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Washington DC 20460

Office of Research and Development
Office of Health and Environmental
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Environmental Criteria and
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Cincinnati OH 45268

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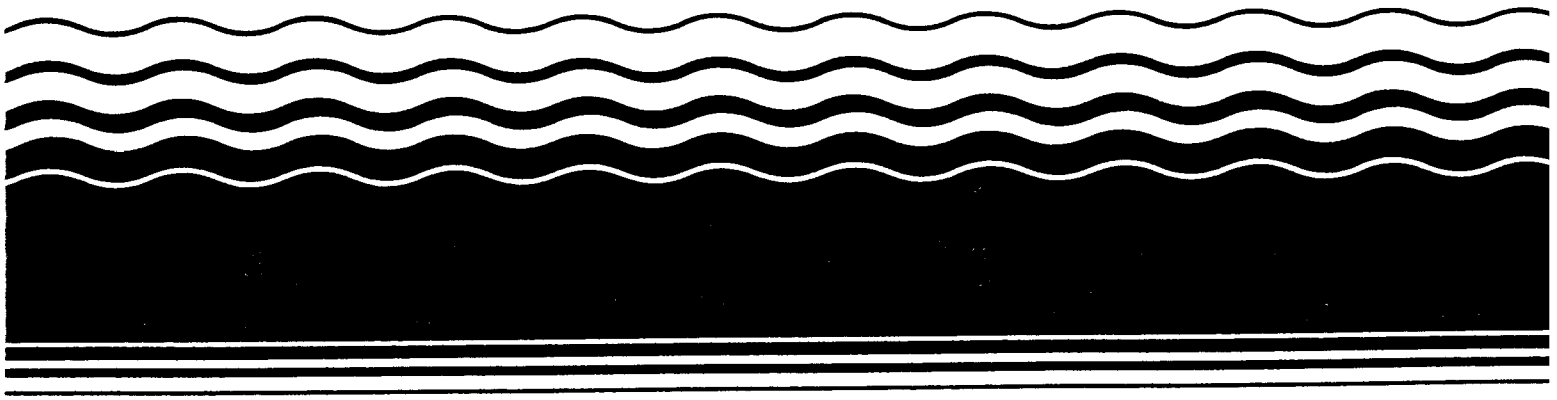
HEALTH EFFECTS ASSESSMENT FOR MANGANESE (AND COMPOUNDS)



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U.S. Environmental Protection Agency
Office of Research and Development
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Office of Solid Waste and Emergency Response
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DISCLAIMER

This report has been funded wholly or in part by the United States Environmental Protection Agency under Contract No. 68-03-3112 to Syracuse Research Corporation. It has been subject to the Agency's peer and administrative review, and it has been approved for publication as an EPA document. Mention of trade names or commercial products does not constitute endorsement or recommendation for use.

PREFACE

This report summarizes and evaluates information relevant to a preliminary interim assessment of adverse health effects associated with manganese (and compounds). All estimates of acceptable intakes and carcinogenic potency presented in this document should be considered as preliminary and reflect limited resources allocated to this project. Pertinent toxicologic and environmental data were located through on-line literature searches of the Chemical Abstracts, TOXLINE, CANCERLINE and the CHEMFATE/DATALOG data bases. The basic literature searched supporting this document is current up to September, 1984. Secondary sources of information have also been relied upon in the preparation of this report and represent large-scale health assessment efforts that entail extensive peer and Agency review. The following Office of Health and Environmental Assessment (OHEA) sources have been extensively utilized:

U.S. EPA. 1981. Multimedia Criteria for Manganese and Compounds. Environmental Criteria and Assessment Office, Cincinnati, OH. Internal draft.

U.S. EPA. 1982a. Health Assessment Document for Manganese. Environmental Criteria and Assessment Office, Cincinnati, OH. External review draft. EPA 600/8-83-013A. NTIS PB83-217786.

U.S. EPA. 1984. Health Assessment Document for Manganese. Final Report. Environmental Criteria Assessment Office, Cincinnati, OH. EPA-600/8-83-013F. NTIS PB 84-229954

The intent in these assessments is to suggest acceptable exposure levels whenever sufficient data were available. Values were not derived or larger uncertainty factors were employed when the variable data were limited in scope tending to generate conservative (i.e., protective) estimates. Nevertheless, the interim values presented reflect the relative degree of hazard associated with exposure or risk to the chemical(s) addressed.

Whenever possible, two categories of values have been estimated for systemic toxicants (toxicants for which cancer is not the endpoint of concern). The first, the AIS or acceptable intake subchronic, is an estimate of an exposure level that would not be expected to cause adverse effects when exposure occurs during a limited time interval (i.e., for an interval that does not constitute a significant portion of the lifespan). This type of exposure estimate has not been extensively used or rigorously defined, as previous risk assessment efforts have been primarily directed towards exposures from toxicants in ambient air or water where lifetime exposure is assumed. Animal data used for AIS estimates generally include exposures with durations of 30-90 days. Subchronic human data are rarely available. Reported exposures are usually from chronic occupational exposure situations or from reports of acute accidental exposure.

The AIC, acceptable intake chronic, is similar in concept to the ADI (acceptable daily intake). It is an estimate of an exposure level that would not be expected to cause adverse effects when exposure occurs for a significant portion of the lifespan [see U.S. EPA (1980) for a discussion of this concept]. The AIC is route specific and estimates acceptable exposure for a given route with the implicit assumption that exposure by other routes is insignificant.

Composite scores (CSs) for noncarcinogens have also been calculated where data permitted. These values are used for ranking reportable quantities; the methodology for their development is explained in U.S. EPA (1983).

For compounds for which there is sufficient evidence of carcinogenicity, AIS and AIC values are not derived. For a discussion of risk assessment methodology for carcinogens refer to U.S. EPA (1980). Since cancer is a process that is not characterized by a threshold, <u>any</u> exposure contributes an increment of risk. Consequently, derivation of AIS and AIC values would be inappropriate. For carcinogens, q_1^*s have been computed based on oral and inhalation data if available.

ABSTRACT

In order to place the risk assessment evaluation in proper context, refer to the preface of this document. The preface outlines limitations applicable to all documents of this series as well as the appropriate interpretation and use of the quantitative estimates presented.

Data concerning the toxicological consequences of oral exposure to manganese are limited to subchronic evaluations in rodents. An oral AIS (36.8 mg/day) was estimated based on a subchronic rat study that showed effects on serum testosterone levels. An oral AIC of 15.4 mg/day was estimated from a 2-year study in rats in which slightly altered brain biochemistries were observed.

More extensive information is available concerning inhalation effects of manganese. An inhalation AIC of 21 μg/day was calculated based on the determination that occupational exposure to 300 $\mu g/m^3$ is the lowest level associated with mild signs of manganism. Because manganism can occur after a relatively short exposure period, 21 μg/day was also adopted as the inhalation AIS for manganese. A CS of 37.6 was calculated for the obvious neurotoxic signs of manganism noted in workers at 500 $\mu g/m^3$.

ACKNOWLEDGEMENTS

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LIST OF ABBREVIATIONS

ADI	Acceptable daily intake
AIC	Acceptable intake chronic
AIS	Acceptable intake subchronic
BCF	Bioconcentration factor
bw	Body weight
CAS	Chemical Abstract Service
CNS	Central nervous system
CS	Composite score
EMG	Electromyogram
GI	Gastrointestinal
LOAEL	Lowest-observed-adverse-effect level
MED	Minimum effective dose
MTD	Maximum tolerated dose
NOAEL	No-observed-adverse-effect level
ppm	Parts per million
RBC	Red blood cells
RV_d	Dose-rating value
RV_e	Effect-rating value
SGOT	Serum glutamic oxalacetic transaminase
SGPT	Serum glutamic pyruvic transaminase
STEL	Short-term exposure limit
TLV	Threshold limit value
TWA	Time-weighted average

1. ENVIRONMENTAL CHEMISTRY AND FATE

Manganese is a metal belonging to the first Transition Series of the periodic table. Elemental manganese has a CAS Registry number of 7439-96-5. Although manganese can exist in all the valence states from -3 to +7 (Cotton and Wilkinson, 1980), the inorganic chemistry of manganese is dominated by compounds in the +2, +4 and +7 valence states. The primary examples of manganese in the 0 valence state are metal and alloys and the carboxy compound. Selected physical properties of a few environmentally significant manganese compounds are given in Table 1-1.

The principal sources of manganese in the atmosphere are natural processes including continental dust, volcanic gas and dust, and forest fires. The atmospheric flux of manganese due to burning of forests and wood fuel may exceed the combined flux due to other natural and anthropogenic sources. The main anthropogenic sources of manganese are industrial emissions and combustion of fossil fuels (Lantzy and MacKenzie, 1979). In the atmosphere, manganese is expected to be present in particulate form (U.S. EPA, 1982a). The two main mechanisms that may determine the fate of atmospheric manganese are tropospheric chemical reactions and physical removal processes. Atmospheric manganese may undergo photochemical and thermal reaction (U.S. EPA, 1982a). Thus, manganese dioxide may react with SO_2 or NO_2 in the atmosphere, forming $MnSO_4$ and $Mn(NO_3)_2$, respectively. Although such reactions may change the chemical nature of manganese, these reactions may not be directly responsible for the removal of manganese from the atmosphere. Manganese aerosol may be removed from the air through dry fallout or wet precipitation. It has been estimated that the atmospheric residence time

TABLE 1-1

Selected Physical Properties of a Few Manganese Compounds[a]

Element/ Compound	Formula	Molecular Weight	Specific Gravity/ Density	Water Solubility	Vapor Pressure
Manganese	Mn	54.938	7.20	decomposes	1 mm at 1292°C
Manganese (II) chloride	$MnCl_2$	125.84	2.977^{25}_{4}	72.3 g/100 mℓ at 25°C	10 mm at 778°C
Manganese (II) carbonate	$MnCO_3$	114.95	3.125	6.5 mg/100 mℓ at 25°C	NA
Manganese (II) sulfate	$MnSO_4$	151.00	3.25	52 g/100 mℓ at 5°C	NA
Manganese (II) oxide	MnO	70.94	5.43-5.46	insoluble[b]	NA
Manganese (IV) dioxide	MnO_2	86.94	5.026	insoluble[b]	NA
Potassium permanganate	$KMnO_4$	158.04	2.703	6.38 g/100 mℓ at 20°C	NA

[a]Source: Weast, 1980

[b]No further data regarding solubility are available from Weast, 1980.

NA = Not available

for manganese due to such physical removal processes is ~7 days (Cupitt, 1980).

The fate of manganese in aquatic systems may be determined by its ability to undergo chemical and microbiological reactions. In most natural aquatic systems, manganese is expected to be present predominantly in the suspended particulates and sediments as MnO_2 and Mn_3O_4 or both. A small amount of manganese may remain as soluble Mn\\². The maximum concentration of soluble Mn\\² may be limited by the solubility product of $MnCO_3$ and, under certain reducing conditions, by the MnS solubility product. The concentration of soluble chelated manganese in aquatic systems is likely to be less than soluble free manganese ions (U.S. EPA, 1982a). Thus, although manganese may undergo speciation through chemical and microbiological reactions in systems, it may persist in aquatic systems for a long period. By analogy with aquatic iron (U.S. EPA, 1981), the residence time of aquatic manganese may be a few hundred years.

The BCF for manganese in a species of edible fish (striped bass) has been reported to be <10 (U.S EPA, 1982a). Also, significant bioaccumulation of manganese may not occur with organisms of higher tropic level.

Both chemical and microbiological interactions may cause speciation of manganese in soils; soil pH and oxidation-reduction potential of soil may influence the speciation process. It has been suggested that in acid water-logged soils, manganese passes freely into solution and may leach into groundwater. Also, manganese can be leached readily from waste burial sites and from other natural soils into groundwater (U.S. EPA, 1982a).

2. ABSORPTION FACTORS IN HUMANS AND EXPERIMENTAL ANIMALS

2.1. ORAL

As is true of other nutritionally required trace elements, GI absorption of manganese is controlled by homeostatic mechanisms; extent of absorption is dependent upon availability, concentration in the diet, interactions with other metals or other dietary constituents, and age (U.S. EPA, 1982a). Manganese is probably absorbed as the Mn^{++} cation.

Limited quantitative data indicated that under normal conditions GI absorption of manganese is low, averaging ~3% of the ingested manganese. Early studies by Greenberg et al. (1943) with radiomanganese indicated absorption of 3-4% of the orally administered dose in rats. More recently, Pollack et al. (1965) reported absorption of 2.5-3.5% of $^{54}MnCl_2$ given orally to rats.

In 11 healthy human subjects, Mena et al. (1969) determined absorption of ~3±0.5% by combining 100 μCi of $^{54}MnCl_2$ with 200 μg manganese dichloride ($^{55}MnCl_2$) as a carrier. Whole body counts were performed daily for 2 weeks. In additional studies, 6 healthy manganese miners retained 3%, six former manganese miners with chronic manganese poisoning retained 4%, and 13 anemic subjects (type of anemia not specified) retained 7.5% of the radioactivity of $^{54}MnCl_2$ administered orally (Mena et al., 1969). These studies did not consider the possibility of enterohepatic recirculation or GI excretion of manganese.

In rats, Cikrt (1973) reported that enterohepatic circulation appeared to be important. Duodenal uptake of manganese that had been excreted into the bile was ~35%, whereas only 15% of an equivalent dose of manganese dichloride administered intraduodenally was absorbed. Cikrt (1973) concluded that manganese subjected to hepatic metabolism and bile excretion was present in a form more readily absorbed than manganese dichloride.

It is well documented that manganese and iron compete for GI absorption. Several studies have shown that manganese uptake from the gut is increased in iron-deficient humans (Mena et al., 1969; Thomson et al., 1971) and rats (Pollack et al., 1965; Diez-Ewald et al., 1968). Addition of dietary iron decreased manganese uptake from the gut in both humans and rats (Thomson et al., 1971; Thomson and Valberg, 1972) and resulted in decreased whole body retention of manganese (Kostial et al., 1980). Addition of manganese to the diets of iron-deficient animals (Leach and Lilburn, 1978) or addition of excessive manganese to the diets of normal animals (species not specified) (U.S. EPA, 1982a) resulted in depressed blood hemoglobin concentrations, which were reversed by dietary supplementation with iron. In humans, Mena et al. (1969) showed that intestinal absorption of manganese was closely associated with absorption of iron; anemic subjects had a 2-fold greater retention of manganese than did normal subjects.

Thomson and Valberg (1972) and Thomson et al. (1971) found that manganese competes with iron and cobalt for binding sites in the process of uptake from the lumen into the mucosal cells of the intestine and in the process of transfer across the mucosal cells into the circulation. In humans and rats, these investigators have shown that manganese absorption is by diffusion when high levels of iron are present and by active transport when iron levels are normal or low. They also determined that the binding sites for uptake from the lumen of the bowel are different from the binding sites for transfer to the circulation, since changes in uptake occurred without concomitant changes in transfer to the body. Gruden (1977a,b, 1979) suggested that transmucosal transport of manganese was influenced by iron more than was intestinal uptake. Cikrt and Vastal (1969) showed that transport took place primarily across the mucosa of the duodenum and ileum.

Other elements (cadmium, nickel) have been shown to enhance retention of manganese in laboratory animals (Lassiter et al., 1969, 1970; Burch et al., 1975; Schroeder et al., 1974; Schroeder and Nason, 1976).

Age appears to be inversely related to manganese absorption and retention. Mena et al. (1974) reported that intestinal absorption in infant and young rats was ~4-fold greater than absorption in adult animals. Rabar (1976) and Kostial et al. (1978) observed much higher manganese absorption in artificially fed suckling rats (~40%) than in adult animals (<4%). Adult rats fed a milk diet absorbed more manganese (6.4%) than those on a "normal" diet (0.05%), indicating that both age and diet affected the degree of manganese absorption and retention.

2.2. INHALATION

Following inhalation exposure, manganese absorption into the bloodstream occurs only if particles are sufficiently small to be able to reach the alveoli (WHO, 1980). Larger particles are removed by mucociliary clearance. Water solubility of individual manganese compounds greatly influences the degree of absorption from the pulmonary alveoli.

Mena et al. (1969) exposed 21 human volunteers to nebulized solutions or suspensions of ^{54}Mn-labeled manganese chloride or manganese oxide (concentration and duration of exposure not specified). About 40-70% of the manganese deposited in the lungs was recovered in the feces within 4 days, indicating relatively little pulmonary absorption of manganese (U.S. EPA, 1982a). Quantitative studies of manganese absorption following inhalation exposure in animals could not be located in the available literature.

3. TOXICITY IN HUMANS AND EXPERIMENTAL ANIMALS

3.1. SUBCHRONIC

3.1.1. Oral. In a discussion reviewing the acute toxicity of manganese and its compounds, the U.S. EPA (1982a) indicated that toxicity associated with oral exposure was likely to be less than toxicity associated with parenteral routes of administration. Toxicity also varied with the chemical form; manganese cations are more toxic than the anionic form and the bivalent cation appears to be ~3 times more toxic than the trivalent cation (U.S. EPA, 1975). Relatively water-insoluble compounds (manganese oxide) tend to be less toxic than more water-soluble compounds (Holbrook et al., 1975). From acute toxicity data, the U.S. EPA (1982a) concluded that rats are more sensitive to manganese and its compounds than are mice or guinea pigs. Finally, it appears that pretreatment with small amounts of metal can induce tolerance to higher, even lethal, doses (Yoshikawa, 1974), perhaps by induction of the synthesis of proteins involved in the metabolism of the metal (Jones et al., 1979).

Pertinent data regarding the toxicity to humans of subchronic oral exposure to manganese or its compounds could not be located in the available literature. Subchronic oral exposure of animals has not been well studied.

One of the two common syndromes associated with chronic inhalation exposure in humans involves the CNS. Most of the subchronic oral studies in animals were designed to investigate the effects of manganese on CNS function. These studies are summarized in Table 3-1. To investigate this syndrome in animals, Wassermann and Wassermann (1977) exposed rats to manganese at 2000 ppm in the diet for 10 weeks. Treatment did not result in signs of extrapyramidal neurologic disease. Kimura et al. (1978) found that feeding 2000 ppm manganese chloride (564 ppm manganese) for 3 weeks resulted in a

TABLE 3-1

Subchronic Oral Studies with Manganese

Species	Compound	Exposure	Dose of Mn: mg/kg/day	Effects	Reference
Rat	manganese chloride	2000 ppm Mn in diet for 10 weeks	100[a]	no evidence of extrapyramidal disease	Wassermann and Wassermann, 1977
Rat	$MnCl_2$	2000 ppm (564 ppm Mn) in diet for 3 weeks	28.2[a]	slight decrease in brain serotonin, increased circulating serotonin, decreased blood pressure	Kimura et al., 1978
Rat	Mn_3O_4	50, 400, 1100 or 3550 ppm Mn in diet through gestation and 224 days of age	2.25, 18, 50 or 160	no signs of extrapyramidal neurologic disease	Carter et al., 1980; Rehnberg et al., 1980, 1981, 1982; Laskey et al., 1982
Mouse	Mn_3O_4	1050 ppm Mn in diet from day 15 of gestation until male offspring reached 90 days of age	136.5[a]	reduced fresh organ weights of testes and secondary sex glands	Gray and Laskey, 1980
Rat	Mn_3O_4	0, 350, 1050 or 3500 ppm Mn in diet from day 1 of gestation to offspring age of 224 days	17.5, 52.5 or 175[a]	testes weight in males unaffected; serum testosterone decreased at 1050 ppm level; male reproductive performance unaffected; fertility in 3500 ppm females depressed	Laskey et al., 1982
Rat	$MnCl_2$	200 ppm in drinking water for 10 weeks	20[b]	proliferated endoplasmic reticulum, prominent Golgi, multiple rough endoplasmic cisternae in liver	Wassermann and Wassermann, 1977
Rat	$MnCl_2$	5000 ppm (2180 ppm Mn) in drinking water for 7 months	306	no signs of extrapyramidal disease, moderate pyknosis of neurons in caudate nucleus, decreased brain levels of dopamine and homovanillic acid	Bonilla and Diez-Ewald, 1974
Rat	$MnCl_2$	10,000 ppm (4360 ppm Mn) in drinking water for 2 months	~600	increased concentration of γ-aminobutyric acid in the brain	Bonilla, 1978a,b
Rat	$MnCl_2$	0.01 or 5.0 mg Mn^{2+}/ml in drinking water for 8 months	0, 10 or 500[b]	spontaneous motor activity; significantly increased in 1st month, decreased in 7th and 8th months; effect not dose-related	Bonilla, 1984

TABLE 3-1 (cont.)

Species	Compound	Exposure	Dose of Mn: mg/kg/day	Effects	Reference
Rat	$MnCl_2$	0.01 mg/mℓ in drinking water for 12 months	0.44[c]	ultrastructural alteration of post-synapse and neuronal soma and neuronal atrophy; decreased brain dopamine content	Nakashima, 1983
Rat	$MnCl_2 \cdot 4H_2O$	0, 1, 10 or 20 mg/mℓ in drinking water from conception up to 120 days of age	0, 22, 220 or 440[d]	rate of body weight gain: markedly depressed in 20 mg/mℓ rats; these rats not used in other studies; no effect on 1 or 10 mg/mℓ rats organ weights: unaffected at 1 or 10 mg/mℓ at 60 days organ protein content: unaffected at 1 or 10 mg/mℓ at 60 days monoamine oxidase activity in various organs: unaffected at 1 or 10 mg/mℓ at 60 days behavioral response to amphetamine administration: greatly ($p<0.05$) reduced in 1 mg/mℓ rats at 80 days of age (only level tested) synaptosomal uptake of amines: significantly ($p<0.005$) increased uptake of dopamine (but not of several other neurotransmitter amines) in 10 mg/mℓ rats (only level tested) at 80 days of age; temporary decrease in dopamine uptake in 1 mg/mℓ rate at 70-90 days but not 100-120 days of age (only level tested)	Leung et al., 1982a,b; Lai et al., 1982 a,b

[a]Calculated by applying the assumption that rats eat food equivalent to 5% of their body weight/ day or mice eat food equivalent to 13% of their body weight/day; concentration of Mn provided by investigator

[b]Calculated by applying the assumption that rats weigh 0.35 kg and drink 35 mℓ of water daily; concentration of Mn provided by investigator

[c]Calculated as b above, corrected for Mn as 44% of $MnCl_2$

[d]Calculated as b above, corrected for Mn as 22% of $MnCl_2 \cdot 4H_2O$

slight decrease in brain serotonin in rats. Exposure of rats to 5000 ppm manganese chloride in drinking water (2180 ppm manganese) for 7 months failed to trigger signs of extrapyramidal disease, but did result in moderate pyknosis of some neurons in the caudate nucleus and significantly decreased brain concentrations of dopamine and homovanillic acid (Bonilla and Diez-Ewald, 1974).

High levels of manganese have been associated with depressed reproductive performance in both male and female animals. Gray and Laskey (1980) exposed mice to a casein-based diet containing 1050 ppm manganese as Mn_3O_4 from day 15 of pregnancy. Male offspring were maintained on the same diet from birth until 90 days of age when they were killed and examined; interim kills were also conducted. Wet weights of preputial glands, seminal vesicles and testicles measured at 58, 73 and 90 days after birth were lower in exposed animals than in control animals. In a follow-up study to evaluate the effects of exposure to Mn_3O_4 and concurrent iron deficiency on reproductive development, groups of Long-Evans rats were exposed to 0, 350, 1050 or 3500 ppm manganese added to a normal or an iron-deficient diet (Laskey et al., 1982). Exposure was initiated on day 1 of gestation and continued through offspring age of 224 days. Testes weights were unaffected at all dose levels. A decrease in serum testosterone was noted in males exposed to 1050 ppm, but no interference with reproductive performance was noted. Fertility in females exposed to 3500 ppm was depressed as measured by the percent of rats pregnant after mating.

Excessive intake of manganese was suspected as a cause of depressed hemoglobin levels associated with chronic manganese poisoning in humans. Matrone et al. (1959) found that 2000 ppm manganese depressed hemoglobin formation in both rabbits and piglets. Hartman et al. (1955) found that

2010 ppm manganese in the diet of lambs interfered with hemoglobin regeneration. Carter et al. (1980) exposed groups of Long-Evans rats to diets containing 50 (normal dietary level), 400, 1100 or 3550 ppm manganese. At each dietary level of manganese some rats were maintained on a normal iron and some on an iron-deficient diet. Exposure was during the prenatal and postnatal periods. Among the normal iron-fed groups, no effects on erythrocyte count, mean cell volume or hematocrit were associated with manganese. At 1100 ppm manganese, statistical analysis revealed a significant decrease in serum creatinine and increases in serum calcium and phosphorus. Rats aged 24-100 days developed a microcytic anemia on the low-iron diets, which was exacerbated by higher levels of manganese.

Manganese has been associated with decreased blood pressure related to elevated blood levels of serotonin released from different tissues. Kimura et al. (1978) determined that dietary exposure to 564 ppm manganese produced a significant increase in circulating serotonin and a concomitant decrease in blood pressure. Details of protocol were not reported.

Wassermann and Wassermann (1977) gave rats drinking water with an extra dose of 200 ppm manganese chloride to study ultrastructural changes in the liver associated with exposure to levels of manganese known to be nontoxic. Details of protocol were not reported. These authors interpreted the finding of proliferated smooth and rough endoplasmic reticulum, prominent Golgi apparatus and the occurrence of multiple rough endoplasmic cisternae as an adaptive process to increased exposure to manganese chloride. Only hemosiderosis in the Kupfer cells was noted in monkeys given 345 mg manganese/kg bw (duration of exposure unspecified) (Pentschew et al., 1963).

Leung et al. (1982a,b) and Lai et al. (1982a,b) exposed rats from conception up to 120 days of age to drinking water containing 0, 1, 10 or 20

mg/mℓ of manganese chloride ($MnCl_2 \cdot 4H_2O$). Effects on rate of body weight gain, organ weights and protein content, enzyme activities, synaptosomal uptake of neurotransmitter amines and behavioral response to amphetamine administration were measured. Growth rate was markedly depressed only in the 20 mg/mℓ group; hence, other parameters were evaluated only at the 1 and 10 mg/mℓ level. The behavioral response to amphetamine was altered in rats at 1 mg/mℓ, and significant but transient alterations in synaptosomal neurotransmitter uptake were noted at both the 1 and 10 mg/mℓ levels.

In a Japanese study available only as an English abstract, rats exposed to drinking water containing 10 mg $MnCl_2 \cdot 4H_2O$/mℓ for 12 months had neuronal atrophy and ultrastructural alteration of the postsynapse and neuronal soma (Nakashima, 1983). In another experiment, it appeared that spontaneous motor activity was altered in rats exposed to drinking water that provided 0.1 or 5.0 mg Mn^{2+}/mℓ for 8 months (Bonilla, 1984). Spontaneous activity of the treated rats was increased during the first month but decreased during the 7th and 8th months of treatment.

3.1.2. Inhalation. Although symptoms of chronic manganese poisoning in humans can appear within 4-5 months after exposure to very high occupational exposures (62.5-250 mg/m³) (Ansola et al., 1944a,b), manganese toxicity is most likely to be observed after prolonged exposure. Because inhalation exposure to manganese is likely to be occupational, repeated inhalation exposure of humans to manganese will be discussed in Section 3.2.2. Symptoms of extrapyramidal disease are a major manifestation of chronic manganese toxicity in man. Small laboratory rodents such as mice, rats and guinea pigs do not manifest neurological syndromes typical of those in man (Hambidge and Lassiter, 1973; Cotzias et al., 1964).

Several inhalation studies using manganese compounds have been performed in laboratory animals primarily to investigate the effects on the lungs. These studies are summarized in Table 3-2.

The study by Ulrich et al. (1979a,b,c) investigated the toxicity of Mn_3O_4 in rats and monkeys exposed to manganese at levels of 0.0116, 0.1125 or 1.152 mg/m³ continuously for 9 months. Several parameters of toxicity (clinical observations, hematology, clinical blood chemistries, pulmonary function, electromyograms, limb tremor, histopathology and tissue manganese data) were evaluated in this extensive investigation. Each treatment group consisted of 15 male and 15 female Spraque-Dawley rats and 4 male and 4 female squirrel monkeys. Body weight gains were accelerated in rats of either sex exposed to 1.152 mg/m³. Hemoglobin concentrations and RBC were slightly elevated in both rats and monkeys of either sex exposed to 1.152 mg/m³. It was unclear if the slightly elevated hemoglobin concentrations and RBC were related to exposure to Mn_3O_4 or the low background level of carbon monoxide which resulted from the combination method used to generate Mn_3O_4. Among blood chemistries, only a slight ($p<0.05$) depression in serum phosphorus in high dose group male rats was associated with exposure to Mn_3O_4. Organ weights were comparable among all groups of monkeys and rats. Histopathological evaluations failed to reveal adverse effects related to Mn_3O_4 exposure. In particular, special staining of the brain failed to reveal any alterations or degenerative changes.

Pulmonary function tests (dynamic compliance, pulmonary flow resistance, respiratory rate, tidal volume and number of breaths required to reduce expired air from 80% nitrogen to 1% nitrogen while breathing pure oxygen) were performed on all monkeys at time 0 (pre-exposure), 1, 3, 6 and 9 months of exposure, and on one-half of the monkeys (not killed for histological

TABLE 3-2

Effects of Subchronic Inhalation Exposure to Compounds of Manganese

Species	Compound	Concentration of Manganese	Exposure	TWA Dose* (mg/kg/day)	Effects	Reference
Rabbit	MnO_2	10-20 mg/m³	4 hours/day, 3 months	2.6-5.3	No pathological changes in lungs	Ehrishmann, 1935
Cat	MnO_2	10-20 mg/m³	21 hours/day, 15 months	3.3-6.7	No pathological changes in lungs	Ehrishmann, 1935
Cat	MnO_2	10-20 mg/m³, then 150 mg/m³	21 hours/day, 15 months 4 hours/day for additional 15 months	6.4-8.1	No pathological changes in lungs	Ehrishmann, 1935
Guinea pig	ferromanganese	2350 mg/m³	8 hours/day, 6 months	419.0	No pathological changes in lungs	Heine, 1943
Guinea pig	ferromanganese	2350 mg/m³	8 hours/day, 7.5 months	419.0	Ferromanganese had no effect on mortality induced by challenge with pneumococci.	Heine, 1943
Rat	MnO_2	50 mg, intratracheal	single dose	142.9	Most animals had normal pulmonary histology; some had nodules of dust, macrophages and thin reticular fiber.	Singh et al., 1977
Mice	MnO_2	3 mg/m³	22 hours/day, 2 weeks	4.6	Inflammatory changes, generally reversible after 2 months, at which time desquamation of bronchial epithelium was observed.	Nishiyama et al., 1975
Mice	MnO_2	0.7 mg/m³	22 hours/day, 2 weeks	1.1	Same as above	Nishiyama et al., 1975
Rat	Mn_3O_4	0.0116, 0.1125 or 1.152 mg/m³	continuous for 9 months	0.008, 0.084 or 0.9	No treatment-related effects on pulmonary function, hematology, EMG, clinical chemistry, histology or CNS function. Elevated tissue levels of Mn.	Ulrich et al., 1979a,b,c
Monkey	Mn_3O_4	0.0116, 0.1125 or 1.152 mg/m³	continuous for 9 months	0.004, 0.045 or or 0.461	No treatment-related effects on pulmonary function, hematology, EMG, clinical chemistry, histology or CNS function. Elevated tissue levels of Mn.	Ulrich et al., 1979a,b,c

TABLE 3-2 (cont.)

Species	Compound	Concentration	Exposure	TWA Dose[a] (mg/kg/day)	Effects	Reference
Monkey	Mn_3O_4	0.072 mg/m³	continuous for 12 months	0.03	No behavioral or other visual manifestations of toxicity.	Coulston and Griffin, 1977
Monkey	Mn_3O_4	0.36 mg/m³	continuous for 23 weeks	1.4	No signs of toxicity during treatment or a 10-month post-treatment observation period. Examination of tissues revealed no treatment-related changes.	Coulston and Griffin, 1977
Monkey	MnO_2	3 mg/m³	22 hours/day, 5 months	1.1	Pulmonary congestion	Nishiyama et al., 1975
Monkey	MnO_2	0.7 mg/m³	22 hours/day, 5 months	0.3	Less severe pulmonary congestion appeared later.	Nishiyama et al., 1975
Monkey	MnO_2	3 mg/m³	22 hours/day, 10 months	1.1	Elevated serum SGOT, SGPT, MAO, Ca, Mg; elevated Mn in brain, lungs, hide, bile and kidneys. 2/3 showed mild tremors of fingers and decreased pinch force; reduced dexterity in movement of upper limbs.	Nishiyama et al., 1977
Monkey	MnO_2	0.7 mg/m³	22 hours/day, 10 months	0.3	Same as above, except no neurologic signs. Clinical chemistries and tissue levels of Mn were only mildly affected.	Nishiyama et al., 1977

*TWA dose of manganese calculated from the following data: rabbit body weight 1.13 kg, inhalation rate 1.6 m³/day; cat body weight 3.3 kg, inhalation rate 1.26 m³/day; guinea pig body weight 0.43 kg, inhalation rate 0.23 m³/day; rat body weight 0.35 kg, inhalation rate 0.26 m³/day; mouse body weight 0.03 kg, inhalation rate 0.05 m³/day; monkey body weight 3.5 kg, inhalation rate 1.4 m³/day.

examination after 9 months of exposure) after an additional 6-month recovery period. Although low-dose group males had a significantly increased tidal volume and mid- and high-dose group males had significantly increased airway resistance, Ulrich et al. (1979c) stated that "taken as a whole, the data did not indicate any adverse effects [that] could be attributed to the Mn aerosol exposure."

A total of 112 EMG and limb tremor oscillograph records were evaluated. Of these, 14 were considered to demonstrate possible abnormalities. The distribution of these possibly abnormal records among pre-exposure animals and control as well as treatment groups led Ulrich et al. (1979c) to conclude that there was "no indication of any exposure-related effect on electromyograms or limb tremor."

Tissue levels of manganese reflected exposure to Mn_3O_4. Rats showed increased ($p<0.05$) levels of manganese in kidneys, lungs (mid- and high-dose groups) and blood (high-dose groups). Monkeys had elevated ($p<0.05$) levels of manganese in the kidneys (mid- and high-dose groups), lung (low- and mid-dose groups), spleen and blood (high-dose groups). Ulrich et al. (1979a,b,c) concluded that neither rats nor monkeys exhibited any signs of toxicity associated with inhalation of 0.0116-1.152 mg manganese/m^3 continuously for 9 months.

Nishiyama et al. (1975) investigated the pulmonary toxicity of MnO_2 in monkeys by exposing them to manganese at levels of 3 or 0.7 mg/m^3 for 22 hours/day for 5 months. Pulmonary congestion was observed at both dosages, but at the lower dose it appeared later and was less severe. In this study, 0.3 mg/kg/day, associated with exposure to 0.7 mg/m^3, appeared to be a LOAEL. Subsequently, Nishiyama et al. (1977) exposed three monkeys to 3 mg manganese/m^3 and two monkeys to 0.7 mg manganese/m^3 (as MnO_2), 22

hours/day for 10 months to investigate the biochemical and neurotoxic effects of long-term exposure. A control group of three monkeys was maintained. High-dose group monkeys exhibited elevated serum concentrations of SGOT, SGPT, monoamine oxidase, calcium and magnesium compared to controls. Substantially elevated manganese levels were determined in brain, lung, hide, hair, bile and kidney, compared to controls and low-dose group monkeys. Mild tremors of the fingers, decreased pinch force and reduced dexterity of upper limbs were observed and considered to be evidence of neurologic damage analogous to that observed in humans suffering from chronic manganese toxicity. No neurologic signs were observed in the low-dose group monkeys. Elevations in serum SGOT were similar to those observed in the high-dose group; SGPT and monoamine oxidase were more elevated in low-dose than high-dose or control group monkeys. Elevations of serum calcium and magnesium in low-dose monkeys were slightly less than those observed in high-dose monkeys, but considerably higher than those observed in control monkeys. Generally, tissue levels in low-dose monkeys were somewhat intermediate between levels determined in high-dose and control monkeys, except that pulmonary levels were similar in all exposed monkeys and levels in hide and hair were similar to those of controls. In a subsequent report (presumably further results from the same study), these authors reported that the monkeys exposed to 700 $\mu g/m^3$ showed pathologic changes in the lungs following 10 months of exposure (Suzuki et al., 1978). This appears to represent the lowest reported LOAEL.

Coulston and Griffin (1977) exposed seven rhesus monkeys to 100 $\mu g/m^3$ Mn_3O_4 particulate 24 hours/day for up to 66 weeks, and found no exposure-related adverse effects.

3.2. CHRONIC

3.2.1. Oral. Only one report of chronic oral exposure of humans to manganese has been located in the available literature. Kawamura et al. (1941) reported the case of water consumption from wells contaminated by manganese from dry cell batteries buried nearby. After the outbreak of chronic manganese intoxication, water from the wells was tested and found to contain 14.3 mg manganese/ℓ. Over a period of 6 weeks, the concentration was reported to have decreased to 4.2 mg/ℓ. A total of 16 people were affected with symptoms of extrapyramidal dysfunction such as lethargy, increased muscle tone and spasms, tremors and mental disturbances. Elderly people seemed to be most severely affected and children were least affected. Autopsy of one case showed atrophy of the globus pallidum and disappearance of its neurons. Moderate congestion of the brain, spinal cord and meninges was observed. Meningeal edema was particularly prominent in the area of the occiput. Levels of manganese in well water during the outbreak were not monitored.

The only chronic oral studies of manganese toxicity in laboratory animals was the continuation of the drinking water studies in rats (see Section 3.1.1.). In this experiment, rats were exposed to drinking water containing $MnCl_2 \cdot 4H_2O$ at 1 mg/mℓ from conception to termination at >2 years of age (Leung et al., 1981; Lai et al., 1982c), to test the effects of chronic manganese exposure on monoamine oxidase and NAD-linked isocitric dehydrogenase activities in the brain of aged rats. Monoamine oxidase activity was marginally significantly elevated in young but not aged rats treated with manganese in the cerebellum but not in five other regions of the brain. The biological significance of this finding is doubtful.

Isocitric dehydrogenase activities did not appear to be affected by treatment with manganese.

3.2.2. Inhalation. Several reports of chronic inhalation exposure of humans to manganese were located in the available literature. In most cases, these reports do not contain sufficient exposure data to be useful in risk assessment. These data are summarized in Table 3-2. The U.S. EPA (1982a, 1984) provides an excellent review and discussion of the clinical aspects of manganism (chronic manganese toxicity resulting from inhalation exposure). The brief discussion of manganism which follows is taken from that document.

Effects of chronic manganese toxicity are most severe on the CNS. Signs of toxicity can result from exposure to manganese aerosols for only a few months (Ansola et al., 1944b), although exposure for longer periods of time is usually required. Damage may be is reversible if exposure is terminated at an early stage. Barbeau et al. (1976), however, reported that symptoms worsened in some patients after exposure had ceased. Cotzias et al. (1968) indicated that elevated tissue levels of manganese are not necessary for confirmation of chronic manganese toxicity.

Cotzias (1962) described three phases of manganism. The first phase begins insidiously with anorexia, asthenia, abnormal psychotic behavior and occasional criminal acts. Severe somnolence followed by insomnia are noted. Headache and leucocytopenia occur, which confuses differential diagnosis with viral encephalitis. The second phase initiates the onset of extrapyramidal disease, clumsy articulation often resulting in muteness. A mask-like face and general clumsiness and lack of skilled movements are characteristic. The third phase is characterized by severe rigidity, and the limbs manifest a "cogwheel" phenomenon. Tremors occur which become exacerbated by

emotion, stress, fatigue or trauma. Indifference, interrupted by laughing or crying spells, occurs. Autonomic dysfunction, manifested by excessive salivation or sweating, often occurs.

As noted in Table 3-3, levels of manganese as low as 0.30 mg/m^3 (ferromanganese plant, Saric et al., 1977), 0.44 mg/m^3 (welding fumes, Chandra et al., 1981) and 0.5 mg/m^3 (manganese mine, Schuler et al., 1957) have been associated with neurological evidence of manganism.

Exposure to atmospheric manganese may also result in bronchitis and pneumonitis in humans. The respiratory symptoms observed in the following studies are considered to be due to the inhalation of particulate matter rather than the inhalation of manganese per se, because the respiratory symptoms observed are not those of manganism and are those that result from the inhalation of particulates not containing manganese (U.S. EPA, 1982b).

Nogawa et al. (1973) studied subjective symptoms and ventilatory function in 1258 junior high school students housed in a school 100 m from a ferromanganese plant and in a similar group of 648 students housed 7 km away. The following subjective symptoms were elevated in the manganese exposed group: presence of sputum in winter on arising, presence of sputum in summer, wheezing, clogged nose, frequent colds and throat symptoms. Affected ventilatory parameters included: lower mean values for forced expiratory volume, lower mean values for 1 second capacity and lower ratios of 1 second capacity to maximum expiratory flow.

Mild signs of chronic bronchitis (raising phlegm in the morning and during the day and/or night for at least 3 winter months for at least 2 years) were observed in a small percentage of workers exposed to dust containing manganese at 0.005-0.040 mg/m^3 in an electrode plant (Saric and Lucic-Palaic, 1977).

TABLE 3-3

Studies of Manganism in Humans and Exposure-Response Relationship

Type of Exposure	Exposure Level (mg Mn/m³)	Duration of Exposure	Number of Exposed Workers	Number Affected (%), Pathological Findings	Reference
Ore crushing mill	<30 <30	3.3 years average NR	9 25	0 manganism 11 (44%) manganism	Flinn et al., 1940
Manganese mine	62.5-250	178 days	72	12 (16.5%) manganism	Ansola et al., 1944a,b
Manganese mine	250-450	~1 month to 10 years	NR	manganism - 150 cases observed in workers in two mines	Rodier, 1955
Manganese mine	0.5-46	8.2 years	370	15 (4%) manganism	Schuler et al., 1957
Ferromanganese	0.45-0.6	NR	994	167 (16.8%), some neurological signs and symptoms	Gorodnova, 1967[a]
Industrial plants	<5 >5	NR NR	38 117	0 7 (6%) manganism 15 (12.8%) suspected manganism	Tanaka and Lieben, 1969
Dry-cell battery	6.8-42.2	7.5 years average (1-16 years)	36	8 (22.2%) neuropsychiatric manifest	Emara et al., 1971
Ferromanganese dust or manganese oxide fumes	2.1-12.9 (dust) 0.12-13.3 (oxide)	variable NR	71 NR	5 (7%) manganism manganism	Smyth et al., 1973
Ferromanganese	0.61-1.2	NR	200	91 (45.5%) neurological abnormalities	Kovaltchuk and Brodski, 1973[a]
Ferromanganese	3.2-8.6	NR	100	40 (40%) slight neurological abnormalities	Suzuki et al., 1973a,b,c[b]
Ferromanganese plant	0.30-20.44	varied 27% <4 years 9.8% >20 years	369	62 (16.8%) slight neurological signs	Saric et al., 1977
Junior high school within 100 m of ferromanganese plant	0.003-0.011[c]	NR	1258 students	NR: $p<0.05$ increased incidence of symptoms related to the throat, decreased lung function, compared with 648 students in school 7 km from factory[d]	Nogawa et al., 1973
Electrode factory	0.005-0.040	NR	102[e] 190[f]	11(10.8) chronic bronchitis[d] 28(14.7) chronic bronchitis[d]	Saric and Lucic-Palaic, 1977

TABLE 3-3 (cont.)

Type of Exposure	Exposure Level (mg Mn/m³)	Duration of Exposure	Number of Exposed Workers	Number Affected (%), Pathological Findings	Reference
Electrode plant	0.002-0.030 (levels to which the control population was exposed)	NR	190	11 (5.8%) slight neurological signs	Saric et al., 1977
Welding fumes	0.44-0.99	20.2 (mean years)	20	5 (25%) slight neurological signs	Chandra et al., 1981
	0.5-0.8	21.0 (mean years)	20	10 (50%) slight neurological signs	
	0.88-2.6	14.1 (mean years)	20	9 (45%) slight neurological signs	

[a]Original articles not available for review

[b]English abstract only

[c]Determined by the U.S. EPA (1984) based on analogy to dustfall data from the United States. Later declared invalid by the U.S. EPA (Stara, 1985).

[d]The U.S. EPA (Stara, 1985) has determined that the respiratory signs observed are due to the presence of inhaled particulate rather than manganese per se.

[e]Nonsmokers

[f]Total workers; includes present, former and nonsmokers

NR = Not reported

Lloyd-Davies (1946) reported a high incidence of pneumonia in workers employed in the manufacture of potassium permanganate in 1938-1945. Workers also complained of bronchitis and upper respiratory irritation. Based on the MnO_2 content of dust in the plant, the manganese content of the air was estimated at 0.1-13.7 mg/m³. Almost all particles were <1μ in size and ~80% were <0.2 μ. The levels of exposure to manganese estimated in this study are at least 2.5 times as great as the lower level, associated with chronic bronchitis, estimated by Saric and Lucic-Palaic (1977).

Pertinent data regarding chronic inhalation exposure of animals to manganese compounds could not be located in the available literature.

3.3. TERATOGENICITY AND OTHER REPRODUCTIVE EFFECTS

3.3.1. Oral. Few reports associating oral exposure to manganese with reproductive effects in humans have been located in the available literature. Impotency has been reported as one of the manifestations of manganese toxicity in humans (Penalver, 1955). Rodier (1955) reported impotency in 83% of his patients, and Mena et al. (1967) reported impotency in 8/13 of their cases of manganese toxicity. Mandzgaladze (1967) reported that the incidence of stillbirths and spontaneous abortions appeared to increase with the increasing duration of occupational exposure of the husbands to manganese.

Gray and Laskey (1980) investigated the retardation of reproductive development associated with chronic dietary exposure. Male CD-1 mice were exposed to a purified diet to which 0 or 1050 ppm manganese as Mn_3O_4 had been added from day 15 of gestation to 90 days after birth. Wet weights of preputial glands, seminal vesicles and testes measured at 58, 73 and 90 days were significantly lower in exposed mice than in control mice. Body and liver weights were unaffected by treatment.

Subsequently, Laskey et al. (1982) fed groups of female Long-Evans rats iron-sufficient or iron-deficient diets containing 0, 350, 1050 or 3500 ppm manganese as Mn_3O_4. A significant decrease in serum testosterone was observed in male rats exposed to 1050 ppm manganese, but no reduction in male fertility was noted. Female fertility, as measured by the percent of pregnant rats, was reduced by exposure to 3500 ppm manganese in the diet, but not by lower dietary concentrations.

Pertinent data associating terata with oral exposure to manganese could not be located in the available literature.

3.3.2. Inhalation. Pertinent data associating inhalation exposure of humans or animals to manganese with reproductive effects could not be located in the available literature.

3.4. TOXICANT INTERACTIONS

As discussed in Section 2.1., iron deficiency anemia results in greater absorption of orally administered manganese (Mena et al., 1969). Since iron and manganese compete with each other for absorption, it may be assumed that iron deficiency may exacerbate the toxicity of manganese. No other studies of the interactions of manganese with xenobiotics were located in the available literature.

4. CARCINOGENICITY

4.1. HUMAN DATA

Pertinent data regarding the carcinogenicity of manganese or its compounds in humans could not be located in the available literature.

4.2. BIOASSAYS

4.2.1. Oral. Furst (1978) administered manganese powder to F344 rats. Groups of 25 rats of each sex received doses of 10 mg of manganese suspended in trioctanoin by gavage twice monthly for 12 months. When compared to the incidence of lymphosarcomas/leukemia and fibrosarcomas in vehicle-treated controls, no increase was noted in manganese-exposed rats. No other studies of carcinogenicity due to oral exposure of animals to manganese or its compounds were located in the available literature.

4.2.2. Inhalation. Pertinent data regarding carcinogenicity in either humans or laboratory animals related to inhalation exposure to manganese or its compounds could not be located in the available literature.

4.3. OTHER RELEVANT INFORMATION

Few data concerning the mutagenicity of manganese or its compounds have been located in the available literature. Demerec and Hanson (1951) demonstrated that $MnCl_2$ caused a genetic reversion in a strain of Escherichia coli dependent upon streptomycin for its growth. Similarly, Flessel (1977) demonstrated that manganese was mutagenic in experiments with Salmonella, though details of protocol and results were lacking.

Umeda and Nishimura (1979) investigated the ability of $MnCl_2$ and potassium permanganate to cause chromosomal aberrations in C3H mouse mammary carcinoma cells. Aberrations were noted in 5% of the cells exposed to $MnCl_2$ at a concentration of 10^{-3} M and in 17% of the cells exposed to a concentration of 10^{-4} M potassium permanganate. Dikshith and Chandra (1978) failed to demonstrate chromosomal damage in spermatogonia or bone

marrow cells of rats orally exposed to 50 μg $MnCl_2$/kg/day for 180 days. Jorgenson et al. (1978) failed to demonstrate heritable translocation defects in the offspring of F_1 males from male mice given manganese sulfate for 7 weeks before mating.

Nishioka (1975) reported a weakly positive effect for $MnCl_2$, $Mn(NO_3)_2$, $MnSO_4$ and $Mn(CH_3COOH)_2$, but a negative effect for $KMnO_4$ in a rec (recombination) assay using Bacillus subtilis strains H17 and M45. Negative results in the rec assay were reported for $Mn(NO_3)_2$, $Mn(CH_3COOH)_2$ and $MnCl_2$, which was highly cytotoxic (Kanematsu et al., 1980; Kada et al., 1980). Orgel and Orgel (1965) showed that divalent manganese is also mutagenic in the bacteriophage T4. Treatment of T4-infected E. coli at concentrations of 10^{-2} M increased the proportions of rapid lysic mutants from <0.04 to ~1%.

Manganese was moderately effective in enhancing viral transformation of Syrian hamster embryo cells (Casto et al., 1979). The composition of the medium greatly influenced the mutagenic response. Hsie et al. (1979) found that preparation of a medium deficient in divalent cations resulted in a greater frequency of spontaneous mutations associated with $MnCl_2$.

4.4. WEIGHT OF EVIDENCE

Furst (1978) administered a trioctanoin suspension of manganese powder by gavage to rats twice monthly for 12 months. No statistically significant increase in the incidence of neoplasia was found. In concurrent studies, manganese powder, manganese acetylacetonate and manganese dioxide were injected intramuscularly in rats and mice. Manganese acetylacetonate appeared to cause a significantly increased incidence of injection site fibrosarcoma; mean latency period was 17 months.

No other studies associating manganese or its compounds with carcinogenicity in animals were located in the available literature. Stoner et al. (1976) tested $MnCl_2$ for carcinogenicity in the strain A mouse lung tumor system. Mice were injected intraperitoneally 3 times/week for 22 injections. The dose levels used represented the MTD and 1:2 and 1:5 dilutions of that concentration. Necropsy examinations 30 weeks after the first injection revealed no increase in the incidence of lung tumors compared to untreated or physiological saline-treated controls. Urethane-treated (positive control) mice suffered a 100% incidence of lung tumors.

DiPaolo (1964) injected DBA mice either subcutaneously or intraperitoneally with 0.1 mℓ of 1% $MnCl_2$ in aqueous solution twice weekly for 6 months. Although the incidence of lymphosarcomas in treated mice appeared to be increased over the incidence in negative controls and tumors appeared earlier in treated mice than in control mice, the incidence of tumors in treated mice was not significantly different from that in the negative controls.

Sunderman et al. (1974, 1976) failed to induce injection site tumors in Fischer rats given single intramuscular injections of manganese powder. Furthermore, these authors showed that addition of equimolar amounts of manganese dust to nickel subsulfide significantly depressed tumorigenesis due to nickel subsulfide. Under similar experimental conditions, Sunderman et al. (1980) showed that manganese dust also inhibited local sarcoma induction by benzo[a]pyrene.

The National Cancer Institute is conducting a cancer bioassay of manganese sulfate given by gavage to rats and mice. Applying the criteria for evaluating the overall weight of evidence for carcinogenicity in humans proposed by the Carcinogen Assessment Group of the U.S. EPA (Federal Register, 1984), manganese is best designated a Group D - Not Classified - substance.

5. REGULATORY STANDARDS AND CRITERIA

A summary of current regulatory standards and criteria for manganese and its compounds is presented in Table 5-1. The ACGIH (1980) set the ceiling limit for manganese dust at 5 mg/m³, based on reports of no cases of manganism reported in 25 ore-handlers exposed to MnO_2 dust concentrations of 1-5 mg/m³. On the basis of two Russian studies suggesting toxicity to low levels of manganese cyclopentadienyl tricarbonyl, the ACGIH (1980) has set the TLV for manganese from manganese cyclopentadienyl tricarbonyl at 0.1 mg/m³ manganese and the STEL at 0.3 mg/m³ manganese. For manganese tetroxide fume, the ACGIH (1980) has set the TLV at 1 mg/m³ manganese and the STEL at 3 mg/m³ manganese. For 1984, the ACGIH (1983) has recommended a TLV for manganese fume of 1 mg/m³ and a STEL of 3 mg/m³.

In Illinois, a much lower criterion in ambient air, 0.006 µg/m³, has been recommended by the Illinois Institute of Environmental Quality (IIEQ, 1975).

The U.S. EPA (1976) has set the freshwater criterion at 0.05 mg/ℓ based on the organoleptic threshold for manganese, and the marine water criterion at 0.1 mg/ℓ to protect consumers of seafood.

TABLE 5-1

Regulatory Standards and Criteria

Standard or Criterion	Value	Reference
Mn dust: ceiling limit	5 mg/m³	ACGIH, 1980
Mn fume: TLV	1 mg/m³	ACGIH, 1983
STEL	3 mg/m³	
Mn as cyclopentadienyl tricarbonyl: TLV	0.1 mg Mn/m³	ACGIH, 1980
STEL	0.3 mg Mn/m³	
Mn tetroxide: TLV	1.0 mg Mn/m³	ACGIH, 1980
STEL	3.0 mg Mn/m³	
Respirable Mn for occupational exposure	0.3 mg/m³	WHO, 1980
Ambient air criterion	0.006 μg/m³	IIEQ, 1975
Organoleptic criterion in freshwater	0.05 mg/ℓ	U.S. EPA, 1976
Marine water criterion	0.1 mg/ℓ	U.S. EPA, 1976

6. RISK ASSESSMENT

6.1. ACCEPTABLE INTAKE SUBCHRONIC (AIS)

6.1.1. Oral. As discussed in Section 3.1.1., reports of human toxicity to subchronic oral exposure to manganese or its compounds could not be located in the available literature. Several references to subchronic oral exposure were found in U.S. EPA (1982a), but few were suitable for use in risk assessment. Wassermann and Wassermann (1977) failed to produce symptoms of extrapyramidal disease in rats exposed to 2000 ppm manganese in the diet. Proliferated endoplasmic reticulum and other compensatory ultrastructural changes in the liver were noted in rats given 200 ppm $MnCl_2$ in the drinking water. Kimura et al. (1978) associated slightly depressed brain serotonin with 564 ppm manganese (as the chloride) in rats. Gray and Laskey (1980) demonstrated retarded sexual development in male mice exposed to 1050 ppm manganese as Mn_3O_4. In a follow-up study, this level was shown to cause decreased testosterone in male rats without interference with reproductive function (Laskey et al., 1982). In these studies, 1050 ppm manganese in the diet constituted a LOAEL in mice (136.5 mg/kg/day) and rats (52.5 mg/kg/day), assuming that mice and rats eat food equivalent to 13 and 5% of their body weight/day, respectively. Carter et al. (1980) reported a decrease in serum creatinine and increases in serum calcium and phosphorus in rats, associated with a dietary level of 1100 ppm manganese. In this study, 1100 ppm manganese (55 mg/kg/day, food intake equivalent to 5% of body weight) represented a NOAEL.

Several studies of the effects of manganese on the brains of rats have been performed (see Table 3-1). Bonilla and Diez-Ewald (1974) observed mild histological changes in rats given $MnCl_2$ in the drinking water at 306 mg Mn/kg bw/day. More recently, Bonilla (1984) observed alterations in spon-

taneous motor activity of rats receiving 10 or 500 mg Mn/kg bw/day as $MnCl_2$ in the drinking water. The alterations were not consistent and not dose-related; they are probably not biologically significant or representative of a toxic response to manganese.

In another series of investigations (Leung et al., 1982a,b; Lai et al., 1982a,b), rats were given drinking water from conception to 120 days of age at levels of 1 or 10 mg/mℓ of $MnCl_2 \cdot 4H_2O$. Organ weights, protein contents and monoamine oxidase acitivities were unaffected at either level. Significant alteration in dopamine uptake at synaptosomes was noted at 10 mg/mℓ and altered response to amphetamine-induced hyperactivity was observed at 1.0 mg/mℓ. Histopathological examinations of the brain were not performed in this study. The effects observed in the absence of signs of toxicity or altered behavior were judged not to be adverse.

Nakashima (1983) indicated ultrastructural changes and neuronal atrophy in rats treated with $MnCl_2$ at 0.01 mg/mℓ in the drinking water for 12 months. This study was available only as an English abstract and it is suspected that the reported dosage is incorrect. Applying the assumptions footnoted in Table 3-1, this level results in a manganese intake of 0.44 mg/kg bw/day. According to the NAS (1978), diets for laboratory rodents should contain 50 ppm Mn. Assuming rats eat food equivalent to 5% of their body weight/day, this level amounts to an intake of 2.5 mg/kg bw/day. The data of Nakashima (1983) as reported in the English abstract are therefore considered unreliable and are excluded from consideration in risk assessment.

The study by Laskey et al. (1982) was chosen to derive an oral AIS. The animal dose of 52.5 mg/kg/day associated with decreased serum testosterone but normal reproductive performance is multiplied by 70 kg, the assumed body weight of man, and divided by an uncertainty factor of 100: a factor of 1 to

account for interspecies extrapolation because manganese is a required trace element in the nutrition of rats and probably also in humans, a factor of 10 to extrapolate from a LOAEL to a NOAEL, and a factor of 10 to provide greater protection to especially sensitive populations, such as those suffering from iron-deficiency anemia. The resultant AIS is 36.8 mg/man/day for subchronic oral exposure to manganese.

6.1.2. Inhalation. Studies of the toxicity of manganese as MnO_2 by inhalation exposure were primarily related to effects on the lungs (Ehrishmann, 1935; Ulrich et al., 1979a,b,c; Nishiyama et al., 1975; Coulston and Griffin, 1977). The signs produced probably represent the effects of particulate matter, rather than manganese per se, on the respiratory tract, since the signs observed were those of particulate matter in the air (U.S. EPA, 1982b) and were not those of manganism. Therefore, an AIS is not calculated for manganese based on the respiratory signs observed in these studies. Exposure of humans to manganese would probably result from occupational or other anthropogenic exposure and would, therefore, potentially be chronic. The AIC for inhalation exposure, 21 μg/day, is therefore adopted as the AIS (see Section 6.2.2).

6.2. ACCEPTABLE INTAKE CHRONIC (AIC)

6.2.1. Oral. Although Kawamura et al. (1941) described an outbreak of chronic manganese toxicity associated with contaminated well water, exposure data were insufficient for use in risk assessment. The only chronic study in animals was the continuation of the drinking water study in rats in which monoamine oxidase and isocitric dehydrogenase activities were measured in aged rats treated for >2 years with $MnCl_2 \cdot 4H_2O$ at 1 mg/mℓ (Leung et al., 1981; Lai et al., 1982c). No adverse effects were observed. An AIC can be calculated from these data. Applying the assumptions footnoted in

Table 3-1, this exposure corresponds to a dose of 22 mg Mn/kg bw/day. An AIC is calculated by multiplying the animal dose by 70 (the assumed body weight of humans) and dividing by an uncertainty factory of 100: a factor of 10 to reflect the unknown in extrapolating from rats to humans and another factor of 10 to afford additional protection for unusually sensitive members of the population. An AIC of 15.4 mg/day for a 70 kg human results, which is not >6.2 times the human adult dietary allowances for manganese recommended by the NRC (1980).

6.2.2. Inhalation. Occupational inhalation exposure to levels of manganese as low as 0.3 mg/m³ (Saric et al., 1977), 0.44 mg/m³ (Chandra et al., 1981) or 0.5 mg/m³ (Schuler et al., 1957) were associated with neurologic evidence of manganism (see Section 3.2.2.). A review of the epidemiologic data regarding manganism (the neurotoxic syndrome associated with manganese) indicates that occupational exposure to $\geq$5000 μg/m³ is clearly related to occurrence of the syndrome. The evidence that manganism occurs at atmospheric levels <500 μg/m³ is judged to be equivocal and it is concluded that 300 μg/m³ is the lowest level at which symptoms of manganism had been documented. Accepting 300 μg/m³ as the threshold for manganism in humans allows derivation of an AIC. The AIC is calculated by assuming that humans inhale 10 m³ of air during the workday and by expanding exposure from 5 to 7 days/week. An uncertainty factor of 100 is applied, a factor of 10 to convert from a LOAEL to a NOAEL and another factor of 10 to afford greater protection for unusually sensitive individuals. These calculations result in an AIC of 21 μg/day.

The toxicity of manganese was reviewed and a CS was calculated for neural effects in animals, exposed both orally and by inhalation, and for manganism in occupationally exposed humans. A CS of 37.6, based on manga-

nism in humans, was selected as most appropriately representing the toxicity of manganese. A review of the human data indicates that occupational exposure to 500 μg/m³ was the lowest concentration clearly related to the occurrence of symptoms. Assuming workers inhale 10 m³ of air on the job and work 5 days/week, this exposure converts to 3571 μg/day or 3.6 mg/day. This MED corresponds to an RV_d of 4.7. The effects observed, neurological symptoms of manganism, are assigned an RV_e of 8. A CS of 37.6 is calculated as the product of RV_d and RV_e.

6.3. CARCINOGENIC POTENCY (q_1*)

6.3.1. Oral. Only one study (Furst, 1978) of the carcinogenicity of orally administered manganese was located in the available literature. No significantly increased incidence of cancer was associated with manganese in this study; hence, no q_1* for oral exposure can be calculated.

6.3.2. Inhalation. Pertinent data regarding the carcinogenicity of manganese in humans or animals exposed by inhalation could not be located in the available literature. A review of the reports of humans or animals exposed to manganese by inhalation for prolonged periods (see Section 3.2.2.) has failed to reveal cancer associated with exposure to manganese. Therefore, no q_1* for inhalation exposure can be calculated.

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APPENDIX

Summary Table for Manganese and Compounds

	Species	Experimental Dose/Exposure	Effect	Acceptable Intake (AIS or AIC)	Reference
Inhalation					
AIS	human	300 μg/m³ occupational	threshold for mangansim	21 μg/day	Saric et al., 1977
AIC	human	300 μg/m³ occupational	threshold for manganism	21 μg/day	Saric et al., 1977
Maximum composite score	human	500 μg/m³ occupational (RV_d=4.7)	neurologic symptoms of manganism (RV_e=8)	37.6	Stara, 1985;
Oral					
AIS	rat	52.5 mg/kg/day	decreased serum testosterone	36.8 mg/day	Laskey et al., 1982
AIC	rat	22 mg/kg/day	slightly altered isocitrate activities in brain	15.4 mg/day	Leung et al., 1981; Lai et al., 1982c