON EXPANSION OF THE RANDOLPH-HOLBROOK TREATMENT FACILITY AND DEP PERMITS AND APPROVALS.

| | |
|---|---|
| ESTIMATED CAPITAL COST: | $306,000 |
| ESTIMATED 0 & M (PRESENT WORTH): | $68,100 |
| ESTIMATED TOTAL COST (PRESENT WORTH): | $374,000 |

#SCAA

II. SUMMARY OF THE COMPARATIVE ANALYSIS OF ALTERNATIVES

SECTION 121(B) (1) OF CERCLA PRESENTS SEVERAL FACTORS THAT, AT A MINIMUM,

EPA IS REQUIRED TO CONSIDER IN ITS ASSESSMENT OF ALTERNATIVES. BUILDING UPON THESE SPECIFIC STATUTORY MANDATES, THE NATIONAL CONTINGENCY PLAN ARTICULATES NINE EVALUATION CRITERIA TO BE USED IN ASSESSING THE INDIVIDUAL REMEDIAL ALTERNATIVES. IN ADDITION, FOR THIS OPERABLE UNIT, THE CRITERIA FROM "GUIDANCE DOCUMENT OF PROVIDING ALTERNATE WATER SUPPLIES" (OSWER DIRECTIVE 9355.03-03) WERE ALSO USED. THESE CRITERIA ALLOW FOR A MORE FOCUSED AND DETAILED ANALYSIS OF AN ALTERNATE WATER SUPPLY ALTERNATIVE THAN WOULD THE NINE CRITERIA ALONE. THOSE CRITERIA ARE CONSISTENT WITH THE NINE CRITERIA AND CAN BE INTERCHANGED IN THE FFS AS FOLLOWS:

| | |
|---|---|
| 1. OVERALL PROTECTION OF HUMAN HEALTH AND THE ENVIRONMENT | PUBLIC HEALTH ANALYSIS AND ENVIRONMENTAL ANALYSIS |
| 2. COMPLIANCE WITH ARARS | COMPLIANCE WITH AAARS |
| 3. LONG-TERM EFFECTIVENESS AND PERMANENCE | PERFORMANCE AND RELIABILITY |
| 4. REDUCTION OF MOBILITY, TOXICITY OR VOLUME THROUGH TREATMENT | NOT APPLICABLE |
| 5. SHORT-TERM EFFECTIVENESS | TIMELINESS AND SAFETY |
| 6. COST | COST |
| 7. IMPLEMENTABILITY | IMPLEMENTABILITY/ CONSTRUCTABILTY |
| 8. STATE ACCEPTANCE | STATE ACCEPTANCE |
| 9. COMMUNITY ACCEPTANCE | COMMUNITY ACCEPTANCE |

A DETAILED ANALYSIS WAS PERFORMED ON THE ALTERNATIVES USING THE EVALUATION CRITERIA IN ORDER TO SELECT A SITE REMEDY. THE FOLLOWING IS A SUMMARY OF THE COMPARISON OF EACH ALTERNATIVE'S STRENGTHS AND WEAKNESSES WITH RESPECT TO THE EVALUATION CRITERIA. THESE CRITERIA AND THEIR DEFINITIONS ARE AS FOLLOWS:

THRESHOLD CRITERIA

THE TWO THRESHOLD CRITERIA DESCRIBED BELOW MUST BE MET IN ORDER FOR THE ALTERNATIVES TO BE ELIGIBLE FOR SELECTION IN ACCORDANCE WITH THE NCP.

1. OVERALL PROTECTION OF HUMAN HEALTH AND THE ENVIRONMENT ADDRESSES WHETHER OR NOT A REMEDY PROVIDES ADEQUATE PROTECTION AND DESCRIBES HOW RISKS POSED THROUGH EACH PATHWAY ARE ELIMINATED, REDUCED OR CONTROLLED THROUGH TREATMENT, ENGINEERING CONTROLS, OR INSTITUTIONAL CONTROLS.

2. COMPLIANCE WITH APPLICABLE OR RELEVANT AND APPROPRIATE REQUIREMENTS (ARARS) ADDRESSES WHETHER OR NOT A REMEDY WILL MEET ALL OF THE ARARS OF OTHER FEDERAL AND STATE ENVIRONMENTAL LAWS AND/OR PROVIDE GROUNDS FOR INVOKING A WAIVER.

PRIMARY BALANCING CRITERIA

THE FOLLOWING FIVE CRITERIA ARE UTILIZED TO COMPARE AND EVALUATE THE ELEMENTS OF ONE ALTERNATIVE TO ANOTHER THAT MEET THE THRESHOLD CRITERIA.

3. LONG-TERM EFFECTIVENESS AND PERMANENCE ADDRESSES THE CRITERIA THAT ARE UTILIZED TO ASSESS ALTERNATIVES FOR THE LONG-TERM EFFECTIVENESS AND PERMANENCE THEY AFFORD, ALONG WITH THE DEGREE OF CERTAINTY THAT THEY WILL PROVE SUCCESSFUL.

4. REDUCTION OF TOXICITY, MOBILITY, OR VOLUME THROUGH TREATMENT ADDRESSES THE DEGREE TO WHICH ALTERNATIVES EMPLOY RECYCLING OR TREATMENT THAT REDUCES TOXICITY, MOBILITY, OR VOLUME, INCLUDING HOW TREATMENT IS USED TO ADDRESS THE PRINCIPAL THREATS POSED BY THE SITE.

5. SHORT-TERM EFFECTIVENESS ADDRESSES THE PERIOD OF TIME NEEDED TO ACHIEVE PROTECTION AND ANY ADVERSE IMPACTS ON HUMAN HEALTH AND THE ENVIRONMENT THAT MAY BE POSED DURING THE CONSTRUCTION AND IMPLEMENTATION PERIOD, UNTIL CLEANUP GOALS ARE ACHIEVED.

6. IMPLEMENTABILITY ADDRESSES THE TECHNICAL AND ADMINISTRATIVE FEASIBILITY OF A REMEDY, INCLUDING THE AVAILABILITY OF MATERIALS AND SERVICES NEEDED TO IMPLEMENT A PARTICULAR OPTION.

7. COST INCLUDES ESTIMATED CAPITAL AND OPERATION AND MAINTENANCE (O&M) COSTS, AS WELL AS PRESENT-WORTH COSTS.

MODIFYING CRITERIA

THE MODIFYING CRITERIA ARE USED ON THE FINAL EVALUATION OF REMEDIAL ALTERNATIVES GENERALLY AFTER EPA HAS RECEIVED PUBLIC'S COMMENT ON THE RI/FS AND PROPOSED PLAN.

8. STATE ACCEPTANCE ADDRESSES THE STATE'S POSITION AND KEY CONCERNS RELATED TO THE PREFERRED ALTERNATIVE AND OTHER ALTERNATIVES, AND THE STATE'S COMMENTS ON ARARS OR THE PROPOSED USE OF WAIVERS.

9. COMMUNITY ACCEPTANCE ADDRESSES THE PUBLIC'S GENERAL RESPONSE TO THE ALTERNATIVES DESCRIBED IN THE PROPOSED PLAN AND RI/FS REPORT.

A DETAILED TABULAR ASSESSMENT OF EACH ALTERNATIVE ACCORDING TO THE CRITERIA CAN BE FOUND IN TABLE 5-3 OF THE FEASIBILITY STUDY.

FOLLOWING THE DETAILED ANALYSIS OF EACH INDIVIDUAL ALTERNATIVE, A COMPARATIVE ANALYSIS, FOCUSING ON THE RELATIVE PERFORMANCE OF EACH ALTERNATIVE AGAINST THE CRITERIA, WAS CONDUCTED. THIS COMPARATIVE ANALYSIS CAN BE FOUND IN TABLE 3.

THE SECTION BELOW PRESENTS THE CRITERIA AND A BRIEF NARRATIVE SUMMARY OF THE ALTERNATIVES AND THE STRENGTHS AND WEAKNESSES ACCORDING TO THE DETAILED AND COMPARATIVE ANALYSIS.

1. OVERALL PROTECTION OF HUMAN HEALTH AND THE ENVIRONMENT

AW-1, AW-2, AND AW-3 WOULD ALL BE PROTECTIVE OF HUMAN HEALTH AND THE ENVIRONMENT BY PROVIDING CLEAN DRINKING WATER BY TREATMENT. EACH OF THESE ALTERNATIVES IS EQUALLY PROTECTIVE SINCE MAXIMUM CONTAMINANT LEVELS (MCLS) WILL BE ACHIEVED FOR ALL COMPOUNDS AFTER TREATMENT.

2. COMPLIANCE WITH ARARS

EACH ALTERNATIVE WAS EVALUATED FOR COMPLIANCE WITH ARARS, INCLUDING CHEMICAL-SPECIFIC, ACTION-SPECIFIC, AND LOCATION SPECIFIC ARARS. AW-1 AND AW-3 MEET THEIR RESPECTIVE ARARS. AW-2 MAY NOT MEET THE REQUIREMENTS OF EXECUTIVE ORDER 11990 (PROTECTION OF WETLANDS). SINCE THE PRESENT VOLUME OF WATER BEING DIVERTED FROM THE FARM RIVER IS UNKNOWN, IT IS NOT POSSIBLE TO QUANTIFY THE IMPACT THAT AN ADDITIONAL 0.31 MGD DIVERSION WOULD HAVE ON DOWNSTREAM WETLANDS. AW-NA WOULD MEET APAAS WHEN THE RANDOLPH-HOLBROOK TREATMENT FACILITY IS UPGRADED TO INCLUDE IRON AND MANGANESE TREATMENT.

3. LONG-TERM EFFECTIVENESS AND PERMANENCE

ALTERNATIVE AW-1 OFFERS THE GREATEST DEGREE OF LONG-TERM EFFECTIVENESS AND PERMANENCE. AW-1 IS EXPECTED TO BE CAPABLE OF SUPPLYING 0.31 MGD BASED ON PREVIOUS USAGE OF DONNA ROAD AQUIFER AT 0.5 MGD.

ALTERNATIVES AW-2 AND AW-3 ALSO OFFER LONG-TERM PROTECTIVENESS AND PERMANENCE BUT, NOT TO AS GREAT A DEGREE AS AW-1. AS NOTED ABOVE, DIVERTING AN ADDITIONAL 0.31 MGD FROM THE FARM RIVER MAY HAVE NEGATIVE IMPACTS ON DOWNSTREAM WETLANDS; THEREFORE, IT IS POSSIBLE THAT WITHDRAWAL MIGHT NEED TO BE LIMITED AT TIMES OF LOW FLOW. THIS POTENTIAL REDUCES THE DEGREE OF CERTAINTY THAT AW-2 WILL PROVE SUCCESSFUL, AND THUS MAKES ALTERNATIVE AW-2 LESS EFFECTIVE IN MEETING EPA'S GOAL OF PROVIDING A WATER SOURCE TO MEET THE LOST DEMAND. FOR ALTERNATIVE AW-3, SINCE NO WATER IS CURRENTLY BEING DIVERTED, IT IS LESS LIKELY THAN AW-2 THAT A LOW FLOW CONDITION WOULD OCCUR.

ALTERNATIVE AW-NA WILL NOT REPLACE THE LOST DEMAND, AND WILL RESULT IN CONTINUED RELIANCE ON EXISTING WATER SUPPLY AND TREATMENT SYSTEMS; IT IS NEITHER EFFECTIVE IN THE LONG-TERM NOR WILL IT PROVIDE A PERMANENT REPLACEMENT OF THE LOST WATER DEMAND.

4. REDUCTION OF MOBILITY, TOXICITY, OR VOLUME THROUGH TREATMENT

THE REDUCTION OF MOBILITY, TOXICITY AND VOLUME THROUGH TREATMENT WAS DETERMINED NOT TO BE APPLICABLE TO THIS OPERABLE UNIT SINCE SITE CONTAMINANTS ARE NOT BEING TREATED UNDER THIS OPERABLE UNIT.

5. SHORT-TERM EFFECTIVENESS

AS NOTED ABOVE, SINCE THIS ROD DOES NOT INVOLVE TREATMENT OF SITE CONTAMINANTS, THE SHORT-TERM EFFECTIVENESS CRITERIA CAN NOT BE EVALUATED USING THE TIME FRAME FOR PROTECTION OF HUMAN HEALTH AND THE ENVIRONMENT. THIS CRITERION CAN, HOWEVER, BE USED TO EVALUATE THE TIME FRAME NECESSARY FOR IMPLEMENTATION. ALTERNATIVES AW-1, AW-2 AND AW-3 ALL REQUIRE ISSUANCE OF A WITHDRAWAL PERMIT UNDER THE MASSACHUSETTS WATER MANAGEMENT ACT AND EACH MUST ALSO GO THROUGH THE MASSACHUSETTS DEPARTMENT OF ENVIRONMENTAL PROTECTION (DEP) SOURCE APPROVAL PROCESS. IT IS ESTIMATED THAT TWO TO

THREE YEARS WILL BE REQUIRED TO DEVELOP ALTERNATIVES AW-1, AW-2 OR AW-3. ALTHOUGH IT APPEARS THAT AW-2 AND AW-3 ARE EQUIVALENT IN SHORT-TERM EFFECTIVENESS TO AW-1, THERE ARE TWO FACTORS WHICH IMPACT THE START OF IMPLEMENTATION OF ALTERNATIVES AW-2 OR AW-3 THAT ARE OUTSIDE THE CONTROL OF EITHER EPA OR DEP, WHICH MAKE IT IMPOSSIBLE TO PREDICT WHEN THE PROCESS WOULD BEGIN. THOSE FACTORS ARE: (1) THE SCHEDULE FOR INCREASING THE CAPACITY OF THE RANDOLPH-HOLBROOK WATER TREATMENT FACILITY, AND (2) THE SCHEDULE FOR UPGRADING THE RANDOLPH-HOLBROOK WATER TREATMENT FACILITY TO ACHIEVE THE SECONDARY MAXIMUM CONTAMINANT LEVELS (SMCLS) FOR MANGANESE. BECAUSE OF THIS DEPENDENCY, IMPLEMENTATION OF ALTERNATIVES AW-2 AND AW-3 ARE CONSIDERED LESS TIMELY THAN AW-1.

ALTERNATIVE AW-NA DOES NOT REQUIRE PERFORMANCE OF ANY ACTIVITIES, AND WILL NOT REQUIRE ANY TIME TO IMPLEMENT. HOWEVER, IT IS CONSIDERED INEFFECTIVE IN THE SHORT-TERM SINCE IT DOES NOT MEET EPA'S OBJECTIVE TO PROVIDE A WATER SOURCE.

6. IMNLEMENTABILITY

NO ENGINEERING PROBLEMS ARE FORESEEN FOR CONSTRUCTION OF THE WELLFIELD AND REQUIRED WATER TREATMENT FACILITIES FOR AW-1 OR DIVERSIONS UNDER ALTERNATIVE AW-2 AND AW-3. FOR AW-1 THE ESTIMATED 16-BY-30-FOOT TREATMENT BUILDING WILL FIT WITHIN AVAILABLE SPACE AT THE END OF DONNA ROAD, AND ACCESS FOR FACILITY CONSTRUCTION AND FOR O&M PERSONNEL WOULD BE VIA EXISTING STREETS. AS FOR ALTERNATIVES AW-2 AND AW-3, STRUCTURES ARE ALREADY IN PLACE FOR DIVERTING THE FARM AND COCHATO RIVERS; THEREFORE AW-2 AND AW-3 ARE EASILY IMPLEMENTABLE FROM A TECHNICAL STANDPOINT.

THE MAJOR CONCERN WITH IMPLEMENTABILITY OF ALTERNATIVES AW-2 AND AW-3 IS EPA'S LACK OF CONTROL OVER THE PLANS AND SCHEDULE OF THE RANDOLPH-HOLBROOK JOINT WATER BOARD TO INCREASE CAPACITY AND UPGRADE TREATMENT.

SINCE NO NEW CONSTRUCTION WOULD BE NECESSARY TO IMPLEMENT ALTERNATIVE AW-NA, THE IMPLEMENTABILITY OF THE NO-ACTION ALTERNATIVE IS HIGH. THIS ALTERNATIVE CAN BE CONSIDERED ALREADY IMPLEMENTED.

7. COST

THE ESTIMATED PRESENT WORTH VALUE OF EACH ALTERNATIVE IS AS FOLLOWS:

COST COMPARISON

| | | CAPITAL COSTS | O&M COSTS (1) ($/YEAR) | PRESENT WORTH |
|---|---|---|---|---|
| AW-NA | NO ACTION | $ 0 | 0 | 0 |
| AW-1 | REACTION OF DONNA ROAD AQUIFER | 992,000 | 23,000 | 1,118,000 |
| AW-2 | INCREASED DIVERSION OF THE FARM RIVER | 306,000 | 8,000 | 374,000 |

| | | | | |
|---|---|---|---|---|
| AW-3 | COCHATO RIVER DIVERSION | 306,000 | 8,000 | 374,000 |

(1) O&M COSTS ARE NOT EPA'S RESPONSIBILITY, AND EPA WILL NOT PROVIDE O&M FUNDS; HOWEVER, O&M COSTS FOR A TWENTY YEAR PERIOD WERE INCLUDED IN THE ESTIMATES TO ENABLE COMPARISON OF TOTAL PROJECT COSTS

8. STATE ACCEPTANCE

THE DEP HAS BEEN INVOLVED WITH THE SITE FROM THE EARLY 1970'S AND THROUGHOUT THE CERCLA PROCESS. AT THE REQUEST OF DEP, EPA HAS INCLUDED AN ADDITIONAL PROVISION IN THIS ALTERNATIVE. THIS ADDITIONAL PROVISION INVOLVES THE USE OF THE FARM RIVER DIVERSION SHOULD THE DONNA ROAD AQUIFER BE UNABLE TO PROVIDE THE ENTIRE 0.31 MGD. THE DEP HAS REVIEWED THE ALTERNATE WATER SUPPLY FOCUSED FEASIBILITY STUDY AND CONCURS WITH THE SELECTED ALTERNATE WATER SUPPLY ALTERNATIVE.

9. COMMUNITY ACCEPTANCE

THE COMMENTS RECEIVED DURING THE PUBLIC COMMENT PERIOD AND THE DISCUSSIONS DURING THE PROPOSED PLAN AND FEASIBILITY STUDY PUBLIC MEETING ARE SUMMARIZED IN THE ATTACHED DOCUMENT ENTITLED "THE RESPONSIVENESS SUMMARY" (APPENDIX A). GENERALLY, ALL COMMENTERS AGREED WITH EPA'S PROPOSED REMEDY. COMMENTERS DID WANT ASSURANCES, HOWEVER, THAT 0.31 MGD OF WATER WOULD BE PROVIDED. AS OUTLINED IN SECTION XI, IN RESPONSE TO COMMENTS RECEIVED DURING THE PUBLIC COMMENT PERIOD, EPA HAS INCLUDED IN THE SELECTED REMEDY A PROVISION TO SUPPLEMENT THE WATER PUMPED FROM THE DONNA ROAD AQUIFER IF DONNA ROAD IS UNABLE TO PRODUCE 0.31 MGD. COMMENTERS, PARTICULARLY THE BAIRD & MCGUIRE TASK FORCE, WERE STRONGLY AGAINST AW-3 (COCHATO RIVER) AS AN ALTERNATE WATER SUPPLY, DUE TO A PERCEPTION THAT THE COCHATO RIVER SURFACE WATER CONTAINS CONTAMINATION FROM THE BAIRD & MCGUIRE SITE.

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X. TEE SELECTED REMEDY

AS INDICATED IN SECTION II.A ABOVE, THIS ROD IS FOR OPERABLE UNIT #4, ALTERNATE WATER SUPPLY; OPERABLE UNITS #1 AND #2 WERE ADDRESSED IN THE 1986 ROD AND OPERABLE UNIT #3 WAS ADDRESSED IN THE 1989 ROD.

A. DESCRIPTION OF REMEDIAL COMPONENTS

AFTER EVALUATING ALL OF THE FEASIBLE ALTERNATIVES USING THE CRITERIA FOR REMEDY SELECTION, EPA HAS SELECTED AW-1, THE REACTIVATION OF THE DONNA ROAD AQUIFER, AS THE ALTERNATE WATER SUPPLY TO REPLACE THE LOST DEMAND RESULTING FROM CONTAMINATION OF THE SOUTH STREET WELLFIELD. AW-1 CAN BE BROKEN INTO FOUR COMPONENTS: (1) PERMITTING/PRE-DESIGN STUDIES, (2) GROUNDWATER EXTRACTION, (3) TREATMENT, AND (4) DELIVERY TO DISTRIBUTION SYSTEM. EACH COMPONENT IS DESCRIBED BELOW.

1. PERMITTING/PRE-DESIGN STUDIES

SINCE THE DONNA ROAD AQUIFER IS NOT PART OF THE BAIRD & MCGUIRE SITE,

SECTION 121(E), WHICH WAIVES THE ADMINISTRATIVE PERMITTING REQUIREMENTS FOR REMEDIAL ACTIONS CONDUCTED ON-SITE, IS NOT APPLICABLE; THEREFORE ALL NECESSARY FEDERAL, STATE AND LOCAL PERMITS MUST BE OBTAINED FOR THIS REMEDIAL ACTION. TWO PERMITS WHICH WILL BE CRITICAL TO THE TIMELY IMPLEMENTATION OF THIS REMEDY WILL BE A WATER WITHDRAWAL PERMIT AS REQUIRED BY THE MASSACHUSETTS WATER MANAGEMENT ACT AND A NEW SOURCE APPROVAL AS REQUIRED BY THE DEP "GUIDELINES AND POLICIES FOR PUBLIC WATER SUPPLIES" DOCUMENT.

THE RANDOLPH-HOLBROOK JOINT WATER BOARD CURRENTLY HAS A WATER WITHDRAWAL PERMIT WHICH AUTHORIZES THEM TO WITHDRAW A TOTAL OF 3.27 MGD FROM THE FOLLOWING FOUR POINTS: SOUTH STREET WELL NO. 1 (WHICH WAS CLOSED IN 1982), DONNA ROAD WELLFIELD, RICHARDI RESERVOIR AND THE GREAT POND/UPPER RESERVOIR. THE JOINT WATER BOARD IS CURRENTLY OPERATING CLOSE TO THAT 3.27 MGD CAPACITY; THE ADDITION OF 0.31 MGD WILL EXCEED THE PERMITTED CAPACITY THUS REQUIRING A NEW PERMIT. IN ADDITION TO A NEW PERMIT FOR TOTAL VOLUME OF WATER, UNDER THE MASSACHUSETTS WATER MANAGEMENT ACT THE ADDITION OF A NEW WELL CONSTITUTES A NEW WITHDRAWAL POINT AND WILL ALSO REQUIRE A NEW PERMIT.

THE APPLICATION PROCESS FOR THE WITHDRAWAL PERMIT CONSISTS OF:

PREPARATION OF AN APPLICATION PACKAGE INCLUDING BUT NOT LIMITED TO:

* GENERAL SYSTEM INFORMATION
* HISTORIC AND PROJECTED WITHDRAWALS
* WATER DEMAND ESTIMATES
* PREPARATION BY THE TOWN OF HOLBROOK OF A WATER CONSERVATION PROGRAM AND TIMETABLE OF IMPLEMENTATION
* ALTERNATIVES TO THE WITHDRAWAL
* POTENTIAL EFFECTS OF THE WITHDRAWAL ON SURROUNDING WATER BASED USERS (E.G., WETLANDS, ASH AND WILDLIFE, RECREATION)
* ACCEPTANCE BY MASSACHUSETTS DEPARTMENT OF WATER SUPPLY UNDER THE SOURCE APPROVAL GUIDELINES

* NOTIFICATION OF ABUTTERS AND PUBLICATION OF NOTICE OF INTENT TO WITHDRAW WATER:

* RESPONSE TO ANY PUBLIC COMMENTS

DEP ALSO REQUIRES A SOURCE APPROVAL FOR ANY PUBLIC DRINKING WATER SUPPLY OVER 100,000 MGD. THE SOURCE APPROVAL PERMIT PROCESS IS OUTLINED IN THE "GUIDELINES AND POLICIES FOR PUBLIC WATER SUPPLIES" DOCUMENT. THE PROCESS INCLUDES THE FOLLOWING NINE STEPS:

1. EXPLORATORY PHASE;
2. SITE EXAM REQUEST;
3. SITE EXAM;
4. PUMP TEST APPROVAL;
5. PUMP TEST PROPOSAL REVIEW AND APPROVAL;
6. PUMP TEST;
7. PUMP TEST REPORT;
8. FINAL REPORT; AND
9. APPROVAL.

THIS PROCESS IS EXPECTED TO TAKE SIX (6) MONTHS TO ONE YEAR. FURTHER DETAILS OF EACH OF THE NINE STEPS CAN BE FOUND IN APPENDIX A OF THE FFS.

ALTHOUGH ALL STUDIES AND HISTORICAL DATA INDICATE THE DONNA ROAD AQUIFER SHOULD BE ABLE TO MEET THE 0.31 MGD LOST DEMAND UNDER THE SOURCE APPROVAL PROCESS, DEP MAY LIMIT THE PUMPING OF THE WELLS BASED ON THE SAFE YIELD (THE MAXIMUM RATE AT WHICH THE SYSTEM CAN BE EXPECTED TO DELIVER WATER CONTINUALLY UNDER A DEFINED SET OF DROUGHT CONDITIONS) OF THE AQUIFER. SHOULD THE DONNA ROAD AQUIFER BE UNABLE TO PROVIDE THE ENTIRE LOST DEMAND OF 0.31 MGD, ANY INCREMENTAL DIFFERENCE BETWEEN 0.31 MGD AND THE AMOUNT OF WATER THE DONNA ROAD AQUIFER PROVIDES WILL BE OBTAINED BY INCREASING THE DIVERSION OF THE FARM RIVER. IF HOWEVER, THE PRODUCTION OF GROUND WATER FROM DONNA ROAD IS INSUFFICIENT TO SUPPORT THE BALANCE BETWEEN THE REMEDY SELECTION CRITERIA, EPA WILL REEXAMINE THE REMEDY. EPA ANTICIPATES THAT A WATER PRODUCTION FROM DONNA ROAD OF LESS THAN 0.21 MAY PROMPT SUCH A REEVALUATION.

2. GROUNDWATER EXTRACTION

THE EXTRACTION SYSTEM IS CONCEPTUALIZED AS TWO 12-INCH DIAMETER WELLS APPROXIMATELY 40 FEET DEEP, AND 800 TO 1,000 FEET APART, ALIGNED PERPENDICULAR TO GROUNDWATER FLOW. SUBMERSIBLE PUMPS LOCATED IN EACH WELL WILL EXTRACT WATER AND PUMP IT DIRECTLY TO TREATMENT UNITS. IT IS ANTICIPATED THAT THE PUMPS WILL BE TURNED ON AND OFF BY PRESSURE/DEMAND. THE EXACT NUMBER AND LOCATION OF THE WELLS WILL BE REFINED DURING THE HYDROGEOLOGIC INVESTIGATIONS NECESSARY FOR THE DEP'S SOURCE APPROVAL PROCESS.

3. TREATMENT

NATIONAL PRIMARY DRINKING WATER REGULATIONS (NPDWR) (40 CFR 141, SUBPART R) REQUIRE THAT PUBLIC WATER SYSTEMS SUPPLIED BY A GROUNDWATER SOURCE UNDER THE DIRECT INFLUENCE OF SURFACE WATER PROVIDE FILTRATION AND DISINFECTION TREATMENT PROCESSES, UNLESS THE SUPPLIER CAN DEMONSTRATE THAT THE RAW WATER SOURCE MEETS STRINGENT CRITERIA FOR BACTERIA AND OTHER MICROBIOLOGICAL CONTAMINANTS. THE FILTRATION TREATMENT STEPS PROPOSED FOR IRON AND MANGANESE CONTROL AND THE SUBSEQUENT DISINFECTION STEP WILL SATISFY THE REQUIREMENTS OF 40 CFR 141, SUBPART H.

AS LEVELS OF IRON AND MANGANESE IN THE DONNA ROAD AQUIFER EXCEED FEDERAL DRINKING WATER STANDARDS, INCLUDED IN THIS ALTERNATIVE, AS WITH ALL THE POSSIBLE ALTERNATIVES, IS A POTASSIUM PERMANGANATE TREATMENT SYSTEM. THE IRON AND MANGANESE TREATMENT SYSTEM CONSISTS OF ADDING POTASSIUM PERMANGANATE TO THE EXTRACTED WATER. THE POTASSIUM PERMANGANATE THEN CAUSES THE IRON AND MANGANESE TO PRECIPITATE OUT OF THE WATER. THE PROCESS IS THEN FOLLOWED BY GREENSAND FILTRATION. THE GREENSAND ACTS AS A FILTER TO FURTHER REMOVE PRECIPITATE (FIGURE 2).

ALTHOUGH THE TREATMENT METHOD IS WELL ESTABLISHED, A PILOT TEST WILL BE PERFORMED TO ASSURE ITS EFFECTIVENESS BEFORE DESIGN AND IMPLEMENTATION.

4. DISTRIBUTION SYSTEM

TREATED GROUNDWATER WILL BE PIPED TO THE CURRENT DISTRIBUTION SYSTEM WHICH IS WITHIN A FEW HUNDRED FEET OF THE RANDOLPHHOLBROOK WATER DISTRIBUTION

MAIN. NO MODIFICATIONS TO THE DISTRIBUTION SYSTEM ARE ANTICIPATED.

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## II. STATUTORY DETERMINATIONS

THE REMEDIAL ACTION SELECTED FOR IMPLEMENTATION AT THE BAIRD & MCGUIRE SITE IS CONSISTENT WITH CERCLA AND, TO THE EXTENT PRACTICABLE, THE NCP. THE SELECTED REMEDY IS PROTECTIVE OF HUMAN HEALTH AND THE ENVIRONMENT, ATTAINS ARARS AND IS COST EFFECTIVE. ADDITIONALLY, THE SELECTED REMEDY UTILIZES ALTERNATE TREATMENT TECHNOLOGIES OR RESOURCE RECOVERY TECHNOLOGIES TO THE MAXIMUM EXTENT PRACTICABLE.

### A. THE SELECTED REMEDY IS PROTECTIVE OF HUMAN HEALTH AND THE ENVIRONMENT

THE REMEDY AT THIS SITE WILL PERMANENTLY REDUCE THE RISKS POSED TO HUMAN HEALTH AND THE ENVIRONMENT BY ELIMINATING, REDUCING OR CONTROLLING EXPOSURES TO HUMAN AND ENVIRONMENTAL RECEPTORS THROUGH TREATMENT, ENGINEERING CONTROLS, OR INSTITUTIONAL CONTROLS; MORE SPECIFICALLY, SINCE WATER FROM THE DONNA ROAD AQUIFER MEETS ALL MCLS, AND MASSACHUSETTS MAXIMUM CONTAMINANT LEVELS (MMCLS) EXCEPT SODIUM, AND CAN MEET ALL MAXIMUM CONTAMINANT LEVEL GOALS (MCLGS), SECONDARY MAXIMUM CONTAMINANT LEVELS (SMCLS) WITH TREATMENT THE REMEDY IS CONSIDERED PROTECTIVE OF HUMAN HEALTH AND THE ENVIRONMENT. IMPLEMENTATION OF THE SELECTED REMEDY WILL NOT POSE UNACCEPTABLE SHORT-TERM RISKS OR CROSS-MEDIA IMPACTS, SINCE ANY WETLAND IMPACTS WILL BE MITIGATED, IF NECESSARY, BY THE SOURCE APPROVAL PROCESS LIMITING PUMPING RATES.

### B. THE SELECTED REMEDY ATTAINS APPLICABLE REQUIREMENTS

THIS REMEDY WILL ATTAIN ALL APPLICABLE FEDERAL AND STATE REQUIREMENTS THAT APPLY TO THE SITE. SINCE THIS REMEDY IS BEING CONDUCTED ENTIRELY OFF-SITE ONLY APPLICABLE REQUIREMENTS, INCLUDING OBTAINING ALL APPLICABLE PERMITS WILL BE REQUIRED. ENVIRONMENTAL LAWS FROM WHICH APPLICABLE REQUIREMENTS FOR THE SELECTED REMEDIAL ACTION ARE DERIVED, AND THE SPECIFIC APPLICABLE REQUIREMENTS INCLUDE:

CHEMICAL SPECIFIC

SAFE DRINKING WATER ACT
MASSACHUSETTS DRINKING WATER REGULATIONS

LOCATION SPECIFIC

EXECUTIVE ORDER 11990 (WETLANDS PROTECTION)
FISH AND WILDLIFE COORDINATION ACT
CLEAN WATER ACT
RIVERS AND HARBORS ACT OF 1899
RESOURCE CONSERVATION AND RECOVERY ACT (LAND BAN) MASSACHUSETTS WETLANDS PROTECTION ACT MASSACHUSETTS WATERWAYS ACT MASSACHUSETTS SURFACE WATER QUALITY STANDARDS MASSACHUSETTS GROUND WATER QUALITY STANDARDS MASSACHUSETTS WATER QUALITY CERTIFICATION AND CERTIFICATION OF DREDGING MASSACHUSETTS WATER MANAGEMENT ACT
MASSACHUSETTS SUPERVISION OF INLAND WATERS

ACTION SPECIFIC

OCCUPATIONAL SAFETY AND HEALTH ACT
MASSACHUSETTS GUIDELINES & POLICIES FOR PUBLIC
WATER SYSTEMS

A DISCUSSION OF WHY THESE REQUIREMENTS ARE APPLICABLE MAY BE FOUND IN THE FFS REPORT AT PAGES 2-1 THROUGH 2-23 AND PAGES 5-33 THROUGH 5-55.

1. CHEMICAL-SPECIFIC APPLICABLE REQUIREMENTS

A. SAFE DRINKING WATER ACT

SINCE THE PURPOSE OF THIS FFS WAS TO DEVELOP A DRINKING WATER SOURCE TO REPLACE THE LOST DEMAND FROM THE SOUTH STREET WELLS, THE NATIONAL PRIMARY DRINKING WATER REGULATIONS (NPDWR) WHICH ESTABLISH MAXIMUM CONTAMINANT LEVELS (MCLS) THAT SPECIFY THE MAXIMUM PERMISSIBLE LEVEL OF A CONTAMINANT IN WATER USED AS A PUBLIC WATER SUPPLY ARE APPLICABLE.

NATIONAL SECONDARY DRINKING WATER REGULATIONS ESTABLISH SECONDARY MAXIMUM CONTAMINANT LEVELS (SMCLS), ARE ALSO APPLICABLE AND CAN BE MET WITH TREATMENT.

B. MASSACHUSETTS DRINKING WATER REGULATIONS

AS WITH THE NATIONAL PRIMARY DRINKING WATER REGULATIONS, SINCE THE PURPOSE OF THIS REMEDY IS TO ESTABLISH A DRINKING WATER SOURCE FOR THE TOWN OF HOLBROOK, THE MASSACHUSETTS DRINKING WATER REGULATIONS (310 CMR 22.00) ARE APPLICABLE TO THIS REMEDY. DATA INDICATE THAT WATER FROM THE DONNA ROAD AQUIFER MEETS ALL DCLS EXCEPT FOR SODIUM (27 MG/L VERSUS 20 MG/L). THE MMCL FOR SODIUM IS BASED ON THE AMOUNT OF SODIUM RECOMMENDED FROM DRINKING WATER FOR INDIVIDUALS ON A REDUCED-SODIUM DIET. DEP GENERALLY DOES NOT SHUT DOWN A WATER SUPPLY BECAUSE SODIUM LEVELS SLIGHTLY EXCEED THE MMCL; RATHER, IT REQUIRES THE WATER SUPPLIER TO NOTIFY PERSONS SERVED BY THE WATER SUPPLY OF THE SODIUM LEVELS AND POSSIBLE WAYS OF CORRECTING THE SITUATION (310 CMR 22.16), THUS THIS REQUIREMENT CAN BE MET.

2. LOCATION-SPECIFIC ANNLICABLE REQUIREMENTS

A. EXECUTIVE ORDER 11990 (WETLANDS PROTECTION)

EXECUTIVE ORDER 11990, WETLANDS PROTECTION, IS APPLICABLE TO ACTIONS INVOLVING CONSTRUCTION OF FACILITIES IN WETLANDS OR ALTERATIONS OF WETLAND PROPERTY. SINCE AW-1 IS LOCATED IN A WETLAND, THE WETLAND EXECUTIVE ORDER IS APPLICABLE.

B. FISH AND WILDLIFE COORDINATION ACT

THE FISH AND WILDLIFE COORDINATION ACT (16 USC 661 ET SEQ.) REQUIRES THAT BEFORE ISSUING A FEDERAL PERMIT OR UNDERTAKING ANY FEDERAL ACTION THAT CAUSES THE IMPOUNDMENT (WITH CERTAIN EXEMPTIONS), DIVERSION, OR OTHER CONTROL OR MODIFICATION OF ANY BODY OF WATER, THE APPLICABLE FEDERAL AGENCY MUST CONSULT WITH (1) THE APPROPRIATE STATE AGENCY EXERCISING JURISDICTIONS OVER WILDLIFE RESOURCES; (2) THE US FISH AND WILDLIFE

SERVICE (USFWS) AND THE NATIONAL MARINE FISHERIES SERVICE, WITHIN THE DEPARTMENT OF INTERIOR; AND (3) THE NATIONAL MARINE FISHERIES SERVICE, WITHIN THE DEPARTMENT OF COMMERCE. SINCE AW-1 IS TO TAKE PLACE IN THE TROUT BROOK BOTTOMLAND THIS ACT IS APPLICABLE.

C. CLEAN WATER ACT

SECTION 402 OF THE CLEAN WATER ACT (CWA) REGULATES THE DISCHARGE OF POLLUTANTS INTO NAVIGABLE WATERS OF THE US A NATIONAL POLLUTANT DISCHARGE ELIMINATION SYSTEM (NPDES) PERMIT MUST BE OBTAINED FROM EPA OR A DELEGATED STATE AGENCY FOR SUCH A DISCHARGE. THE DISCHARGE OF FILTER BACKWASH FROM A WATER TREATMENT FACILITY TO A SURFACE WATER BODY WOULD REQUIRE AN NPDES PERMIT.

SECTION 404 OF THE CWA REGULATES THE DISCHARGE OF DREDGED AND FILL MATERIALS TO WATERS OF THE US FILLING WETLANDS WOULD BE CONSIDERED A DISCHARGE OF FILL MATERIAL TO WATERS OF THE US IF CONSTRUCTION OF ACCESS ROADS IN THE TROUT BROOK BOTTOMLAND ARE DEEMED NECESSARY DURING THE PERMITTING PROCESS OR PRE-DESIGN STUDIES, IT WOULD BE CONSIDERED A DISTURBANCE OF A WETLAND AND SECTION 404 OF THE CWA WOULD BE APPLICABLE.

D. RIVERS AND HARBORS ACT OF 1899

SECTION 10 OF THE RIVERS AND HARBOR ACT OF 1899 REQUIRES AUTHORIZATION FROM THE SECRETARY OF THE ARMY, ACTING THROUGH THE US ARMY CORPS OF ENGINEERS (USACE), FOR THE CONSTRUCTION OF ANY STRUCTURE IN OR OVER ANY "NAVIGABLE WATER OF THE US ," THE EXCAVATION FROM OR DEPOSITION OF MATERIAL IN SUCH WATERS, OR ANY OBSTRUCTION OR ALTERATION IN SUCH WATERS. SHOULD ADDITIONAL DIVERSION BE NEEDED TO SUPPLEMENT THE DONNA ROAD SUPPLY BY USING THE FARM RIVER, THIS ACT WOULD BE CONSIDERED APPLICABLE.

E. RESOURCE CONSERVATION AND RECOVER ACT (LAND BAN) SINCE THIS ROD DOES NOT INVOLVE THE DISPOSAL OR TREATMENT OF HAZARDOUS SUBSTANCES, LAND BAN REQUIREMENTS ARE NOT APPLICABLE.

F. MASSACHUSETTS WETLANDS PROTECTION ACT.

AT THE STATE LEVEL, SIMILAR TO THE WETLANDS EXECUTIVE ORDER, WETLANDS AND LAND SUBJECT TO FLOODING ARE PROTECTED UNDER THE MASSACHUSETTS WETLANDS PROTECTION ACT (MGL, CHAPTER 131) AND WETLANDS REGULATIONS AT 310 CMR 10.00. SINCE AW-1 INVOLVES WORK IN THE WETLANDS, THE ACT IS APPLICABLE.

G. MASSACHUSETTS WATERWAYS ACT

THE MASSACHUSETTS WATERWAYS ACT (MGL, CHAPTER 91) AND REGULATIONS AT 310 CMR 9.00 REQUIRE THAT A LICENSE FROM DEP BE OBTAINED FOR ANY WORK IN OR OVER ANY TIDELANDS, RIVER OR STREAM (WITH RESPECT TO WHICH PUBLIC FUNDS HAVE BEEN EXPENDED), OR GREAT POND, OR ANY OUTLET THEREOF. FARM AND COCHATO RIVERS ARE CONSIDERED TO BE SUBJECT TO THESE REGULATIONS. SHOULD ADDITIONAL DIVERSION BE NEEDED TO SUPPLEMENT THE DONNA ROAD SUPPLY BY USING THE FARM RIVER, THIS ACT WOULD BE CONSIDERED APPLICABLE.

H. MASSACHUSETTS SURFACE WATER OUALITY STANDARDS AND GROUND WATER QUALITY STANDARDS

THE MASSACHUSETTS SURFACE WATER QUALITY STANDARDS AND GROUND WATER QUALITY STANDARDS (314 CMR 4.00 AND 314 CMR 6.00, RESPECTIVELY) SET FORTH PROCEDURES TO BE USED BY THE STATE IN CLASSIFYING SURFACE WATER AND GROUNDWATER ACCORDING TO THE USES WHICH THE CLASS IS INTENDED TO PROTECT. FOR EACH CLASS, THE MOST SENSITIVE BENEFICIAL USES ARE IDENTIFIED AND MINIMUM CRITERIA FOR WATER QUALITY ARE ESTABLISHED. THE REGULATIONS ESTABLISH THREE CLASSES FOR INLAND SURFACE WATERS ACCORDING TO THE MOST SENSITIVE AND THEREFORE GOVERNING USES THE CLASSES ARE INTENDED TO PROTECT. IN ACCORDANCE WITH 314 CMR 4.04 AND 6.04, THE QUALITY OF SURFACE WATER WILL BE MAINTAINED AND PROTECTED TO SUSTAIN EXISTING BENEFICIAL USES. IN ADDITION, WATER WHOSE QUALITY IS OR BECOMES HIGHER WILL BE MAINTAINED AT THAT HIGHER LEVEL OF QUALITY UNLESS LIMITED DEGRADATION IS AUTHORIZED. SINCE AW-1 INVOLVES SURFACE WATER DISCHARGE PERMITS, THE STANDARDS ARE APPLICABLE.

I. MASSACHUSETTS WATER QUALITY CERTIFICATION AND CERTIFICATION OF DREDGING

FOR ACTIVITIES THAT REQUIRE A DEP WETLANDS ORDER OF CONDITIONS TO DREDGE OR FILL WATERS OR WETLANDS, A CHAPTER 91 WATERWAYS LICENSE, A USAGE PERMIT, OR ANY MAJOR PERMIT ISSUED BY EPA (E.G.CWA NPDES PERMIT), A MASSACHUSETTS DIVISION OF WATER POLLUTION CONTROL WATER QUALITY CERTIFICATION PURSUANT TO 314 CMR 9.00 IS REQUIRED. AS IN SECTION XI.B.2.C ABOVE, IF AN ADDITIONAL ACCESS ROAD IS NECESSARY THEN THIS CERTIFICATION IS APPLICABLE.

J. MASSACHUSETTS WATER MANAGEMENT ACT

UNDER THE MASSACHUSETTS WATER MANAGEMENT ACT (MGL CHAPTER 21G) AND REGULATIONS (310 CMR 36.00), DEP, IN CONJUNCTION WITH THE EXECUTIVE OFFICE OF ENVIRONMENTAL AFFAIRS WATER RESOURCE COMMISSION, IMPLEMENTS A PROGRAM TO ASSESS AND REGULATE THE USE OF WATER IN THE STATE, PLAN FOR FUTURE WATER NEEDS, AND ASSESS THE SAFE YIELDS OF ALL RIVER BASINS.

THE PROGRAM REQUIRES REGISTRATION WITH THE DEP DIVISION OF WATER SUPPLY (DWS) OF WITHDRAWALS OF GROUND OR SURFACE WATER IN MASSACHUSETTS ABOVE AN DAILY AVERAGE OF 100,000 GALLONS FOR A QUARTER YEAR. A PERMIT MUST BE OBTAINED PRIOR TO MAKING A NEW WITHDRAWAL IN EXCESS OF THE THRESHOLD VOLUME FROM A WATER SOURCE OR CONSTRUCTING THE MEANS TO MAKE THE WITHDRAWAL. A NEW WITHDRAWAL ALSO INCLUDES AN INCREASE ABOVE THE REGISTERED WITHDRAWAL IN EXCESS OF THE THRESHOLD VALUE OF 100,000 GALLONS PER DAY. ALTERNATIVE AW-1 INCLUDES A WITHDRAWAL OVER THE THRESHOLD, A NEW WITHDRAWAL AND AN INCREASE ABOVE THE REGISTERED WITHDRAWAL, THUS THE WATER MANAGEMENT ACT IS APPLICABLE.

K. MASSACHUSETTS SUPERVISION OF INLAND WATERS ACT

SECTION 111, MGL CHAPTERS 159 AND 160, GIVES GENERAL OVERSIGHT AND CARE OF ALL INLAND WATERS AND OF ALL STREAMS, PONDS AND UNDERGROUND WATERS USED BY ANY CITY OR TOWN IN THE COMMONWEALTH AS SOURCES OF WATER. THE PROVISION REQUIRES RECORDKEEPING BY DEP. SINCE THE DONNA ROAD AQUIFER IS AN UNDERGROUND WATER, THIS ACT IS APPLICABLE.

3. ACTION-SPECIFIC APPLICABLE REQUIREMENTS

A. OCCUPATIONAL SAFETY AND HEALTH ACT

THE OCCUPATIONAL SAFETY AND HEALTH ADMINISTRATION (OSHA) STANDARDS (I.E., 29 CFR 1910, 1904, AND 1926) APPLY TO WORKER SAFETY, AND REQUIRE EMPLOYERS TO COMMUNICATE RISKS AT THE WORKPLACE TO EMPLOYEES. OSHA STANDARDS MUST BE COMPLIED WITH DURING ALL SITE WORK.

B. MASSACHUSETTS GUIDELINES & POLICIES FOR PUBLIC WATER SYSTEMS

THE DEP DWS PUBLISHED A DOCUMENT THAT PROVIDES GUIDANCE FOR THE EXPLORATION, EVALUATION, TREATMENT, STORAGE/DISTRIBUTION, AND PROTECTION OF NEW PUBLIC WATER SUPPLY SOURCES (DEP, 1990). FOR ALL GROUNDWATER WITHDRAWALS, THE DOCUMENT SPECIFIES AN EXPLORATION PHASE, SITE EXAM, FIVE-DAY PUMP TEST, REQUIREMENTS FOR DELINEATING THREE AFFECTED ZONES, AND A FINAL REPORT.

C. THE SELECTED REMEDIAL ACTION IS COST-EFFECTIVE

IN THE AGENCY'S JUDGMENT, THE SELECTED REMEDY IS COST-EFFECTIVE, I.E., THE REMEDY AFFORDS OVERALL EFFECTIVENESS PROPORTIONAL TO ITS COSTS. IN SELECTING THIS REMEDY, ONCE EPA IDENTIFIED ALTERNATIVES THAT ARE PROTECTIVE OF HUMAN HEALTH AND THE ENVIRONMENT AND THAT ATTAIN, OR, AS APPROPRIATE, WAIVE APPLICABLE REQUIREMENTS, EPA EVALUATED THE OVERALL EFFECTIVENESS OF EACH ALTERNATIVE BY ASSESSING THE RELEVANT THREE CRITERIA--LONG TERM EFFECTIVENESS AND PERMANENCE; REDUCTION IN TOXICITY, MOBILITY, AND VOLUME THROUGH TREATMENT; AND SHORT-TERM EFFECTIVENESS, IN COMBINATION. THE RELATIONSHIP OF THE OVERALL EFFECTIVENESS OF THIS REMEDIAL ALTERNATIVE WAS DETERMINED TO BE PROPORTIONAL TO ITS COSTS. THE COSTS OF THIS REMEDIAL ALTERNATIVE ARE: $992,000 IN CAPITAL COSTS, AND $23,000 ANNUALLY FOR 20 YEARS FOR OPERATION AND MAINTENANCE, RESULTING IN A TOTAL NET PRESENT WORTH OF $1,188,000.

EACH OF THE ALTERNATIVES EVALUATED IS PROTECTIVE OF HUMAN HEALTH AND THE ENVIRONMENT; HOWEVER, WHEN EVALUATED IN CONJUNCTION WITH SHORT- AND LONG-TERM EFFECTIVENESS AND PERMANENCE, ALTERNATIVE AW-1 IS THE MOST COST-EFFECTIVE. AW-1 WILL PROVIDE A SEPARATE WATER SOURCE THAT HAS BEEN SHOWN TO BE ABLE TO PRODUCE IN EXCESS OF THE 0.31 MGD LOST DEMAND. ALTERNATIVE AW-1 IS MOST EFFECTIVE IN THE SHORT-TERM SINCE, UNLIKE AW-2 AND AW-3 IT IS NOT DEPENDENT ON THE RANDOLPH-HOLBROOK JOINT WATER BOARD FOR UPGRADE OF THE TREATMENT PLANT. ALTERNATIVE AW-2 MAY IMPACT DOWNSTREAM WETLANDS WHICH COULD CAUSE WATER WITHDRAWAL TO BE RESTRICTED. AS NOTED ABOVE, THE REDUCTION OF MOBILITY, TOXICITY AND VOLUME WAS DETERMINED NOT TO BE APPLICABLE TO THIS OPERABLE UNIT BECAUSE SITE CONTAMINANTS ARE NOT BEING TREATED UNDER THIS REMEDY.

D. THE SELECTED REMEDY UTILIZES PERMANENT SOLUTIONS AND ALTERNATIVE TREATMENT OR RESOURCE RECOVERY TECHNOLOGIES TO THE MAXIMUM EXTENT PRACTICABLE

ONCE THE AGENCY IDENTIFIED THOSE ALTERNATIVES THAT ATTAIN OR, AS APPROPRIATE, WAIVE APPLICABLE REQUIREMENTS AND THAT ARE PROTECTIVE OF HUMAN HEALTH AND THE ENVIRONMENT, EPA ATTEMPTS TO IDENTIFY WHICH ALTERNATIVE UTILIZES PERMANENT SOLUTIONS AND ALTERNATIVE TREATMENT TECHNOLOGIES OR RESOURCE RECOVERY TECHNOLOGIES TO THE MAXIMUM EXTENT

PRACTICABLE. THIS DETERMINATION WAS MADE BY DECIDING WHICH ONE OF THE IDENTIFIED ALTERNATIVES PROVIDES THE BEST BALANCE OF TRADE-OFFS AMONG ALTERNATIVES IN TERMS OF: 1) LONG-TERM EFFECTIVENESS AND PERMANENCE; 2) REDUCTION OF TOXICITY, MOBILITY OR VOLUME THROUGH TREATMENT; 3) SHORT-TERM EFFECTIVENESS; 4) IMPLEMENTABILITY; AND 5) COST. THE BALANCING TEST EMPHASIZED LONG-TERM EFFECTIVENESS AND PERMANENCE AND THE REDUCTION OF TOXICITY, MOBILITY AND VOLUME THROUGH TREATMENT; AND CONSIDERED THE PREFERENCE FOR TREATMENT AS A PRINCIPAL ELEMENT, THE BIAS AGAINST OFF-SITE LAND DISPOSAL OF UNTREATED WASTE, AND COMMUNITY AND STATE ACCEPTANCE. THE SELECTED REMEDY PROVIDES THE BEST BALANCE OF TRADE-OFFS AMONG THE ALTERNATIVES. AS THE SCOPE OF THIS OPERABLE UNIT DOES NOT INCLUDE TREATMENT OF SITE CONTAMINANTS, EACH ALTERNATIVE, INCLUDING THE SELECTED REMEDY, UTILIZES PERMANENT SOLUTIONS AND ALTERNATIVE TREATMENT TECHNOLOGIES OR RESOURCE RECOVERY TECHNOLOGIES TO THE MAXIMUM EXTENT PRACTICABLE.

E. THE PREFERENCE FOR TREATMENT WHICH PERMANENTLY AND SIGNIFICANTLY REDUCES THE TOXICITY, MOBILITY OR VOLUME OF THE HAZARDOUS SUBSTANCES AS A PRINCIPAL ELEMENT IS NOT APPLICABLE TO THE SELECTED REMEDY

THE REDUCTION OF MOBILITY, TOXICITY AND VOLUME WAS DETERMINED NOT TO BE APPLICABLE TO THIS OPERABLE UNIT SINCE TREATMENT OF SITE CONTAMINANTS IS NOT AN OBJECTIVE OF THIS OPERABLE UNIT.

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III. DOCUMENTATION OF SIGNIFICANT CHANGES

EPA PRESENTED A PROPOSED PLAN (PREFERRED ALTERNATIVE) FOR REMEDIATION OF THE SITE ON JUNE 26, 1990. THE ALTERNATE WATER SUPPLY PREFERRED ALTERNATIVE WAS AW-1 REACTIVATION OF THE DONNA ROAD AQUIFER. THIS ALTERNATIVE INCLUDED THE FOLLOWING FOUR ELEMENTS: (1) PERMITTING/PRE-DESIGN STUDIES, (2) GROUNDWATER EXTRACTION, (3) TREATMENT, AND (4) DELIVERY TO DISTRIBUTION SYSTEM. BASED ON PUBLIC COMMENT, THE FOLLOWING TWO COMPONENTS WERE ADDED TO THE SELECTED ALTERNATIVE:

1. SHOULD THE DONNA ROAD AQUIFER BE UNABLE TO PROVIDE THE ENTIRE LOST DEMAND OF 0.31 MGD, ANY INCREMENTAL DIFFERENCE BETWEEN 0.31 MGD AND THE AMOUNT OF WATER THE DONNA ROAD AQUIFER PROVIDES WILL BE OBTAINED BY INCREASING THE DIVERSION OF THE FARM RIVER. IF HOWEVER, THE PRODUCTION OF GROUND WATER FROM DONNA ROAD IS INSUFFICIENT TO SUPPORT THE BALANCE BETWEEN THE REMEDY SELECTION CRITERIA, EPA MAY REEXAMINE THE REMEDY. EPA ANTICIPATES THAT A WATER PRODUCTION FROM DONNA ROAD OF LESS THAN 0.21 MAY PROMPT SUCH A REEVALUATION; AND

2. IN ADDITION TO THE ROUTINE MONITORING REQUIRED AT PUBLIC DRINKING WATER SUPPLIES, A YEARLY ROUND OF SAMPLING, FULL TCL ORGANICS, TAL INORGANICS AND PESTICIDES WILL BE PERFORMED.

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111. STATE ROLE

THE MASSACHUSETTS DEPARTMENT OF ENVIRONMENTAL PROTECTION HAS REVIEWED THE VARIOUS ALTERNATIVES AND HAS INDICATED ITS SUPPORT FOR THE SELECTED REMEDY. THE STATE HAS ALSO REVIEWED THE ALTERNATE WATER SUPPLY FOCUSED FEASIBILITY STUDY TO DETERMINE IF THE SELECTED REMEDY IS IN COMPLIANCE WITH APPLICABLE OR RELEVANT AND APPROPRIATE STATE ENVIRONMENTAL LAWS AND REGULATIONS. THE STATE OF MASSACHUSETTS CONCURS WITH THE SELECTED REMEDY FOR THE BAIRD & MCGUIRE SITE ALTERNATE WATER SUPPLY STUDY. A COPY OF THE DECLARATION OF CONCURRENCE IS ATTACHED AS APPENDIX C. IN ACCORDANCE WITH SECTION 104 OF CERCLA, MASSACHUSETTS IS RESPONSIBLE FOR 10 PERCENT OF THE COST OF THE REMEDIAL ACTION. IN THE CASE OF THE SELECTED REMEDY THE COMMONWEALTH'S SHARE IS ESTIMATED TO BE 118,800.

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## RESPONSIVENESS SUMMARY
## PREFACE

THE US ENVIRONMENTAL PROTECTION AGENCY (EPA) HELD A 30-DAY PUBLIC COMMENT PERIOD FROM JUNE 27, 1990 TO JULY 26, 1990 TO PROVIDE AN OPPORTUNITY FOR INTERESTED PARTIES TO COMMENT ON THE WATER SUPPLY FOCUSED FEASIBILITY STUDY (FFS) AND THE JUNE 1990 PROPOSED PLAN PREPARED FOR THE BAIRD & MCGUIRE SUPERFUND SITE IN HOLBROOK, MASSACHUSETTS. THE FFS EXAMINES AND EVALUATES VARIOUS OPTIONS, CALLED REMEDIAL ALTERNATIVES, TO REPLACE THE LOST DEMAND ARISING FROM BAIRD AND MCGUIRE INDUSTRIAL ACTIVITIES. EPA HAS DEFINED THE LOST DEMAND AS THE DAILY RATE OF GROUNDWATER PRODUCTION THAT THE TOWN OF HOLBROOK HISTORICALLY IMPOSED ON THE SOUTH STREET WELLS FOR USE WITHIN THE TOWN, AND SUBSEQUENTLY LOST AS A RESULT OF BAIRD AND MCGUIRE INDUSTRIAL ACTIVITIES. EPA IDENTIFIED ITS PREFERRED ALTERNATIVE FOR REPLACING THE LOST DEMAND IN THE PROPOSED PLAN ISSUED IN JUNE 1990, BEFORE THE START OF THE PUBLIC COMMENT PERIOD.

TO FACILITATE AN EFFICIENT CLEANUP OF THE SITE, EPA HAS DIVIDED ITS INVESTIGATION OF THE BAIRD & MCGUIRE SITE INTO FOUR SEGMENTS, KNOWN AS OPERABLE UNITS. A REMEDIAL INVESTIGATION (RI) AND FEASIBILITY STUDY FOR THE FIRST TWO OPERABLE UNITS (GROUNDWATER AND ON-SITE SOIL CONTAMINATION, RESPECTIVELY) WAS CONDUCTED BETWEEN 1983 AND 1986. EPA HELD A FORMAL PUBLIC COMMENT PERIOD ON ITS PREFERRED ALTERNATIVE FOR ADDRESSING THESE CONTAMINATED AREAS AND, IN SEPTEMBER 1986, SIGNED A RECORD OF DECISION (ROD) THAT ESTABLISHED EPA'S PLANS FOR CLEANUP OF THE FIRST TWO OPERABLE UNITS. EXTRACTION AND ON-SITE TREATMENT WERE THE TECHNOLOGIES CHOSEN BY EPA TO ADDRESS GROUNDWATER; EXCAVATION AND ON-SITE INCINERATION WERE THE APPROACHES CHOSEN TO ADDRESS SOIL CONTAMINATION. THE THIRD OPERABLE UNIT FOR THE SITE FOCUSED ON SITE-RELATED CONTAMINATION FOUND IN THE COCHATO RIVER SEDIMENTS AND ADJACENT WETLANDS. IN 1989, EPA COMPLETED A FFS FOR THE THIRD OPERABLE UNIT AND HELD A PUBLIC COMMENT PERIOD ON IT'S PREFERRED ALTERNATIVE FOR ADDRESSING THESE CONTAMINATED AREAS. IN SEPTEMBER 1989 EPA SIGNED A ROD THAT ESTABLISHED ANOTHER STEP IN EPA'S PLAN FOR SITE CLEANUP: CONTAMINATED SEDIMENTS WILL BE EXCAVATED AND INCINERATED AT THE INCINERATOR THAT WILL BE LOCATED ON-SITE FOR SOIL TREATMENT AT THE BAIRD & MCGUIRE SITE. THIS ROD FOR THE FOURTH OPERABLE UNIT AND EVALUATES REMEDIAL ALTERNATIVES TO REPLACE MUNICIPAL WATER SUPPLIES LOST AS A RESULT OF SITE-RELATED CONTAMINATION.

THE PURPOSE OF THIS RESPONSIVENESS SUMMARY IS TO DOCUMENT EPA RESPONSES

TO THE QUESTIONS AND COMMENTS RAISED DURING THE PUBLIC COMMENT PERIOD ON THE FOURTH OPERABLE UNIT, THE PROPOSED PLAN, AND THE WATER SUPPLY FOCUSED FEASIBILITY STUDY. EPA WILL CONSIDER ALL OF THESE QUESTIONS AND COMMENTS BEFORE SELECTING A FINAL REMEDIAL ALTERNATIVE TO ADDRESS REPLACEMENT OF THE LOST DEMAND.

THIS RESPONSIVENESS SUMMARY IS DIVIDED INTO THE FOLLOWING SECTIONS:

I. OVERVIEW OF REMEDIAL ALTERNATIVES CONSIDERED IN THE DRAFT FOCUSED FEASIBILITY STUDY, INCLUDING THE PREFERRED ALTERNATIVE-THIS SECTION BRIEFLY OUTLINES THE REMEDIAL ALTERNATIVES EVALUATED IN THE FFS AND THE PROPOSED PLAN, INCLUDING EPA'S PREFERRED ALTERNATIVE.

II. BACKGROUND ON COMMUNITY INVOLVEMENT AND CONCERNS-THIS SECTION PROVIDES A BRIEF HISTORY OF COMMUNITY INTEREST AND CONCERNS REGARDING THE BAIRD & MCGUIRE SITE.

III. SUMMARY OF COMMENTS RECEIVED DURING THE PUBLIC COMMENT PERIOD AND EPA RESPONSES-THIS SECTION SUMMARIZES THE ORAL AND WRITTEN COMMENTS RECEIVED FROM THE PUBLIC DURING THE PUBLIC COMMENT PERIOD AND PROVIDES EPA RESPONSES TO THESE COMMENTS.

IV. REMAINING CONCERNS-THIS SECTION DESCRIBES ISSUES THAT MAY CONTINUE TO BE OF CONCERN TO THE COMMUNITY DURING THE DESIGN AND IMPLEMENTATION OF EPA'S SELECTED REMEDY FOR REPLACING THE LOST DEMAND AT THE BAIRD & MCGUIRE SITE. EPA WILL ADDRESS THESE CONCERNS DURING THE REMEDIAL DESIGN AND REMEDIAL ACTION (RD/RA) PHASE OF THE REPLACEMENT PROCESS.

IN ADDITION, TWO ATTACHMENTS ARE INCLUDED IN THIS RESPONSIVENESS SUMMARY. ATTACHMENT A PROVIDES A LIST OF THE COMMUNITY RELATIONS ACTIVITIES THAT EPA HAS CONDUCTED TO DATE AT THE BAIRD & MCGUIRE SITE. ATTACHMENT B CONTAINS A COPY OF THE TRANSCRIPT FROM THE INFORMAL PUBLIC HEARING HELD ON JULY 17, 1990.

## I. OVERVIEW OF REMEDIAL ALTERNATIVES CONSIDERED IN THE DRAFT FEASIBILITY STUDY, INCLUDING THE PREFERRED ALTERNATIVE

EPA HAS IDENTIFIED A SPECIFIC OBJECTIVE FOR THE WATER SUPPLY FOCUSED FEASIBILITY STUDY. THE OBJECTIVE IS TO IDENTIFY A CANDIDATE WATER SOURCE THAT WILL REPLACE THE 0.31 MILLION GALLONS PER DAY (MGD) LOST DEMAND IN AN ENVIRONMENTALLY SOUND, COST-EFFECTIVE MANNER WITHOUT PLACING ADDITIONAL STRESS ON THE GREAT POND RESERVOIR SYSTEM OR EXISTING WATER TREATMENT FACILITIES.

EPA HAS SCREENED AND EVALUATED SEVERAL POTENTIAL REPLACEMENT ALTERNATIVES FOR THE BAIRD & MCGUIRE SITE IN THE WATER SUPPLY FOCUSED FEASIBILITY STUDY. THE FFS DESCRIBES ALTERNATIVES FOR REPLACING THE LOST DEMAND, AS WELL AS THE SCREENING CRITERIA USED TO NARROW THE LIST TO FOUR POTENTIAL REMEDIAL ALTERNATIVES. EACH OF THESE ALTERNATIVES IS DESCRIBED BRIEFLY BELOW.

NO ACTION (AW-NA). IN THIS ALTERNATIVE, THE LOST DEMAND WOULD NOT BE REPLACED.

ALTERNATIVE 1 (AW-1): REACTIVATION OF THE DONNA ROAD AQUIFER. IN THIS ALTERNATIVE, THE DONNA ROAD AQUIFER WOULD BE REACTIVATED BY INSTALLING NEW WELLS; WATER WOULD THEN BE BROUGHT TO THE SURFACE USING SUBMERSIBLE PUMPS. THE WATER WOULD THEN BE TREATED IN AN ON-SITE TREATMENT PLANT TO REMOVE IRON AND MANGANESE. TREATED WATER WOULD BE DISINFECTED PRIOR TO BEING PUMPED TO THE EXISTING HOLBROOK WATER DISTRIBUTION SYSTEM.

IN THE PROPOSED PLAN ISSUED PRIOR TO THE PUBLIC COMMENT PERIOD, EPA RECOMMENDED THIS ALTERNATIVE AS ITS PREFERRED REMEDY FOR ADDRESSING THE LOST DEMAND.

ALTERNATIVE 2 (AW-2): INCREASED FARM RIVER DIVERSION. IN THIS ALTERNATIVE, AN ADDITIONAL 0.31 MGD WOULD BE DIVERTED FROM THE FARM RIVER INTO THE RICHARDI RESERVOIR TO REPLACE THE LOST DEMAND. WATER WOULD BE TREATED TO REMOVE IRON AND MANGANESE AND THEN BE DISINFECTED AT THE RANDOLPH-HOLBROOK JOINT WATER TREATMENT PLANT.

ALTERNATIVE 3 (AW-3): COCHATO RIVER DIVERSION. IN THIS ALTERNATIVE, THE DIVERSION OF THE COCHATO RIVER INTO THE RICHARDI RESERVOIR WOULD BE RE-ESTABLISHED TO SUPPLY THE 0.31 MGD LOST DEMAND. WATER WOULD BE TREATED TO REMOVE IRON AND MANGANESE AND THEN BE DISINFECTED AT THE RANDOLPH-HOLBROOK JOINT WATER TREATMENT PLANT.

ADDITIONAL INFORMATION ON EACH OF THE REMEDIAL ALTERNATIVES CAN BE FOUND IN THE FOCUSED FEASIBILITY STUDY FOR THE WATER SUPPLY OPERABLE UNIT, COPIES OF WHICH ARE LOCATED IN THE HOLBROOK PUBLIC LIBRARY AND THE EPA RECORDS CENTER AT 90 CANAL STREET IN BOSTON, MASSACHUSETTS.

## II. BACKGROUND ON COMMUNITY INVOLVEMENT AND CONCERNS

THE BAIRD & MCGUIRE SITE IS LOCATED ON SOUTH STREET IN THE TOWN OF HOLBROOK, MASSACHUSETTS, APPROXIMATELY 14 MILES SOUTH OF BOSTON. FOR OVER 70 YEARS, BAIRD & MCGUIRE, INCORPORATED OPERATED A CHEMICAL MIXING AND BATCHING FACILITY AT THE SITE, FORMULATING HOUSEHOLD AND INDUSTRIAL PRODUCTS SUCH AS FLOOR WAXES, WOOD PRESERVATIVES, PESTICIDES AND SOLVENTS. WIDESPREAD CONTAMINATION BY A VARIETY OF ORGANIC AND INORGANIC CHEMICALS, INCLUDING DIOXIN, EXISTS AT THE SITE.

THE BAIRD & MCGUIRE PROPERTY IS APPROXIMATELY EIGHT ACRES IN SIZE, AND ORIGINALLY CONSISTED OF AN OFFICE BUILDING, STORAGE BUILDING, TANK FARM, LABORATORY BUILDING, AND MIXING BUILDING. THE SITE IS LOCATED NEAR THE WESTERN BANK OF THE COCHATO RIVER, AND IS APPROXIMATELY 1,500 FEET AWAY FROM THE HOLBROOK SOUTH STREET WELL FIELD.

APPROXIMATELY 2.5 MILES DOWNSTREAM OF THE SITE, THE COCHATO RIVER FLOWS PAST THE RICHARDI RESERVOIR, WHICH SERVES AS A SECONDARY SURFACE WATER RESERVOIR FOR THE TOWNS OF HOLBROOK, RANDOLPH, AND BRAINTREE, MASSACHUSETTS. PRIOR TO A BREACH IN THE BAIRD & MCGUIRE CREOSOTE LAGOON IN 1983, WATER FROM THE COCHATO RIVER WAS DIVERTED INTO THE RICHARDI RESERVOIR THROUGH SURFACE WATER INTAKES. THESE INTAKES HAVE BEEN CLOSED SINCE MARCH 1983.

THE BAIRD & MCGUIRE SITE WAS ADDED TO THE NATIONAL PRIORITIES LIST (NPL) IN DECEMBER 1982, MAKING IT ELIGIBLE TO RECEIVE FEDERAL FUNDS FOR

INVESTIGATION AND CLEANUP UNDER THE SUPERFUND PROGRAM. IN 1983, EPA CONDUCTED A REMOVAL ACTION AFTER A WASTE LAGOON OVERFLOWED INTO THE COCHATO RIVER; A SECOND REMOVAL ACTION WAS CONDUCTED IN 1985 WHEN DIOXINS WERE DISCOVERED IN SITE SOILS. FURTHER WORK WAS CONDUCTED AT THE SITE DURING THE 1987 IRM, INCLUDING THE REMOVAL OF CERTAIN SITE BUILDINGS AND PLACEMENT OF A TEMPORARY CAP OVER SITE SOILS TO PREVENT CONTACT WITH CONTAMINANTS. THE TANK FARM AND MIXING BUILDINGS WERE DEMOLISHED BY EPA DURING A 1987 INITIAL REMEDIAL MEASURE (IRM) WHICH WAS CONDUCTED TO ADDRESS ASPECTS OF SITE CONTAMINATION PRIOR TO IMPLEMENTING LONG-TERM REMEDIAL MEASURES.

COMMUNITY CONCERN SURROUNDING CONTAMINATION AT THE BAIRD & MCGUIRE SITE HAS BEEN HIGH SINCE THE EARLY 1980S WHEN DRINKING WATER WELL CONTAMINATION IN THE VICINITY OF THE SITE WAS FIRST DETECTED. REGIONAL MEDIA COVERAGE OF SITE-RELATED ACTIVITIES HAS BEEN EXTENSIVE. COMMUNITY INVOLVEMENT HEIGHTENED IN EARLY 1985 WHEN A NATIONAL ENVIRONMENTAL ORGANIZATION BECAME ACTIVE AT THE SITE, AND OVER 250 LETTERS FROM RESIDENTS EXPRESSING THEIR CONCERNS WERE RECEIVED BY EPA. IN ADDITION, A LOCAL CITIZENS' GROUP, PEOPLE UNITED TO RESTORE THE ENVIRONMENT (PURE), WAS FORMED AT THAT TIME.

FOLLOWING RELEASE OF THE 1985 RI, EPA HELD A PUBLIC MEETING TO PRESENT THE RESULTS OF THE RI ON JUNE 10, 1985. OVER 200 PEOPLE ATTENDED THE MEETING AND PRESENTED A PETITION CONTAINING OVER 1,000 SIGNATURES. PRINCIPAL CONCERNS EXPRESSED IN THE PETITION INCLUDED REQUESTS FOR FENCING OF THE SITE; A COMPREHENSIVE HEALTH STUDY; REMOVAL OF SITE BUILDINGS; DIVERSION OF THE TOWN WATER MAIN PASSING THROUGH THE SITE; TESTING OF COCHATO RIVER WATER QUALITY; A MEETING WITH THE EPA REGIONAL ADMINISTRATOR; AND, CITIZEN INVOLVEMENT IN THE DEVELOPMENT OF SITE CLEANUP PLANS.

EPA PROMISED TO RESPOND TO THESE REQUESTS, AND ALSO INVITED CITIZENS AND OFFICIALS TO ESTABLISH AN INFORMAL CITIZENS ADVISORY COMMITTEE TO WORK WITH THE AGENCY. THIS COMMITTEE, KNOWN AS THE BAIRD & MCGUIRE TASK FORCE, WAS ORGANIZED SOON AFTERWARDS WITH BROAD REPRESENTATION FROM BOTH RESIDENTS AND LOCAL OFFICIALS. EPA HAS MET REGULARLY WITH THE TASK FORCE TO PRESENT NEW SITE INFORMATION AND DISCUSS ISSUES OF CONCERN TO THE COMMUNITY.

PUBLIC INTEREST INCREASED AGAIN IN JULY 1985, WHEN EPA DISCOVERED LOW LEVELS OF DIOXIN IN SITE SOILS. EPA AND THE MASSACHUSETTS DEPARTMENT OF ENVIRONMENTAL PROTECTION (DEP), FORMERLY MASSACHUSETTS DEPARTMENT OF ENVIRONMENTAL QUALITY ENGINEERING, SUBSEQUENTLY HELD A BRIEFING FOR OFFICIALS AND CITIZENS ON THE IMPLICATIONS OF THIS DISCOVERY AND THE STEPS EPA WOULD TAKE TO ADDRESS POTENTIAL RISKS ASSOCIATED WITH THE DISCOVERY OF DIOXIN. THIS BRIEFING AND SUBSEQUENT SITE-RELATED EVENTS RECEIVED EXTENSIVE MEDIA COVERAGE.

IN 1989, EPA HELD A PUBLIC COMMENT PERIOD AND A PUBLIC MEETING ON THE COCHATO RIVER SEDIMENT STUDY AREA FFS AND PROPOSED PLAN. THE MEETING INCLUDED A PRESENTATION BY THE BAIRD & MCGUIRE TASK FORCE.

EPA CONDUCTED A GROUND-BREAKING CEREMONY ON MAY 11, 1990 TO BEGIN CONSTRUCTION OF THE GROUNDWATER TREATMENT PLANT AUTHORIZED IN THE 1986 ROD. THE EVENT WAS ATTENDED BY LOCAL RESIDENTS AND OFFICIALS AND RECEIVED EXTENSIVE MEDIA COVERAGE.

PUBLIC INVOLVEMENT IN THE SUPERFUND PROCESS HAS CONTINUED AT A HIGH LEVEL THROUGHOUT THE RI/FS PROCESS, AND THE TASK FORCE CONTINUES TO MEET ON A REGULAR BASIS WITH EPA. A PUBLIC MEETING HELD IN JUNE 1990 ON THE WATER SUPPLY FOCUSED FEASIBILITY STUDY AND PROPOSED PLAN WAS ATTENDED BY APPROXIMATELY 15 PERSONS INCLUDING REPRESENTATIVES OF THE TOWN OF HOLBROOK AND THE BAIRD & MCGUIRE TASK FORCE. THE PRINCIPAL COMMUNITY CONCERNS EXPRESSED AT THAT TIME ARE AS FOLLOWS:

RESIDENTS AND OFFICIALS EXPRESSED OVERALL SUPPORT FOR DEVELOPMENT OF THE DONNA ROAD AQUIFER, EPA'S PREFERRED ALTERNATIVE, BUT STATED THAT EPA SHOULD CONDUCT EXTENSIVE GROUNDWATER TESTING TO VERIFY THAT NEARBY INDUSTRIAL ACTIVITIES ARE NOT LIKELY TO CONTAMINATE THE DONNA ROAD AQUIFER.

RESIDENTS AND OFFICIALS STATED THEIR CONCERN THAT IMPLEMENTATION OF THE LOST DEMAND REPLACEMENT BE CONDUCTED AS SOON AS POSSIBLE.

MEETING ATTENDEES OVERWHELMINGLY STATED THEIR OPPOSITION TO REACTIVATION OF THE COCHATO RIVER DIVERSION.

## III. SUMMARY OF COMMENTS RECEIVED DURING THE PUBLIC COMMENT PERIOD AND EPA RESPONSES

THIS RESPONSIVENESS SUMMARY ADDRESSES THE COMMENTS RECEIVED BY EPA CONCERNING THE DRAFT FFS AND PROPOSED PLAN FOR THE WATER SUPPLY OPERABLE UNIT FOR THE BAIRD & MCGUIRE SUPERFUND SITE IN HOLBROOK, MASSACHUSETTS. FOUR SETS OF WRITTEN COMMENTS WERE RECEIVED DURING THE PUBLIC COMMENT PERIOD (JUNE 27-JULY 26, 1990). EIGHT ORAL COMMENTS WERE PRESENTED AT THE JULY 17, 1990 INFORMAL PUBLIC HEARING. COMMENTERS INCLUDED REPRESENTATIVES OF THE BAIRD & MCGUIRE TASK FORCE, THE HOLBROOK BOARD OF SELECTMEN, THE HOLBROOK CONSERVATION COMMISSION, AND A RESIDENT. A COPY OF THE TRANSCRIPT IS INCLUDED AS ATTACHMENT B. COPIES FOR THE TRANSCRIPT ARE ALSO AVAILABLE AT THE HOLBROOK PUBLIC LIBRARY, THE INFORMATION REPOSITORY THAT EPA HAS ESTABLISHED FOR THE SITE; AND AT THE EPA RECORDS CENTER AT 90 CANAL STREET, BOSTON, MASSACHUSETTS, AS A PART OF EPA'S ADMINISTRATIVE RECORD.

THE COMMENTS FROM CITIZENS, ALONG WITH EPA RESPONSES, ARE SUMMARIZED AND ORGANIZED INTO THE FOLLOWING CATEGORIES:

A. COMMENTS REGARDING THE DONNA ROAD AQUIFER;
B. COMMENTS REGARDING THE COCHATO RIVER DIVERSION; AND
C. COMMENTS REGARDING PUBLIC HEALTH CONCERNS.

A LIST OF COMMENTERS CAN BE FOUND ON PAGE ? OF THIS DOCUMENT.

### A. COMMENTS REGARDING THE DONNA ROAD AQUIFER

1. FOUR COMMENTERS REQUESTED THAT EPA ADEQUATELY TEST AND CHARACTERIZE GROUNDWATER QUALITY OF THE DONNA ROAD AQUIFER BEFORE CONSTRUCTION OF GROUNDWATER EXTRACTION AND TREATMENT FACILITIES.

EPA'S RESPONSE 1

THE MASSACHUSETTS GUIDELINES AND POLICIES FOR PUBLIC WATER SYSTEMS DOCUMENT DEFINES A DETAILED TESTING AND EVALUATION PROGRAM THAT MUST BE FOLLOWED IN ORDER FOR THE DONNA ROAD AQUIFER TO BE APPROVED AS A PUBLIC WATER SUPPLY. THE GUIDELINES INCLUDE REQUIREMENTS FOR TESTING THE GROUNDWATER FOR THE PRESENCE OF BOTH ORGANIC AND INORGANIC SUBSTANCES. AS IS REQUIRED UNDER CERCLA, EPA MUST COMPLY WITH ALL APPLICABLE LAWS, AND THEREFORE WILL FOLLOW THE MASSACHUSETTS GUIDELINES IN IMPLEMENTING THE REMEDY.

2. TWO COMMENTERS REQUESTED EPA EVALUATE ADDITIONAL DIVERSION OF THE FARM RIVER, IF FURTHER TESTING INDICATES THE DONNA ROAD AQUIFER CAN NOT REPLACE THE ENTIRE 0.31 MILLION GALLONS PER DAY (MGD) LOST DEMAND.

EPA'S RESPONSE 2

EPA BELIEVES THE DONNA ROAD AQUIFER IS CAPABLE OF REPLACING THE 0.31 MGD LOST DEMAND. THIS IS BASED NOT ONLY ON RECENT AQUIFER MODELING, BUT ALSO ON THE FACT THAT THE TOWN OF HOLBROOK HISTORICALLY WITHDREW 0.5 MGD FROM THE FORMERLY USED WELLFIELD. HOWEVER, IF EVALUATIONS CONDUCTED DURING THE SOURCE APPROVAL PROCESS INDICATE THAT THE ENTIRE 0.31 MGD IS NOT AVAILABLE FROM THE DONNA ROAD AQUIFER, EPA MAY SUPPLEMENT THE AQUIFER BY DIVERTING THE INCREMENTAL DIFFERENCE FROM THE FARM RIVER TO THE RICHARDI RESERVOIR. IF HOWEVER, THE PRODUCTION OF GROUND WATER FROM DONNA ROAD IS INSUFFICIENT TO SUPPORT THE BALANCE BETWEEN THE REMEDY SELECTION CRITERIA, EPA MAY REEXAMINE THE REMEDY.

3. ONE COMMENTER REQUESTED EPA OUTLINE A SCHEDULE TO "FAST-TRACK" THE WATER SUPPLY NEW SOURCE APPROVAL PROCESS.

EPA'S RESPONSE 3

EPA'S ESTIMATE OF THE TIME NEEDED TO OBTAIN NEW SOURCE APPROVAL FOR THE DONNA ROAD AQUIFER IS BASED ON THE EXTENSIVE REQUIREMENTS OF THE MASSACHUSETTS REVIEW AND APPROVAL PROCESS. THE SUPERFUND AMENDMENTS AND REAUTHORIZATION ACT (SARA) REQUIRES THAT EPA FOLLOW ALL APPLICABLE REQUIREMENTS SUCH AS THE MASSACHUSETTS REGULATIONS THAT GOVERN PUBLIC WATER SUPPLIES. SINCE THE SOURCE APPROVAL PROCESS IS A STATE AND NOT A FEDERAL PROGRAM, EPA HAS NO CONTROL OVER ITS DURATION OR REQUIREMENTS. EPA WILL HOWEVER, WORK WITH MA DEP IN ORDER TO IMPLEMENT THE ALTERNATIVE IN A TIMELY MANNER.

4. ONE COMMENTER REQUESTED EPA ESTIMATE THE FUTURE COST OF OPERATING THE DONNA ROAD WELLFIELD TO ENABLE THE TOWN OF HOLBROOK TO EVALUATE THE COST AND BENEFITS OF THE PROPOSED ALTERNATIVE.

EPA'S RESPONSE 4

THE WATER SUPPLY FOCUSED FEASIBILITY STUDY DOCUMENT PREPARED BY EPA'S TECHNICAL CONTRACTOR, WHICH WAS AVAILABLE DURING THE PUBLIC COMMENT PERIOD, ESTIMATES THE ANNUAL OPERATION AND MAINTENANCE COSTS TO BE $23,000. COPIES OF THE DOCUMENT ARE AVAILABLE TO TOWN OFFICIALS AND CITIZENS AT THE HOLBROOK PUBLIC LIBRARY.

5. ONE COMMENTER REQUESTED EPA DEFINE A TESTING PROGRAM IN THE RECORD OF DECISION TO MONITOR TREATED WATER QUALITY AFTER CONSTRUCTION AND

START-UP OF THE PROPOSED WATER TREATMENT FACILITY AT DONNA ROAD.

EPA'S RESPONSE 5

THE PROPOSED DONNA ROAD FACILITY WILL BE SUBJECT TO OPERATIONAL TESTING PROGRAMS ALREADY DEFINED IN THE NATIONAL PRIMARY DRINKING WATER REGULATIONS (40 CFR 141, SUBPART C) AS WELL AS IN MASSACHUSETTS DRINKING WATER REGULATIONS (310 CMR 22.00). THESE REGULATIONS DEFINE THE TYPE AND FREQUENCY OF REQUIRED TESTING AT DONNA ROAD. BASED ON THIS COMMENT, EPA HAS ADDED A PROVISION IN THE ROD WHICH REQUIRES FULL TCL ORGANICS, TAL INORGANICS AND PESTICIDES TESTING ANNUALLY.

6. AN AQUIFER PUMP TEST WILL NEED TO BE PERFORMED AT THE DONNA ROAD SITE DURING THE DESIGN PHASE TO COMPLY WITH MASSACHUSETTS DIVISION OF WATER SUPPLY REGULATIONS.

EPA'S RESPONSE

AN AQUIFER PUMP TEST IS PLANNED AS PART OF THE DETAILED EVALUATION TO OBTAIN SOURCE APPROVAL FOR THE DONNA ROAD AQUIFER.

B. COMMENTS REGARDING THE COCHATO RIVER DIVERSION

7. TWO COMMENTERS REQUESTED THAT EPA NOT CONSIDER REACTIVATION OF THE COCHATO RIVER DIVERSION FOR REPLACING THE LOST DEMAND.

EPA'S RESPONSE 7

EPA CHOSE THE REACTIVATION OF THE DONNA ROAD AQUIFER TO REPLACE THE LOST DEMAND RATHER THAN THE COCHATO RIVER DIVERSION BASED ON THE REMEDY SELECTION CRITERIA. DURING EPA'S EVALUATION AND SUBSEQUENT SELECTION OF THE DONNA ROAD ALTERATIVE, EPA CONSIDERED PUBLIC ATTITUDES REGARDING FUTURE USE OF THE COCHATO WHICH EPA HAD HEARD DURING EPA PUBLIC MEETINGS AND BAIRD & MCGUIRE TASK FORCE MEETINGS.

C. COMMENTS REGARDING HEALTH CONCERNS

8. ONE COMMENTER REQUESTED THAT IMPACTS FROM RELEASES OF HAZARDOUS SUBSTANCES AT TWO BUSINESSES LOCATED ON SOUTH FRANKLIN STREET SOUTHEAST OF THE DONNA ROAD SITE SHOULD BE REVIEWED DURING THE EVALUATION PROCESS.

EPA'S RESPONSE 8

THE MASSACHUSETTS DIVISION OF WATER SUPPLY REQUIRES IN THE SOURCE APPROVAL PROCESS THAT PART OF THE EVALUATION OF THE DONNA ROAD AQUIFER INCLUDE DELINEATION OF A ZONE II AQUIFER PROTECTION ZONE. THIS IS THE AREA OF AN AQUIFER THAT CONTRIBUTES WATER TO A WELL UNDER THE MOST SEVERE PUMPING AND RECHARGE CONDITIONS THAT CAN REALISTICALLY BE ANTICIPATED (I.E., 180 DAYS OF PUMPING, WITH NO RECHARGE FROM PRECIPITATION). THE ZONE II DELINEATION WILL EVALUATE ANTICIPATED IMPACTS, IF ANY, FROM THE BUSINESSES ON SOUTH FRANKLIN STREET.

9. ONE COMMENTER ASKED IF THE CONTAMINANT PLUME FROM THE BAIRD & MCGUIRE SUPERFUND SITE MIGHT REACH AND CONTAMINATE THE DONNA ROAD AQUIFER AS

IT DID THE SOUTH STREET WELLS.

EPA'S RESPONSE 9

EPA BELIEVES, BASED ON THE CURRENT UNDERSTANDING OF AREA HYDROGEOLOGY, CONTAMINATION OF THE DONNA ROAD AQUIFER BY THE BAIRD & MCGUIRE SITE IS UNLIKELY. GROUNDWATER FLOW IN THE VICINITY OF DONNA ROAD AND THE BAIRD & MCGUIRE SITE MOVES DOWNGRADIENT IN A GENERAL NORTHERLY DIRECTION. THE DONNA ROAD SITE IS MORE THAN ONE MILE SOUTH OF THE BAIRD & MCGUIRE SUPERFUND SITE, APPROXIMATELY FOUR TIMES FURTHER THAN THE SOUTH STREET WELLS. THE PROPOSED PUMPING RATE OF 0.31 MGD IS NOT CONSIDERED ADEQUATE TO INDUCE THE BAIRD & MCGUIRE CONTAMINANT PLUME INTO THE CAPTURE ZONE OF THE DONNA ROAD WELLFIELD. LAKE HOLBROOK, LOCATED MIDWAY BETWEEN THE DONNA ROAD SITE AND THE BAIRD & MCGUIRE SUPERFUND SITE, SERVES AS A HYDROLOGIC FLOW BOUNDARY AND WOULD HELP PREVENT CONTAMINANT MIGRATION TOWARD DONNA ROAD. THE COMPUTER MODELING AND ZONE II DELINEATION REQUIRED AS PART OF THE NEW SOURCE APPROVAL PROCESS WILL PROVIDE ADDITIONAL INSIGHT INTO THE NORTHERLY FLOW OF GROUNDWATER PAST THE DONNA ROAD SITE.

10. ONE COMMENTER REQUESTED EPA LIMIT MOVEMENT OF LARGE CONSTRUCTION VEHICLES ON NEIGHBORHOOD STREETS DURING THE PERIODS WHEN CHILDREN ARE GOING OUT TO, OR RETURNING FROM SCHOOL.

EPA'S RESPONSE 10

EPA WILL INSTRUCT CONTRACTORS TO EXERCISE EXTRA CAUTION WHENEVER DRIVING ON NEIGHBORHOOD STREETS AND, TO LIMIT TRAFFIC DURING PERIODS WHEN CHILDREN ARE GOING OUT TO, OR RETURNING FROM SCHOOL.

IV. REMAINING CONCERNS

ISSUES RAISED DURING THE PUBLIC COMMENT PERIOD THAT WILL CONTINUE TO BE OF CONCERN AS THE SITE MOVES INTO THE RD/RA PHASE ARE DESCRIBED BRIEFLY BELOW. EPA WILL CONTINUE TO ADDRESS THESE ISSUES AS MORE INFORMATION BECOMES AVAILABLE DURING THE RD/RA.

1. RESIDENTS AND OFFICIALS STRONGLY URGED EPA TO CONDUCT EXTENSIVE GROUNDWATER SAMPLING TO ENSURE THAT CONTAMINATED GROUNDWATER AND POTENTIAL SOURCES OF GROUNDWATER CONTAMINATION ARE NOT LOCATED IN PROXIMITY OF THE DONNA ROAD AQUIFER.

AS INDICATED ABOVE, THE MASSACHUSETTS DIVISION OF WATER SUPPLY REQUIRES IN THE SOURCE APPROVAL PROCESS THAT PART OF THE EVALUATION OF THE DONNA ROAD AQUIFER INCLUDE DELINEATION OF A ZONE II AQUIFER PROTECTION ZONE. THE ZONE II DELINEATION WILL EVALUATE ANTICIPATED IMPACTS, IF ANY, FROM THE POTENTIAL SOURCES WITHIN THAT ZONE. EPA DOES NOT FEEL THAT SAMPLING, IN ADDITION TO THIS, IS NECESSARY TO ASSURE THE INTEGRITY OF THE DONNA ROAD ALTERNATIVE.

ADDITIONALLY, AS IS OUTLINED IN RESPONSE 5 ABOVE, EPA HAS ADDED THE ADDITIONAL PROVISION OF FULL TCL ORGANICS, TAL INORGANICS AND PESTICIDES ANNUALLY TO THE SELECTED REMEDY.

# Manganese (CASRN 7439-96-5)

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Carcinogenicity Assessment for Lifetime Exposure go

**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 First 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

SUBSTANCE SUMMARY INDEX

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- Uncertainty and Modifying Factors
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- Confidence in the Inhalation RfC
- EPA Documentation and Review

Evidence for Human Carcinogenicity
- Weight-of-Evidence Characterization
- Human Carcinogenicity Data
- Animal Carcinogenicity Data
- Supporting Data for Carcinogenicity

Quantitative Estimate

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.

of Carcinogenic Risk from Oral Exposure

- Summary of Risk Estimates
- Dose-Response Data
- Additional Comments
- Discussion of Confidence

Quantitative Estimate of Carcinogenic Risk from Inhalation Exposure

- Summary of Risk Estimates
- Dose-Response Data
- Additional Comments
- Discussion of Confidence

EPA Documentation, Review and, Contacts

### __I.A.1. Oral RfD Summary

| Critical Effect | Experimental Doses* | UF | MF | RfD |
|---|---|---|---|---|
| CNS effects<br><br>Human Chronic Ingestion Data<br><br>NRC, 1989; Freeland-Graves et al., 1987; WHO, 1973; | NOAEL (food): 0.14 mg/kg-day<br><br>LOAEL: None | 1 | 1 | 1.4E-1 mg/kg-day |

*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 (x) and range (r) of neurologic scores were as follows: Area A (males: x=2.4, r=0-21; females: x=3.0, r=0-18; both x=2.7, r=0-21); Area B (males x=1.6, r=0-6; females: x=5.7 r=0-43; both: x=3.9, r=0-43); and Area C (males: x=4.9, r=0-29; females: x=5.5, r=0-21; both x=5.2, r=0-29). The authors indicate that the difference in mean scores for area C versus A was significantly increased (Mann-Whitney z=3.16, p=0.002 for both sexes combined). In a subsequent analysis, logistic regression indicated that there is a significant difference between areas A and C even when both age and sex are taken into account (Kondakis, 1990).

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.

### __I.A.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 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 MnC12.4H2O). 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 MnC12.4H2O/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 MnCl2.4H2O, Mn(Ac)2.4H2O, MnCO3 and MnO2. 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
Database -- 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,

03/31/1993, 12/14/1993, 05/12/1995

Verification Date -- 05/12/1995

### __I.A.7. EPA Contacts (Oral RfD)

Please contact the IRIS Hotline for all questions concerning this assessment or IRIS, in general, at (301)345-2870 (phone), (301)345-2876 (FAX) or Hotline.IRIS@epamail.epa.gov (internet address).

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## _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 |
|---|---|---|---|---|
| Impairment of neuro-behavioral function | NOAEL: NoneLOAEL: 0.15 mg/cu.m | 1000 | 1 | 5E-5 mg/cu.m |
| Occupational exposure to manganese dioxide | LOAEL(ADJ): 0.05 mg/cu.m<br>LOAEL(HEC): 0.05 mg/cu.m | | | |
| Roels et al., 1992 | | | | |
| Impairment of neuro-behavioral function | NOAEL: NoneLOAEL: 0.97 mg/cu.m | | | |
| Occupational exposure to manganese oxides and salts | LOAEL(ADJ): 0.34 mg/cu.m<br>LOAEL(HEC): 0.34 mg/cu.m | | | |
| Roels et al., 1987 | | | | |

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*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 extrarespiratory 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 extrarespiratory 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 um 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 ug/dL) and urinary Mn (MnU) (0.84 ug/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 NOAEL, the LOAEL 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 LOAEL(HEC) of approximately 0.01 mg/cu.m, which is about five-fold lower than the LOAEL(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 Additonal 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 LOAEL(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 LOAEL(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 LOAEL(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 LOAEL(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 LOAEL for derivation of the RfC is 0.15 mg/cu.m, and the LOAEL(HEC) is 0.05 mg/cu.m.

### __I.B.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

### __I.B.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 Additonal 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 um) preferentially deposit in the pulmonary region, and coarse mode particles (>2.5 um) 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 creatine), 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 $MnCl_2$ and manganese acetate [$Mn(CH_3COO)_2$]; however, the corpus striatal binding characteristics of the +4 valence state of Mn in $MnO_2$ were not substantially different from those of the divalent forms in $MnCl_2$, $Mn(CH_3COO)_2$, 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 ($Mn_2O_3$ and $Mn_3O_4$) 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; Emara 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
Database -- 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 IRIS Hotline for all questions concerning this assessment or IRIS, in

general, at (301)345-2870 (phone), (301)345-2876 (FAX) or Hotline.IRIS@epamail.epa.gov (internet address).

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## _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 Human Carcinogenicity

#### __II.A.1. Weight-of-Evidence Characterization

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 of 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.

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## _II.B. Quantitative Estimate of Carcinogenic Risk from Oral Exposure

Not available.

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## _II.C. Quantitative Estimate of Carcinogenic Risk from Inhalation Exposure

Not available.

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## _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. EPA Review (Carcinogenicity Assessment)

Agency Work Group Review -- 05/25/1988

Verification Date -- 05/25/1988

### __II.D.3. EPA Contacts (Carcinogenicity Assessment)

Please contact the IRIS Hotline for all questions concerning this assessment or IRIS, in general, at (301)345-2870 (phone), (301)345-2876 (FAX) or Hotline.IRIS@epamail.epa.gov (internet address).

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## _III. [reserved]
## _IV. [reserved]
## _V. [reserved]

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## _VI. Bibliography

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 |
| 08/01/1995 | I.A., I.A.6. | EPA's RfD/RfC and CRAVE workgroups were discontinued in May, 1995. Chemical substance reviews that were not completed by September 1995 were taken out of IRIS review. The IRIS Pilot Program replaced the workgroup functions beginning in September, 1995. |
| 11/01/1995 | I.A. | Oral RfD assessment replaced |

| | | |
|---|---|---|
| 11/01/1995 | VI.A. | Oral RfD assessment replaced |
| 05/01/1996 | I.A.7. | Secondary contact's phone number changed |
| 12/01/1996 | II.D.3. | Primary contact removed |
| 04/01/1997 | III., IV., V. | Drinking Water Health Advisories, EPA Regulatory Actions, and Supplementary Data were removed from IRIS on or before April 1997. IRIS users were directed to the appropriate EPA Program Offices for this information. |

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## _VIII. Synonyms

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

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

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