



ENVIRONMENTAL HEALTH CRITERIA FOR
MANGANESE AND ITS COMPOUNDS

Review of work in
the United States of America on
manganese and its compounds
in relation to health
1967-1973*

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PREFACE

The review of work representing the United States contribution on "Manganese and its Compounds in Relation to Health," 1967-1973, has not in every instance been restricted to this seven-year period. Earlier work was sometimes cited for the purpose of providing clarity to the subject matter under discussion. Many important foreign references were omitted, in accordance with instructions, in order to primarily restrict this contribution to a national level. We wish to fully acknowledge the importance of non-U. S. scientific publications in making substantive contributions to the total scientific knowledge concerning manganese and have sincerely appreciated the opportunity of utilizing this information, to the best of our ability, for formulating our national strategy relating to manganese as an environmental pollutant.

1. UNITED STATES OVERVIEW

The purpose of this document is to summarize the current U. S. studies of manganese in relation to its effect upon human health and the environment and to evaluate this knowledge base with a view toward the need to control the release of manganese into the environment from anthropogenic sources in the United States.

Manganese is present as a pollutant in the air over the continental United States. It has been found in measurable amounts in practically all samples of suspended particulate matter collected from the air of some 250 urban areas and in many samples from at least 30 nonurban sites, some of which are quite remote from urban areas. The highest concentrations, as should be expected, are found in areas in the vicinity of ferromanganese alloy plants or related activities. The urban average manganese concentration is around $0.10 \mu\text{g}/\text{m}^3$ with several cities showing annual averages in the 0.50 to $3.27 \mu\text{g}/\text{m}^3$ range. Occasional 24-hour concentrations as high as $14.00 \mu\text{g}/\text{m}^3$ have been observed. Annual

averages as high as $8.30 \mu\text{g}/\text{m}^3$ have occurred in small communities located near a large point source in the highly industrialized Kanawha River Valley of West Virginia. Approximately 80 percent of manganese in the suspended particulate matter from six large cities was associated with particles in the respirable size range; i.e., 5 micrometers or less in diameter. The existence of manganese in the smaller particles favors a widespread distribution of this pollutant. This has been confirmed by the analysis of precipitation samples collected at many remote locations in the United States.

Manganese in the atmosphere will be primarily associated with particulate matter. As a particulate, the principal removal mechanism will be precipitation, gravitational settling, and absorption at the surface. Manganese may be involved in the atmospheric conversion of sulfur dioxide to sulfuric acid. The question remains as to whether or not the manganese concentration in the ambient air is high enough for this purpose. The reaction of manganese dioxide with nitrogen dioxide to form manganese nitrate may occur in the atmosphere.

The natural abundance of manganese and its dynamic behavior in the environment involving physical, chemical, and biological activity makes it difficult to assess the contribution and effects of man-made sources. Much of our knowledge concerning the toxicity of manganese is based upon clinical studies of individuals exposed to high concentrations resulting in manganese poisoning. Much remains unknown about the biochemistry and toxicological effects of manganese. No cases of manganese poisoning have been reported to result from exposure to manganese dust concentrations less than the U. S. recommended threshold limit value of $5 \text{ mg}/\text{m}^3$, although some argue that the safety factor is low for susceptible persons. Based upon the present state of knowledge and available data, the following conclusions can presently be drawn:

1. Adverse health effects may occur from exposure to high concentrations of manganese--particularly dust and fumes.

2. The concentrations of manganese observed in ambient air do not pose a threat to the health and welfare of the general population. Concentrations may reach a significant effect level in the immediate vicinity of major point sources under adverse dispersion conditions. Manganese pollution is a local problem. Widespread use of manganese fuel additives would make man-made emissions more ubiquitous.
3. Manganese pollution of water does not appear to be a problem except possibly in isolated cases of waste disposal.
4. Atmospheric concentrations of manganese observed in urban areas can be attributed to anthropogenic sources. The principal source of atmospheric emissions is metallurgical processing.
5. Particulate control technology available and/or under development should be adequate to maintain the atmospheric concentrations of manganese at an acceptable level. Therefore, emission standards for specific industries may be established in the near future.
6. There is currently no evidence that human exposure to manganese at the levels normally observed in the ambient atmosphere results in adverse health effects.
7. The current state of knowledge and available data do not justify the establishment of national ambient air quality standards for manganese.

2. INTRODUCTION

Background summary (U. S. EPA, 1973)

Manganese is one of the more abundant elements in the earth's crust. It is widely distributed in soils, sediments, rocks, and water and is thought to be present in all organisms. At least 100 minerals contain manganese as an essential element; however, it does not occur naturally as a metal. The concentration of manganese in these categories varies

from a trace to ores containing 50 percent manganese. Soil concentrations range from less than 1 ppm to 7000 ppm with a rough average of about 500 ppm. The concentration of dissolved manganese in sea water is reported as 2 ppb on the average, and in fresh water the concentration ranges from <50 to 850 ppb. Manganese appears to be omnipresent in food-stuff with concentrations ranging from a trace to >250 $\mu\text{g/g}$. The maximum concentrations are found in nuts, cloves, and tea leaves.

Manganese has been classified as an essential trace element for both plants and animals, including man. Manganese deficiency has been observed in plant and animal species, both in field and laboratory experiments; however, minimum human nutritional requirements have not been established. The normal balanced diets consumed by man apparently provide sufficient quantities of manganese to prevent a deficiency. Diets high in milk, sugar, and refined cereals may provide only minimum requirements for children, pregnant women, and diabetics. The daily dietary intake varies widely with an average of approximately 3 to 7 mg manganese.

Manganese deficiency has been reported to result in skeletal abnormalities, reduced glucose tolerance, reduction in oxygen uptake by liver mitochondria, increased fat deposition, growth retardation, brain dysfunction, and decreased fertility. In addition, maternal manganese deficiency may result in offspring with congenital malformations and increases in the number of stillbirths and neonatal deaths.

It is unlikely that the dietary intake will contribute to an excessive body burden of manganese in man, except possibly in the case of extreme local pollution. Generally, organs and tissues do not accumulate large concentrations of manganese. Excretion is normally via the biliary route in the feces.

Manganese is among the trace elements least toxic to mammals; however, exposure to high concentrations resulting from anthropogenic sources has resulted in adverse human health effects. Manganese intoxication in man is primarily the result of inhalation of manganese dust

or fumes, although absorption via the gastrointestinal tract and through the skin have been reported. Exposure to high concentrations of manganese dust results in manganic pneumonia, which is unresponsive to antibiotic treatment and in chronic manganisms--a central nervous system disease first manifested by distorted mentation and exhibiting neurologic effects bearing a similarity with the symptoms of Parkinsonism. Removal of the victim from the polluted environment in the early stages usually clears up manganism; however, in chronic cases, the effects on the central nervous system are not completely reversible. An outbreak of a form of pneumonia in inhabitants of Sauda, Norway, was attributed to the effluent from a ferromanganese plant. An outbreak of manganese poisoning in Japan was attributed to ingestion of manganese-contaminated well water indicating toxic effects of manganese levels above 500 ppm in drinking water.

Threshold limit values for an eight-hour day for occupational exposure to manganese have been established in several countries. These vary by a wide margin; i.e., 0.3 mg/m³ in the USSR, Poland, and Hungary; 10 mg/m³ in Czechoslovakia; 6 mg/m³ in East and West Germany and Yugoslavia; and 5 mg/m³ in the U. S. The standard for drinking water in the U. S. is 0.05 mg/liter, which was based upon aesthetic and economic reasons rather than health.

References for 2. INTRODUCTION

U. S. Environmental Protection Agency (1973) Manganese. Prepared pursuant to Contract No. 68-02-0542 by the NRC-NAS Committee on Biologic Effects of Atmospheric Pollutants.

3. CHEMICAL COMPOSITION AND QUANTITATION

3.1 Distribution

Manganese does not occur naturally as the metal and is considered the twelfth most abundant element in the earth's crust. Manganese is an essential element in at least 100 minerals including sulfides, anhydrous and hydrous oxides, carbonates, anhydrous and hydrous silicates, anhydrous and hydrous phosphates, arsenates, tungstates, and borates. The manganese concentration in the earth's crust varies widely, ranging from near zero to 7000 ppm. Average concentrations have been reported from 500 to 900 ppm. It is found in igneous, sedimentary, and metamorphic rocks. Bowen (1966) lists igneous rocks as containing 950 ppm; shales, 850 ppm; sandstones, 50 ppm; and limestones, 1100 ppm. Deposits of manganese ores are extensive in tropical, subtropical, and the warmer areas of the temperate zone. In addition, an abundance of manganese nodules have been found on the deep ocean floor. Most important, from an environmental view, is its distribution in the soil. The concentration of manganese present in soil is dependent on the parent rocks and will be discussed in more detail in Section 6.

3.2 Purity

No contribution.

3.3 Quantitation

The sampling and analytic procedures used for manganese analysis at the source and in the environment must be properly matched to the possible concentration ranges as well as interfering species.

3.3.1 Sampling

Ambient air particulate. Presently available analytical procedures require collecting the particulate on filters. The filter material must be chosen with great care so that trace amounts of manganese in the filter do not distort the results. Typical glass fiber filters contain about $400 \mu\text{g}/\text{cm}^2$ of manganese whereas organic membrane filters contain

about $10 \mu\text{g}/\text{cm}^2$ (Hwyang, 1972). Specially selected flash-fired glass fiber filters with only $20 \mu\text{g}/\text{cm}^2$ of Mn have been found acceptable by EPA for providing an ambient air detectable limit for Mn of $4 \mu\text{g}/\text{m}^3$ for nonurban samples. The methods of optical spectroscopy, neutron activation, and X-ray fluorescence are all useful and are discussed later in Section 3.3.2.

Ambient air organic manganese. Although it is rather unlikely that manganese could be present in the organic form in the ambient air, it is desirable that a method of air sampling and analysis for these compounds be available. Unfortunately, there does not appear to be any such method at hand in the scientific literature. However, it seems logical that some of the procedures presently being used for the determination of methylcyclopentadienyl manganese carbonyl in gasoline or other liquid fuels might be modified to be suitable for the determination of these compounds in the atmosphere (Bartels & Wilson, 1969).

Water. The following considerations are important in respect to sampling water for manganese: a) selection of sampling sites, b) frequency of sampling, c) sampling equipment, and d) sample preparation (Brown et al., 1970). Particulate matter may be filtered from water using membrane or other suitable filtration material. Once the particulates are collected on a filter, the analytical problems are almost identical to those described for air analysis in subsequent sections. The standard EPA water analysis methods are atomic absorption (U. S. EPA, 1971). The basic sensitivity for manganese ions in solution is $0.01 \mu\text{g}/\text{ml}$ using conventional atomic absorption spectroscopy and $2 \times 10^{-5} \mu\text{g}/\text{g}$ using the technique of flameless atomic absorption spectroscopy. In view of the concentration ranges and the fact that little or no sample preparation is required, atomic absorption spectroscopy is well suited to analysis of manganese in solution. The technique of X-ray Fluorescence would also work very well if a freeze drying operation were employed.

Food. There are no particular difficulties connected with obtaining food samples. Following collection of the samples, the subsequent

handling depends on the method of analysis. Except for analysis by neutron activation, the samples are ashed by wet or dry methods and the manganese is solubilized in acid. For instrumental neutron activation analysis, the sample is analyzed without prior preparation.

Soil. The aim of soil sampling is to obtain a sample representative of a particular area. If the soil in the area is uniform in composition, little sampling error is expected. When the soils are variable in composition, large sampling errors can result. An approximation of the sampling error can be made by obtaining duplicate samples from random sites within the sample area. Analysis of the duplicate samples will reveal the magnitude of the sampling error while duplicate chemical analysis will determine the analytical precision of the laboratory method (U. S. EPA, 1972).

Biological tissue. Estimation of the extent of manganese exposure by examination of biological fluids or tissues has not been shown to be a reliable index of exposure. Analysis of blood or urine from persons with signs or symptoms of manganese poisoning have not shown high blood or urine levels. However, Tanaka & Lieben (1969) did observe a rough correlation between urine levels and average air concentrations. The average concentration of manganese is 1-8 $\mu\text{g/liter}$ for urine and 2-10 $\mu\text{g/100g}$ for blood (Tanaka & Lieben, 1969; Cholak & Hubbard, 1960).

There is some evidence to indicate that manganese may concentrate in hair following exposure to increased concentrations (Rosenstock et al., 1971). This sampling technique is complicated by the fact that manganese in hair is associated with the melanin-containing structures, and very low concentrations are associated with white hair and other unpigmented structures (Cotzias et al., 1964).

Stationary and mobile sources. The two major factors essential in obtaining reliable emission data are a sampling procedure which provides quantitative representative samples and an analytical method with required sensitivity, selectivity, and accuracy.

Sampling of stationary air pollution sources for manganese must be done isokinetically using a sampling train with good efficiency for removing manganese. The source sampling train, EPA Method 5, allows the particulate collected in the probe, on the filter, and in the water impingers to be analyzed for manganese (U. S. EPA, 1971).

Manganese is emitted from mobile sources as a particulate. Concentrations therein vary depending upon the trace manganese levels in the fuel and the concentration of manganese-containing additives to the fuel, if any. Mobile source particulate may be collected by total or proportional sampling of the hot exhaust or by proportional sampling of the exhaust mixed with dilution air which allows cooling and condensation of the higher molecular weight organics associated with short-time ambient exhaust particulate. The latter method provides a more realistic assessment of the primary mobile source particulate mass and composition. Collection under this technique can be with a single filter, multiple filter, beta gauge, or particulate size fractionating devices. The particulate may then be analyzed directly or after dissolution in an appropriate solvent. Gaseous samples may be collected by the cold trap technique or upon chromatographic columns.

3.3.2 Analysis

Optical spectroscopy. The spectrographic method for the determination of trace metals, including manganese, in environmental samples has been used by a number of workers. With suitable variations in sample preparation, available standard methods can be used equally well for air or biological samples in the microgram range (Cholak & Hubbard, 1960; Tipton et al., 1963; Carlberg et al., 1971). In the procedure used by the EPA National Air Surveillance Network (NASN), atmospheric particulate matter is collected in the field on a glass fiber filter, which is returned to the laboratory. A portion of the filter is ashed in a 1 Torr oxygen atmosphere for 1 hour at 150°C. The trace elements are extracted by refluxing for 3 hours using an acid mixture. The analysis of manganese as well as 15 other elements is routinely accomplished by

NASN using a high resolution grating emission spectrometer. The sensitivity for manganese is 10 ng/m^3 , assuming a 2200 m^3 air sample.

The use of atomic absorption analysis for trace metals, including manganese, in the atmosphere has been described recently by Thompson et al. (1970) and Hwang (1972). Using the same extraction procedure as was used for emission spectroscopic analysis, Thompson et al. (1970) report a sensitivity of 1 ng/m^3 , assuming a 2000 m^3 air sample. The method is fairly free of interferences, except for possible matrix effects, which can generally be avoided by dilution of the sample solution so that the dissolved solids content is less than 0.5 percent. When glass-fiber filters are used, silica extracted from the fibers can cause interferences with the determination of manganese, zinc, iron, and possible other elements, unless removed by the presence or addition of calcium to the solution before the sample is subjected to atomic absorption analysis (Salvin, 1968). This method has also been used to determine manganese in water and other material. The sensitivity of the method varies from 1 to $5 \text{ } \mu\text{g/liter}$ depending on the material being analyzed (Thompson et al., 1970). Flameless atomic absorption spectroscopy, a modification of the basic technique, is sensitive to $0.02 \text{ } \mu\text{g/liter}$ of manganese in solution (Hwang, 1972). In view of these concentrations and the fact that little or no sample preparation is required, atomic absorption spectroscopy is well suited to the analysis of manganese in solution.

Neutron activation. Dams et al. (1970) found neutron activation analysis most suitable for the analysis of very low concentrations (nanogram range) of manganese as well as up to 32 other elements. With this method, it is essential to collect the particulate matter on filters which are very low in trace element content. Certain membrane and ashless paper filters have been found to be quite satisfactory. Using a polystyrene filter, a sensitivity of 0.6 ng/m^3 has been achieved by R. C. Jungers (unpublished data, 1973).

Spark source mass spectrometry. This method has been found to be satisfactory for the analysis of manganese in gasoline. The preparation

procedure used involves an oxidation step with bromine after addition of erbium spike. This is followed by freeze drying to remove the liquid and a final drying at 16°C to remove the odors of gasoline. Residues remaining, including trace elements, are mixed with graphite until homogeneous and an electrode is pressed for analysis with the spark source mass spectrometer equipped with photographic plate output.

X-ray Fluorescence. Where speed and cost of analysis are not of major concern, the above mentioned methods are more than adequate. However, the use of an X-ray fluorescence spectrometer offers the opportunity for low-cost, nondestructive elemental analysis. The sensitivity for manganese on a Whatman 4L filter is estimated to be 30 ng/cm². For a 24-hour sampling period, at a flow rate of 7 liters/min-cm², this corresponds to a sensitivity of 3 ng/m³. Birks et al. (1972) has made a complete elemental analysis with much greater sensitivity in 100 seconds using multichannel analyzers with 14 to 24 crystals.

Recent advances in electronics and solid state detectors for X-rays have created widespread interest in energy dispersive X-ray fluorescence spectroscopy (Goulding et al., 1970; Landis et al., 1971; Rhodes et al., 1972; Giaque et al., 1973; and Cooper, 1973). Goulding and Jaklevic (1973) concluded that the use of either X-ray tubes or radioactive sources is the most efficient and cost effective for routine analysis. Goulding and Jaklevic have developed and delivered to the U. S. EPA a prototype automated sampling station and X-ray analysis system. A sensitivity of 5 ng/m³ for manganese is obtained for a 300-second analysis using a copper fluorescer along with a 0.8 µm pore-size millipore filter which has been sampling air for 2 hours. Because of self-absorption effects, the method is impractical for elements with atomic numbers less than 13. X-ray fluorescence may be used to analyze manganese in solutions if the sample is prepared by freeze drying.

Wet chemical methods. The periodate method is the classical wet chemical method of analyzing air samples for manganese (ACGIH, 1958).

It has the advantage that it can be used in almost any chemical laboratory with relatively simple equipment but the sensitivity is rather poor in comparison with that of other methods. The technique has also been widely used for determining total manganese in the soil. However, this method is considered to give a poor estimate of manganese available to plants.

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4. SOURCES OF ENVIRONMENTAL POLLUTION

4.1-4.4 General

The three major use categories for manganese are metallurgical, dry cell battery manufacture, and chemical. Approximately 90 percent of the manganese produced is used in metallurgical processes. For metallurgical purposes, it is used primarily in the form of ferromanganese. Manganese is also used as an alloying agent for steel, aluminum, and copper. Manganese ore, principally manganese dioxide, is used in the chemical industry as an oxidizing agent in the manufacture of hydroquinone (used mainly as a photographic developer); and in the production of chemicals such as potassium permanganate, manganese sulfate, manganese chloride, and manganese oxide. Potassium permanganate is widely used as a fertilizer or fertilizer additive, in animal and poultry feeds, in coloring agents for textiles and ceramics, and paint dryers. Manganese chloride is used in textile dyes, in welding rod fluxes, and in alloying manganese with magnesium. Organic manganese compounds are used in fuel additives as a combustion improver and smoke suppressant in boiler and turbine fuels, and as an antiknock in gasoline.

Production and Use. U. S. production of manganese ores in 1970 was approximately 5000 short tons whereas total consumption of manganese

ore was approximately 2,400,000 short tons. The total U. S. ferromanganese production was about 835,000 short tons. Approximately 90 percent of the manganese consumed in the U. S. is used in the production of iron and steel. (DeHuff, 1970). Steel production forecasts indicate an approximate 20 percent increase from 1970 through 1975 and a 13 percent increase from 1975 through 1980. About 90 percent of the total manganese consumption should follow this same trend.

Stationary Sources. The principle sources of ambient environmental pollution by manganese are emissions from metallurgical processing plants and disposal of waste materials. Emissions to the atmosphere will vary considerably depending upon the process involved and the degree of control exercised. Reliable quantitative emission data are not available. Particle emissions from a ferromanganese blast furnace generally divide into two size ranges; i.e., dust particles >20 microns and fume with particle sizes ranging from 0.1 to 1.0 micron. The dust particles comprise about 20 percent of the total particulate emissions, and fumes about 80 percent. Based upon a number of samples, the manganese content of fume from a ferromanganese blast furnace is approximately 15-25 percent. Manganese fumes from electric ferroalloy furnaces vary widely depending upon the ores used. Particle sizes average about 0.75 microns and manganese content of the fume is roughly 30 percent. In 1970, there were three blast furnaces making ferromanganese and eleven electric furnaces producing ferromanganese and/or silicomanganese.

The average manganese content of dust from iron and steel production, based upon samples from 48 operators, was <5 percent. With the use of available control technology, the unit contribution to the ambient atmospheric concentration of manganese should be relatively small from these operations. Dust from the handling of raw materials in metallurgical processing, and other manufacturing activities such as chemical, fertilizer, fungicides, and dry cell batteries, may result in a local manganese pollution problem.

Due to the several factors causing variations in emissions, a source emission concentration range has been reported for selected stationary sources by Lee and von Lehmden (1973). The range of manganese concentration (ppm) in source emission particulate was as follows: a) lead smelters, 0.01-1.0; b) coal-fired power plants, 1-1000; c) iron and steel foundrys, 10-1000; and d) cement plants and municipal incinerators, 100-1000. Recently coal-fired power plants have been the subject of trace metal emission studies. Bolton, et al. (1973) made a study of the material balance for manganese and, based on results from the electrostatic precipitator inlet and outlet, indicated the efficiency for manganese removal was higher than 90 percent. Other research concerning the manganese concentration of sized fly ash from three coal-fired power plants indicates the manganese concentration was evenly distributed through a particle size range of 1.3->33.0 microns (D.J. von Lehmden, unpublished data, 1973).

Since roughly 90 percent or more of the manganese consumed in the U. S. is used in the production of iron and steel, an emission inventory in a highly industrialized area in which iron and steel manufacturing is prevalent should reflect high emissions from this source. Winchester and Nifong (1969) studied the large industrial area of Chicago, Milwaukee and northwest Indiana and verified iron and steel manufacturing as the predominant source of manganese emissions in that geographical area. The manganese emissions (in short tons per year) from the major air pollution sources were: a) coke burning, 5; b) fuel oil burning, 6; c) coal burning, 67; and d) iron and steel, 5000.

Fuels. As part of EPA's nationwide fuel surveillance network, trace analyzes for manganese have been initiated for gasolines, residual fuel oils, crude oils, coals mined in the U. S., off-the-shelf fuel additives, and several grades of motor oil. Initial results indicate the following ranges of manganese concentrations for the respective fuels: a) gasoline, <0.001-0.03 $\mu\text{g}/\text{ml}$ (R. J. Jungers, unpublished data, 1973);

b) residual fuel oils, 0.012-0.27 ppm (Bryan, et al., 1970); c) crude oils, <0.001-0.15 ppm (Bryan, et al., 1970); d) coal, 5-80 ppm (Shimp, et al., 1972; Swanson, 1972); e) fuel additives, <0.003-2.71 $\mu\text{g}/\text{ml}$; and f) motor oils, <0.004-0.08 $\mu\text{g}/\text{ml}$ (R. J. Jungers, unpublished data, 1973).

Mobile Sources. Manganese compounds have been increasing in use in select mobile source fuels principally as a smoke inhibitor reduction technique. Such a compound was introduced in 1958 as a supplemental antiknock material for use with tetraethyl lead. At the present time, this additive (methylcyclopentadienyl manganese tricarbonyl) is receiving attention as a tetraethyl lead substitute for use in the limited lead/phosphorous fuel required by EPA regulations (Federal Register, Jan. 10, 1973) by July 1, 1974. Current use of this additive is about one million pounds per year, principally as a smoke suppressant in residual oil-fired stationary power plants, stationary gas turbines, and aircraft turbine overhaul facilities. Current use in gasoline is very limited. Present mobile source, gasoline fueled, exhaust particulate studies suggest that manganese exhaust particulate is very similar in size distribution and percent emitted versus burned in the fuel, to lead exhaust particulate. Thus, the mass median equivalent diameter should be 0.1-1.0 micron. Exhaust manganese particulate is principally Mn_3O_4 with traces of Mn_2O_3 present. Current data suggests that none of the parent manganese compound is exhausted. If usage of this additive were increased to include 50 percent of the gasoline used in the U. S. at the concentration of 0.25 g Mn/gal, this would produce an increase of <1.0 $\mu\text{g}/\text{m}^3$ of manganese in urban air based on the assumption that manganese and lead emissions would be proportionate.

Waste Disposal. Disposal of waste products may contribute to the manganese contamination of local water sources. Few cases of manganese contamination of soil have been reported. Such contaminants would result primarily from fertilizers, fly ash, and mine effluents.

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5. ENVIRONMENTAL EXPOSURE LEVELS

5.1 Levels in Air, Water and Food

5.1.1 Air. Few attempts have been made to evaluate the impact of major manganese sources on the ambient air in the immediate vicinity of these sources. Practically all data relating to the extent of manganese pollution have been acquired from studies aimed at the general definition of the nature and extent of air pollution on a national or in a few instances on a local scale. The number of major sources is relatively small, thus restricting somewhat the areas expected to have high levels of manganese in the air. Smaller sources are widespread, consequently,

manganese would be expected to be present as a common pollutant in most atmospheres. The major portion of manganese emitted is in the smaller particles which favor its wide distribution over considerable distances (Sullivan, 1969).

Manganese in Suspended Particulate Matter. Beginning in 1957, samples of suspended particulate matter collected at some 300 urban and 30 nonurban sites have been analyzed for trace metals, including manganese (U. S. EPA, 1957-1968). A summary of the 1000 station years of data for urban and nonurban sites from 1957-1969 categorizes the sites into four different concentration ranges. Annual average manganese concentrations were: $<0.099 \mu\text{g}/\text{m}^3$ for 80.4% of the sites; $0.100-0.199 \mu\text{g}/\text{m}^3$ for 11%; $0.200-0.299 \mu\text{g}/\text{m}^3$ for 4%; and $>0.300 \mu\text{g}/\text{m}^3$ for 4.7%. All nonurban and a majority of urban sites fall into the lowest concentration interval. Since the national average urban concentration is well below $0.20 \mu\text{g}/\text{m}^3$, which is quite low when compared to the TLV of $5 \text{mg}/\text{m}^3$ for occupational exposures, most of the attention should be directed at those sites appearing in the highest concentration interval because they represent maximum environmental exposures. Cities having annual average manganese concentrations of $0.50 \mu\text{g}/\text{m}^3$ or more have been identified for further study. The presence on this list of Johnstown, Pennsylvania, Charleston, West Virginia, and Niagara Falls, New York is to be expected as all are known to have ferromanganese or silicomanganese industries in the immediate areas. The high levels in Canton, Ohio and Gary, Indiana are no doubt related to the use of manganese products in the local steel industries. Sources of the high levels found in Philadelphia, Pennsylvania, Lynchburg, Virginia and Knoxville, Tennessee have not been discovered. Available data do not provide an adequate base for drawing valid conclusions with respect to trends in ambient manganese concentrations.

Manganese measurements were included as part of a comprehensive air pollution study of the Kanawha River Valley in the vicinity of Charleston, West Virginia and provided evidence of high manganese concentrations (U. S. EPA, 1970). The study report offers no clear explanation of the

elevated manganese levels found but it is quite obvious that the major source was the ferromanganese plant in a nearby area with additional contributions from a large coal-burning industrial steam-generation plant in the same general area. The impact of these sources on the surrounding area was clearly shown by both the ambient air and settled dustfall data. The fall and winter ambient air data dramatically demonstrated that with favorable topography and meteorologic conditions, one strong source can exert an influence over a distance of many miles. Residents of the nearby communities have the highest manganese exposures documented to date (the annual averages range from 0.60 to 1.33 $\mu\text{g}/\text{m}^3$). These Kanawha Valley data represent the only documented single source study done in the United States.

Brar, et al. (1970) measured particulate matter collected on April 4, 1968 at 22 sampling stations distributed over the Chicago area. Concentrations of manganese on this particular day ranged from 0.10 to 0.90 $\mu\text{g}/\text{m}^3$ in the city with an overall average of 0.45 $\mu\text{g}/\text{m}^3$. The highest concentrations were found in the Loop and the industrialized southeastern areas. The results of this single day sampling indicated that Chicago's average manganese pollution ranks in the upper 5 percent of the nation's urban areas.

Air Particulate Manganese Size Distribution. Lee, et al. (1972) have determined the concentration of trace metals in quarterly composites of the different particle size range samples collected in six large U. S. urban areas. This study demonstrated quite clearly that at least 50 percent of the mass of suspended manganese was associated with particles having a Stokes equivalent diameter of three micrometers or less and that approximately 80 percent of the manganese was found in the respirable (<5 μm) particle size range. These findings are in agreement with reports which indicate that much of the manganese emitted into the atmosphere is associated with particles in the 0.1 to 5.0 micrometer range.

Manganese from Mobile Source Emissions. The use of manganese containing compounds in fuels is not very widespread at the present time

but may become more significant with the possible substitution of manganese compounds for tetraethyl lead as a primary fuel additive. The Ethyl Corporation, apparently the sole producer of the current manganese compounds used as fuel additives, has estimated that if these manganese compounds are used as a supplement in 50 percent of the gasoline used in the U. S., the most this would add to urban air would be 0.05 to 0.2 $\mu\text{g Mn per m}^3$. An indication of the significance of emission levels of manganese from mobile sources as compared to that from foundries of the iron and steel industry can be seen by the manganese concentrations in the urban air of selected cities for the same year. The country's three largest urban centers have average Mn levels of: New York, 0.03 $\mu\text{g/m}^3$; Los Angeles, 0.03 $\mu\text{g/m}^3$; and Chicago, 0.07 $\mu\text{g/m}^3$. Cities with major foundry facilities closeby show significantly higher Mn levels: Pittsburgh, 0.22 $\mu\text{g/m}^3$; Birmingham, 0.30 $\mu\text{g/m}^3$; and East Chicago, 0.28 $\mu\text{g/m}^3$. (U. S. EPA, 1957-1968).

5.1.2 Water. The manganese content of fresh water consists of dissolved and suspended manganese. In the U. S., most studies of the manganese in fresh water have determined the total amount of manganese in the sample. The surface waters of eight Wisconsin lakes were found by Juday, et al. (1938) to contain between 3 and 23 $\mu\text{g Mn per liter}$. A more recent study by Kleinkopf (1960) of surface waters from lakes in Maine revealed concentrations varying from 0.02 to 87.5 $\mu\text{g Mn per liter}$ and a mean concentration of 3.8 $\mu\text{g Mn per liter}$. Analysis of river water by Wiebe (1930) showed 80 to 120 $\mu\text{g Mn per liter}$ in the Mississippi at Fairport, Iowa. The median manganese concentration of 52 samples from 15 large U. S. rivers was 20 $\mu\text{g Mn per liter}$ (Durum and Hoffty, 1961). The concentration of manganese dissolved in sea water has been reported by Turekion (1969) to vary between 0.4 and 10.0 $\mu\text{g/liter}$ in accordance with his review of numerous studies. Manganese in the public water supplies of the hundred largest U. S. cities ranges from 0.0 to 2.5 mg/liter for treated water. A U. S. Public Health Service study of 969 community water supplies found a maximum concentration of 1.32 mg/liter

of manganese at the consumer's tap. Of course these maximum values occurred infrequently. However, 211 of 2595 samples exceeded the drinking water standard of 0.05 mg Mn per liter.

Kroner and Kopp (1965) reported the manganese concentrations in six major U. S. water systems (Ohio River, Colorado River, Missouri River, Mississippi River, Columbia River, and Great Lakes) to range from 3 to 50 µg Mn per liter. Based upon these values, and assuming a daily water consumption of two liters, the daily ingested dose of manganese from drinking water would range from 6 to 100 µg per day.

5.1.3 Food. The manganese content of various foodstuffs varies markedly as indicated below for major categories:

Category	Range of Mn (µg/g, wet weight)
Grains and cereals	1.2 - 30.8
Dairy products and eggs	0.0 - 1.9
Meat and poultry	0.0 - 0.8
Fish and seafood	0.0 - 0.2
Fruit	0.2 - 4.7
Nuts (edible part only)	0.4 - 35.1
Vegetables	0.2 - 7.8
Fats and oils	0.0 - 5.0

a) Table derived from Peterson and Skinner (1931).

5.2 Occupational Exposure

Only small segments of the population are exposed to manganese levels in excess of the current U. S. TLV of 5 mg/m³ for air (occupational) or the drinking water standard of 50 µg/liter. These population segments occur in the vicinity of manganese mining and refining operations or near production facilities for ferromanganese, steel, aluminum, copper, alloys and voltaic cells.

Inhalation appears to be the major route of absorption in cases of occupational intoxication in man, although absorption through the skin has been reported. Excessive exposures have resulted in chronic manganism, primarily a disease of the central nervous system, following exposure to high concentrations of manganese dust for only a few months. Chilean manganese miners exposed to an atmosphere containing approximately

5000 particles/m³ developed manganism in an average of 178 days. Exposure to manganese polluted atmospheres can also result in manganic pneumonia, a form of lobar pneumonia unresponsive to treatment with antibiotics (Rosenstock, et al., 1971; Whitlock, et al., 1966). The threshold or average dose of manganese causing manganic pneumonia is not known. Man-made pollution, particularly that related to steel industries and the mining of manganese ore, represent potential toxic hazards to those persons working in uncontrolled areas.

5.3 Requirement and Effective Human Exposure

Manganese is classed as an essential trace element in all living things and is quite ubiquitous in its distribution in nature. It is required for normal bone formation and serves a major function as a coenzyme in various metabolic processes, primarily in the mitochondria. However a recommended dietary allowance has not been established for man.

The daily intake of manganese for non-occupationally exposed individuals will vary widely depending primarily upon the diet. Intake from food is much greater than that via inhalation from air or the ingestion of water. Average dietary intake of manganese ranges from 3 to 7 mg per day of which approximately 10 percent is absorbed through the gastrointestinal tract. Manganese uptake from the lung is more efficient than through the gastrointestinal tract by a factor of about three. Manganese absorption through the gastrointestinal tract is correlated with the available iron and iron balance in the body. When adequate iron is available manganese uptake is minimal and when inadequate iron is available manganese uptake is increased. The daily background dose of manganese as estimated by Schroeder, et al. (1966) is as follows: a) inhalation, 2.0 µg; b) water ingestion, 5.0 µg; c) food ingestion, 3000 µg; for a total daily manganese intake of 3007 µg.

It should be noted that although the average intake of manganese from inhalation is small in comparison to food, in the cases of occupational exposure, inhalation appears to be the major route of absorption.

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6. ENVIRONMENTAL DISTRIBUTION AND TRANSFORMATION

6.1 General

Once better sampling techniques and more sensitive analysis techniques become available, a transport model should be developed to describe the global distribution of manganese. The main function of the model would be to provide a mass balance for manganese in order that the emission of these substances into the environment can be related to the various transformations that they undergo and to their ultimate fate. While the major paths by which manganese enters the environment are known, definite measures of the total loss of manganese by the various escape routes is unknown.

Considering the air pollution sources and size distribution of manganese, the prevailing winds will be the main transport mechanism. Therefore, these particles will be deposited on land or water by gravitational settling and diffusion, washout, or rainout. If these mechanisms are dominant, the half life of manganese containing particles in air will depend greatly on size and the amount of atmospheric precipitation. Another transport mechanism to be investigated is re-entrainment of dust and soil into the atmosphere. No data are available at this time to show the significance of this mechanism. Another mechanism to consider is runoff into fresh water and sea water.

6.2 Environmental Transformation and Removal

Once transport mechanisms have been developed for manganese, it will be necessary to determine the ultimate fate of the degradation products in order to model this pollutant. The following transformation and removal processes (sinks) should be considered for manganese.

6.2.1 Dissolution in Fresh Water and Sea Water. All water contains manganese derived from soil and rocks. Sea water manganese is found mostly as MnO_2 , some of which is produced by several genera of bacteria common to soils and ocean muds and which precipitate manganese oxides from manganese salts.

6.2.2 Rainout and Washout. On the basis of atmospheric precipitation sampling for six metals at 32 widespread stations in the United States, Laxrus, et al. (1969) concluded that manganese in atmospheric precipitation was derived primarily from human activity. These precipitate samples yielded an average manganese concentration of 0.012 ppm. The overall data indicate the widespread prevalence of manganese in the air over the whole of the United States. Because the majority of the stations were at relatively isolated sites with respect to major industrial areas, the data do not show the immediate influence of major sources.

6.2.3 Runoff into Fresh Water and Sea Water. Lagerwerff (1967) identified the following five possible sources of soil contamination: aerosols, pesticides, limestone and phosphate fertilizers, manures and sewage sludge, and mine waste: all of which can add to the manganese burden of fresh waters and sea water. Durfor and Becker (1964) state that the concentration of manganese in natural water is generally 0.20 ppm or less, but that ground water and acid mine water may contain more than 10 ppm. The manganese content of reservoir water that has "turned over" may be more than 150 ppm. The average manganese concentration of the untreated surface waters calculated by Laxrus, et al. (1970) from data Durfor and Becker was 0.07 ppm.

6.2.4 Microbiological Utilization in the Soil. Manganese cycles in the soil have been proposed. In these cycles divalent manganese is transformed through biological oxidation to the less available trivalent form and later through dismutation, the Mn^{+++} form is reduced biologically to Mn^{++} . Zajic (1969) states that a dynamic equilibrium exists between all forms. The oxidizing power of higher oxides increases with acidity, therefore, reduction by organic matter is more likely at low pH values. If the oxygen tension is low, biological reduction can take place at any pH value. Bacterial oxidation is very slow or absent in very acid soils and Mn^{++} predominates and organic matter can reduce the higher oxides. In alkaline soils, the divalent form nearly disappears; bacterial oxidation is rapid and reduction by organic matter is slow. In well aerated soils above a pH of 5.5, soil microorganisms can oxidize the divalent form rapidly. The rates of exchange between the various forms is not known at the present time. Manganese exhibits a very pronounced seasonal variation. This is probably due to oxidation and reduction induced by microbial action. Summer seems to favor the manganous form and winter the manganic form though the opposite is said to be true in alkaline soils.

6.2.5 Metabolism and Bioconcentration. Manganese is classified as an essential mineral for man and animals and occurs in minute concentrations in the cells of all living things. Tissue concentrations of manganese average from 0.2 to 0.3 $\mu\text{g/g}$ wet tissue. Those mammalian tissues showing high levels of manganese are bone (3.3 $\mu\text{g/g}$), liver (2.5 $\mu\text{g/g}$), pituitary (2.5 $\mu\text{g/g}$), pancreas (1.9 $\mu\text{g/g}$), and kidney (1.2 $\mu\text{g/g}$). Under average environmental concentrations of manganese, terrestrial mammals concentrate available manganese up to a factor of 10; whereas, fish and marine plants concentrate it by a factor of 100 and 100,000 times respectively.

6.2.6 Uptake by Soil and Plants. Plants apparently absorb manganese primarily in the divalent state. Lowering the soil pH or reducing the soil aeration by flooding or compaction favors the reduction of manganese to the Mn^{++} and thereby increases its solubility and

availability to plants. Heavy fertilization of acid soils without liming (particularly with materials containing chlorides, nitrates, or sulfates) may also increase manganese solubility and availability. The availability of soil manganese is closely related to the activities of microorganisms that alter pH and oxidation-reduction potentials. Under some conditions of pH and aeration, the addition of organic compounds to soil can increase the chemical reduction of manganese and its uptake by plants. The capacity of plants for absorbing manganese varies according to species. For example, in twenty different species of flowering plants, some had a capacity for absorbing manganese which was 20 to 60 times greater than those with the lowest capacity for absorbing the element.

6.3 Photochemical and/or Thermal Reactions in the Lower Atmosphere

Sulfur dioxide, emitted into the atmosphere in the presence of sunlight and water vapor, is converted to sulfur trioxide and then to sulfuric acid. The presence of ammonia or some metallic compounds, including those of manganese, are capable of promoting this reaction (Coughanowr and Krause, 1965; Matteson, et al., 1969; McKay, 1971; Ethyl Corp., 1971). The unanswered questions seem to be related to the degree of concentration of manganese required to do this and the significance of its effect. The available evidence seems to support the contention that a higher concentration of atmospheric manganese than normally observed would be necessary.

Manganese dioxide reacts with nitrogen dioxide, in the laboratory, to form manganous nitrate (Schroeder, 1970), which is toxic (Sax, 1963). There is the possibility of such a reaction occurring in the atmosphere. Much more work in this area is needed before any conclusion can be reached.

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7. PHYSIOLOGICAL AND BIOCHEMICAL FACTORS

7.1 General

Much of the understanding of chronic manganese poisoning is based upon the investigations of Cotzias and co-workers on manganese metabolism including absorption, excretion, turnover rates, and tissue profiles of manganese documented in extensive reviews on the subject (Cotzias, 1958, 1962). Ingested manganese is absorbed through an unknown mechanism of intestinal transport and is concentrated in the liver where it is conjugated with bile salts and is excreted into the intestine. A small percentage, however, is reabsorbed via the enterohepatic circulation and is transported in the plasma in its trivalent form by a B₁ globulin, known as transmanganin.

Manganese is under the regulatory control of the adrenal gland. In work done on manganese disappearance from the whole body using radioactive labelled MnCl₂, Mahoney and Small (1968) showed that the biological half-life of manganese is influenced by several factors among them being: the intake of manganese, state of iron storage, and hemoglobin concentration. They also identified slow and fast components to the manganese disappearance curves from the total body in normal subjects which had respectively 39 and 4 day time lengths. Thus, in summary, the normal metabolism is such that the absorbed metal is concentrated in the liver where it becomes localized in the mitochondria. Although some excess metal may be distributed to the tissues, most is discharged into the bile or excreted via other gastrointestinal routes thereby keeping the manganese profile among various tissues relatively stable.

Skeletal structures, hair, liver, pancreas, and kidney contain concentrations of manganese that are characteristic for the tissues, but vary little among species. Other tissues are reported to contain lower concentrations. Within the cell, the highest concentrations of manganese are in the mitochondria. Generally, organs and tissues do not accumulate large concentrations of manganese.

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8. TOXICOLOGICAL EFFECTS

8.1 General

Several toxicological studies, utilizing experimental animals, have been included in Section 9, since they serve to substantiate observations from the human.

Although manganese deficiency has been extensively investigated, the toxicity of manganese has not been so thoroughly studied. In this section, the dosages and routes of exposure used in a few of the animal studies are given to illustrate manganese toxicity in animals. Baxter, et al. (1965) studied the effects of acute manganese excess in rats by giving $MnCl_2$ subcutaneously in doses of 50 to 1500 mg/kg body weight. Analysis of blood samples at four hours showed increases in hemoglobin, hematocrit, and mean corpuscular volume, as well as serum chloride, phosphorous and magnesium after a dose of 150 mg/kg body weight. Serum calcium and iron were markedly decreased. Maximum response in hematocrit and hemoglobin was induced by 170 to 300 mg/kg and measurable response occurred at 50 mg/kg. Anisocytosis, basophilic stippling and hypochromia of red cells were noted in peripheral blood smears. Necrotic changes in hepatic tissues

were seen at 18 hours following injection of 170 mg/kg or more. There was also an apparent increase in iron content of spleen and liver at 48 hours after injection of 300 mg/kg.

8.2 Liver Involvement in Mn Poisoning

An example of an animal study implicating the liver in the pathogenesis of manganese encephalopathy was done by Witzleben (1969). Rats were dosed with manganese at the rate of 53 to 60 mg/kg body weight and showed that an acute manganese overload causes a rapid and marked decrease in the ability of the liver to clear bilirubin into the bile. He also noted the rapid development of ultrastructural changes characteristically found in many instances of cholestasis. While there are several mechanisms that could be responsible for the reduced bilirubin clearance, he found that reduction in the bile flow rate was present 4 hours after acute manganese overload.

8.3 Mechanisms

Much of the clarification and supporting evidence for the pathophysiology of manganese toxicity was derived from animal studies. Faubye (1970) has clarified the biochemistry of chronic manganese poisoning which appears to be centered upon a decrease in dopamine content of the corpus striatum following a lesion of the nigrostriatal pathway. Several biochemical alterations have been described following such a lesion. The striatal dopamine concentration is decreased (Faull and Laverty, 1969; Poirier and Soukes, 1965), as is its synthesis from L-dopa (Poirier, et al., 1967) and its conversion to homovanillic acid (HVA), its main metabolite (Sharman, et al., 1967). Furthermore, its synthesis from its precursors is also diminished (Poirier, et al., 1969). Levill, et al. (1965) have shown that tyrosine hydroxylase is the rate limiting step in catecholamine and hence dopamine synthesis. Rech, et al. (1966) showed that alpha-methyl tyrosine does inhibit tyrosine hydroxylase activity with a consequent decrease in catecholamine levels in brain stem, caudate nucleus, heart, and spleen. Serotonin was not affected. More recently,

Dairman and Udenfriend (1971) reported that L-dopa administration in rats resulted in a decrease in adrenal tyrosine hydroxylase activity. Hughes, et al. (1966) had also implicated the adrenal gland as a structure involved in chronic manganese poisoning. Dairman and Udenfriend also reported that norepinephrine in the brain was increased due to bypassing the rate limiting step of catecholamine biosynthesis.

Maynard and Cotzias (1955) have shown that manganese accumulates in organs rich in mitochondria and is selectively concentrated within mitochondria. Shimizu and Morikawa (1957) have described the pallidum and striatum as having an abundance of oxidative enzymes. It is quite evident that manganese can affect oxidative enzyme systems whose integrity is needed to continue to supply energy needed for the degradation and synthesis of the various catecholamines that function in synaptic transmission. Mandell and Spooner (1968) have shown that alteration of these compounds may influence behavior when the initial psychiatric phase of chronic manganese poisoning is considered. Von Euler (1965) has shown that some enzymes involved in the biosynthesis of catecholamines, including tyrosine hydroxylase, require oxygen. Furthermore, mechanisms of transport and compartmentalization of the essential compounds require energy, usually in the form of ATP. ATP also provides energy for the active transport of Na^+ and K^+ in maintaining the ionic gradients that establish the resting membrane potential and action potential necessary for neuronal transmission. Decompensation of these processes which are highly sensitive to tissue hypoxia would profoundly alter neural mechanisms and give rise to clinical symptomatology.

Sutherland, et al. (1968) have demonstrated that different biogenic amines have varying capabilities for increasing the production of cyclic-AMP. This relationship between biogenic amines and cyclic-AMP has been clarified by further studies. Cotzias (1969) was among the first to point out the possible relationship between catecholamines, cyclic-AMP and manganese. Using rat liver they observed that the elevation of the intracellular 3', 5'-cyclic-AMP induced by catecholamines, like dopamine,

was accompanied by an impressive intracellular accumulation of manganese. Bentley (1967), in a study of neurohypophyseal hormones in isolated toad bladder, showed that Mn^{++} uncouples processes linking the interaction of oxytocin with the formation of cyclic-AMP, thus, inhibiting the hormone's effect. It was suggested that manganese may cause inhibition of adenylyl cyclase in the membrane of the receptor cell leading to decreased formation of cyclic-AMP. This study provides a good introduction to the area of neuroendocrinology and hypothalamic factors involved in autonomic dysfunction seen in processes such as Parkinson's disease and chronic manganese poisoning.

8.4 Molecular Level Effect

Kornberg (1966) has mentioned that the process such as genetic recombination might be affected by manganese via its influence on enzymes that control DNA structure and metabolism. The subcellular structure of ribosomes is dependent upon divalent cations, usually magnesium, but manganese can be substituted for both the binding of the two ribosomal subunits as well as the binding of M-RNA to the whole ribosome.

8.5 Organic Manganese Compounds

Hysell, et al. (1973) conducted studies with rats to determine the morphologic changes and tissue concentrations of manganese following oral exposure to methylcyclopentadienyl manganese tricarbonyl (MMT). Dosages varied from 15 to 150 mg/kg body weight. All deaths occurred within six days after exposure and by 14 days, the survivors appeared normal. The $LD_{50}/14$ days was 58 mg MMT/kg body weight. The manganese concentrations in tissues from animals dying after exposure was dose dependent and rather high. At 14 days post ingestion, the manganese concentrations has decreased to approximately the normal range. There was no way to determine if the observed toxicity was related to the intact MMT molecule or to some metabolite of the compound. It is apparent, however, that this was not an acute manganese toxicity since acute toxicity occurs at much higher dosage levels than were used and the pattern of hepatic lesions is markedly different. The presence of high levels of manganese in the tissues along with histopathological changes suggest that the manganese was transported there as

a metabolic product of the MMT. In addition, the finding of high levels of manganese in organs which normally have a low manganese content support this hypothesis. Other investigators have reported an acid metabolite in urine following exposure to MMT.

Moore, et al. (1973) conducted studies using rats to investigate the metabolic aspects of MMT. The MMT used in this study was prepared and labeled with radioactive ^{54}Mn . The tissue distribution of manganese among the organs of the rat after a single oral dose of MMT followed a pattern similar to that reported by Schroeder (1970) for the normal distribution of manganese except for the high concentration found in the lung and to a lesser extent in abdominal fat. It was also shown that the retention of manganese was similar following the administration of equal loads of manganese in the form of MMT or MnCl_2 . An additional group of rats was given a tracer level (0.2 $\mu\text{g Mn}$) and the biological half-life compared favorably with the 10 to 15 day half-life reported by Mahoney and Small (1968). Although the retention of manganese was similar for both MMT and MnCl_2 , the route of excretion was different. Following the intravenous administration of MnCl_2 , the manganese was excreted via the feces and only a trace was found in the urine. After MMT administration, manganese was excreted both in the feces and urine. The fate of the MMT molecule, following absorption is not known. Data from these experiments indicate that the metabolism of manganese given as a constituent of MMT is different from that in the form of MnCl_2 . The high levels of manganese in the urine following administration of MMT appear to indicate that either MMT or some organic manganese metabolite of MMT is transported to the kidney where it is further metabolized and inorganic manganese eliminated in the urine. Other sites of MMT metabolism have not been identified, however, evidence from these studies suggests that the liver may be an important site.

The toxicologic effects of exhaust gas from engine combustion of MMT using rats has shown no effects due to manganese exhaust products. Further studies are in progress to more fully assess the problem.

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9. EPIDEMIOLOGICAL AND CLINICAL STUDIES

9.1 Occupational

Manganese poisoning is a hazard in the mining and processing of manganese ores and in the use of manganese alloys in the steel and chemical industries. One principal source is high speed drilling which produces a large amount of manganese dioxide. This, coupled with poor ventilation provides the setting for most of the cases of chronic manganese poisoning reported in the literature although other sources are known. Over 400 cases of chronic manganese poisoning have been described and the clinical symptomatology has been the subject of several reviews and numerous case reports. Chronic manganese poisoning can result after exposure to high concentrations of manganese dust for only a few months although exposure is usually 2 to 3 years. Manganese may be absorbed by inhalation, ingestion, or through the skin, but most effects result from prolonged inhalation. Damage produced is reversible if the patient is removed from exposure, but evidently a sensitivity can develop since persons who have recovered seem to be prone to contracting the illness again. Onset usually occurs after 2 to 3 years of continuous exposure and is characterized by a slow progressive course. Cotzias (1958) has

described three phases: the prodromal period, the intermediate or psychiatric phase, and the period of severe neurological disorders. Another significant aspect of chronic manganese poisoning is marked individual susceptibility since many miners are exposed to manganese dusts but only a small percentage develop symptoms. Rodier (1955) believed that variations in the excretory capacity of the liver and kidney may lead to the accumulation of toxic levels of manganese. Indeed, liver lesions and a decreased bile flow rate have been reported by Witzleben (1969) and will be reviewed later.

9.2 Clinical Studies

The laboratory diagnosis of chronic manganese poisoning is non-specific and as yet there is no specific diagnostic test although urinary manganese concentrations have some value. The usual urinary concentration is 8 to 10 $\mu\text{g/liter}$ and reflects the general level of exposure to manganese. This measurement, however, does not correlate well with the clinical severity of the symptomatology. Blood levels of manganese provide little clinical information and BUN, fasting blood sugar, enzymes and electrolytes are usually normal. Rodier (1955) mentions diminished excretion of 17-ketosteroids in 81 percent of his patients, a relative increase in lymphocytes and decrease in polymorphonuclear leucocytes in 52 percent. Furthermore, there was an increased basal metabolic rate in 57 percent, and manganese content in hair was decreased in 66 percent of his patients with chronic manganese poisoning. Kesic and Hausler (1954), in reviewing and examining the hematological picture in this condition, found increased hemoglobin values and erythrocyte counts and decreased monocyte counts. Cotzias (1966) reported that cerebrospinal fluid findings are also non-specific but do tend to show slightly increased cells and protein content.

9.3 Pathology

There have only been four documented reports of pathological changes in man. One case reported advanced cirrhosis of the liver and only slight degeneration of brain stem tracts. Another remarked upon the neuronal degeneration in the upper segment of the globus pallidus. A third found

diffuse neuronal degeneration in the cerebral cortex, basal ganglia, and cerebellum, however the basal ganglia were clearly affected the most. One other case reported the frontal and parietal cortex involved with focal softening and neuronal degeneration in the corpus striatum, particularly the globus pallidus. It has also been postulated that a vascular lesion, possibly associated with a functional disturbance of the liver, is involved in the pathogenesis. This concept has been further elucidated by Pentschew (1969) in his review of the role that dyscrasic dysergosis and dysoria play in the development of neuropathological lesions. This relationship between hepatic and cerebral factors was investigated further by Geiger, et al. (1954), who concluded that in the absence of certain hepatic humoral factors, the cells of the CNS become impermeable to glucose.

Pentschew (1963), in rhesus monkeys and other animals, demonstrated that experimental manganese encephalopathy was a good model for the study of hepatic dyscrasic dysergosis. After 3 to 6 weeks, monkeys receiving manganese dioxide intramuscularly, showed diffuse astrocytic proliferation of the hemispheric and cerebellar white matter and most significantly, simultaneously in the globus pallidus (lateral pallidum), substantia nigra, and subthalamic nuclei. Also, characterized by almost complete neuronal degenerations in the medial pallidum and subthalamic nuclei. Furthermore, he noted an increase in the glial population in the field H of Forel, zona incerta and magnocellular portion of the habenular nucleus. Diffuse changes included a proliferation of the neuroglia, accompanied by early gliosis in the mid-brain, pons and medulla. In the cerebral cortex there was slight to moderate proliferation of small glial cells. Of interest was the description of a focal lesion of the hippocampus characterized by neuronal degeneration of the pyramidal layer and a dense astrocytosis. Pentschew states that the neuropathological findings showed such striking similarities with those in human cases of manganese encephalopathy that they could be said to be identical.

Pentschew (1963) did additional work with manganese encephalopathy in the cat and found the pallidum was the usual site of diffuse microglial and lymphocytic infiltration. Also demonstrated was a pseudo-encephalitic tissue syndrome proceeded by a classical spongy degeneration which was thought to be within the conceptual framework of chronic sub-edematous transudation (dysoria). Thus, dysoria (vascular lesions) at the cerebral level may be related to dysfunction in the production and/or transport of hepatic humoral factors that have yet to be identified.

Many of the symptoms of chronic manganese poisoning are similar to Parkinson's disease and both have as the basis of their symptomatology abnormal functioning of the extrapyramidal system. Klawans (1970) states that both Parkinson's disease and chronic manganese poisoning have as their basis unantagonized, cholinergic excitation of the corpus striatum secondary to decreased dopaminergic inhibitory input following a lesion of the nigrostriatal tract.

9.4 Interacting Factors

9.4.1 Manganese and Iron Metabolism. Alstatt, et al. (1968) have shown that manganese and iron metabolism are closely related. The high degree of individual susceptibility of miners to chronic manganese poisoning has resulted in attempted explanations by several investigators on the basis of nutritional deficiencies, specifically iron deficient anemia. Mena, et al. (1969) state there is a proportionality between the intestinal absorption of iron and manganese in man and animals in which the gastrointestinal tract is the main portal of entry into the blood as a result of inhaled manganese. Furthermore it has been shown that anemia leads to an increased absorption of both iron and manganese. Chronic exposures to high levels of manganese causes increased hemoglobin values and erythrocyte counts indicating that manganese stimulates erythrocytic activity. This is further clarified in that recovery from secondary nutritional anemia is much prompter following the administration of FeSO_4 and MnCl_2 than with FeSO_4 alone, thus demonstrating the relationship between the manganese effect on

erythrocytosis and its intestinal absorption in anemic individuals. It is well known that iron deficiency anemia will induce erythrocytic activity, however, it has also been shown that non-anemic individuals who have been exposed to manganese dust over a long period of time show an increase in erythrocytic activity.

9.5 Treatment

Treatment of chronic manganese poisoning has recently undergone a basic change reflecting the better understanding of the pathophysiology of the condition. Early attempts using various chelating agents, most specifically EDTA, were of conflicting benefit but did seem to be able to produce some improvement in the condition if treated in its early phase when presumably neuronal destruction had not yet occurred. After structural neurological injury, no improvement could be expected. The results of Penalver (1955) and Tepper (1961) confirm this and they regard the treatment as ineffective. Whitlock, et al. (1966) reported that treatment with intravenous calcium-EDTA mobilized body deposits of manganese as evidenced by increased urinary manganese levels and led to improvement in muscle strength and coordination in 2 to 3 months after treatment. Wynter (1962) had poor results with EDTA in seven cases in the advanced phase but encouraging results in one patient with early symptoms. The essentially negative results with chelating agents has its basis in the fact that increased levels of tissue manganese that would be amenable to such treatment were found only in healthy actively working miners while crippled ex-miners had apparently cleared the manganese loads they once had but did not show any improvement in their neurological picture (Cotzias, et al., 1968). Without any tissue levels remaining to be cleared in the later stages of the disease, chelating agents could hardly be expected to have any beneficial effects except for early cases.

Recognizing that a similar biochemical defect was present in Parkinson's disease, Mena, et al. (1970) used a large amount of L-dopa in six patients. Five showed reduction or disappearance of rigidity

and hypokinesia, and a regaining of the sense of balance. The sixth patient had adverse effects with L-dopa administration but did respond favorably to 5-hydroxytryptophane, a precursor of serotonin. This favorable result was based on the observation that the muscle hypotonia, sometimes present in chronic manganese poisoning but hardly ever found in Parkinsonism, is based upon a low serotonin level in the striatum. Evidence that further implicates serotonin in the condition was demonstrated by Goldstein, et al., 1969 and Poirier, et al. (1966). Dopamine exerts its tremorigenic effect by competing with serotonin for the same receptors which suggests that tremor production is associated with a lowering of serotonin or a change in the ratio of serotonin to dopamine in the striatum. Cotzias (1969) has commented upon the treatment with L-dopa and aspects of it which must be considered further. He brings up the possibility of methionine or choline deficiency resulting from their donation of methyl groups needed for the metabolism of L-dopa as homovanillic acid.

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10. DOSE RESPONSE RELATIONSHIPS

The paucity of material related to this area has been covered generally in Sections 8 and 9.

11. MAXIMUM PERMISSIBLE LEVELS AND ACTIONS

11.1 Maximum Levels

It is generally accepted that the American Conference of Governmental Industrial Hygienists (ACGIH) recommended ceiling value of 5 mg/m^3 carries a low margin of safety for those occupationally exposed. The lowest average concentration at which a case of chronic manganese poisoning was found was 30 mg/m^3 . This was in a manganese mill; the worker was exposed to manganese dioxide dust. Lower exposures produced cases in several steel plants in which workers were exposed to manganese fumes (Whitlock, et al., 1969; Tanaka and Lieben, 1969). Individual susceptibility plays an important role.

The present United States water standard for manganese is 0.05 mg/liter. Presently there are no ambient air quality or stationary or mobile source emission standards for manganese.

11.2 Elimination of Exposures

11.2.1 Control Actions. Occupational chronic manganese poisoning can be controlled if certain preventive measures are taken. These include frequent periodic examinations of all individuals that are exposed to manganese in their work. Individuals, when applying for work in a mine, should be screened for the presence of conditions that might predispose

to manganese toxicity. Such conditions include hepatic and renal disease, blood dyscrasias, organic lesions of the central nervous system, and progressive pulmonary disease. Individual protection measures have been documented by Wynter (1962). They include initial and periodic medical examinations, transfer of individuals who have liver or lung disease to areas of less exposure, and hygienic measures to ensure cleanliness among workers including changing clothes after each shift.

11.2.2 Non-specific Control. Technical measures should be directed mainly toward the drilling and crushing of ores. Dry drilling of blast holes and blasting itself cause dust clouds which remain suspended in the air for long periods of time. Thus, it would be advantageous to blast at the end of the shift so that the men would be out of the mine when the manganese concentration is most intense. Ventilation should be present to remove the dusts, and water spraying should be available to keep the dust down.

11.2.3 Control Devices. The emission of manganese particulates will most likely be controlled at the same time and by the same particulate control equipment that is used on the steel furnaces. There is no assurance, however, that manganese emissions will be reduced proportionately with other particulate emissions due to the high percentage of fine manganese (<1 μm) particulates. Control of manganese from steel furnaces is accomplished by various types of collectors, including electrostatic precipitators, high-efficiency wet scrubbers, and fabric filters. Four physical factors make the dust collection economically difficult: the small particle size (as low as 0.01 μm), the large volume of gas, the high gas temperature, and the low value of the recovered material. Control of emissions from a ferromanganese blast furnace is more difficult than from other furnaces because the waste gas temperature is hotter and the particulate is finer. Electrostatic precipitators have been successful in removing 80 to 90 percent of the particulates. No economical way of using the collected particulate has been developed. The control level, using open hearth sources as an

example, is currently about 40 to 50 percent for all particulate emission control, which would mean about 35 to 45 percent control for manganese emissions.

11.2.4 Manganese Fuel Additives. Hazardous manganese fuel additives may create problems associated with mobile sources as well as stationary sources. Control of emissions from burning fuels containing antiknock and smoke inhibiting additives may require special systems. The hazards of these organic manganese additives are yet to be identified and quantified.

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12. COMMENTS ON THE NATIONAL DATA

The United States national contribution represents a selective and interpretive summary of the U. S. EPA draft task force report on "manganese".

Based upon the presently available data, it is strongly recommended that additional research be initiated to more adequately assess the biological aspects and the transport of manganese in the environment. Most important is the determination of the minimum nutritional requirements, and the safe level of exposure to ensure against adverse effects upon human health and the environment. There currently is no evidence which indicates that exposure to manganese at the levels normally observed in the ambient atmosphere results in adverse health effects; however, the problem has not

been investigated extensively. Concentrations in the immediate vicinity of major sources, during unfavorable meteorological conditions, may reach a level which might prove to be biologically significant. Occupational exposure to manganese is a special problem not generally germane to the problem of ambient air quality.

Current U. S. research includes the following:

1) The determination of manganese in ambient air over the urban and nonurban stations of the U. S. National Air Surveillance Network. Some effort is being expended on the definition of the manganese content of particulate emissions from selected sources but no concurrent work is being done to define the impact of such sources on the adjacent environment.

2) Under EPA sponsorship, the Institute for Medical Research, Yugoslav Academy of Sciences and Arts, is evaluating human exposure to and effects from the emissions of a large ferromanganese plant at Sibenik on the Dalmation coast. Special attention is being given to respiratory and nervous system effects. This study should provide some information on significant exposure levels in ambient air.

3) Studies are underway to investigate the teratologic and pathologic effects, in utero neurochemical and behavioral effects, and in vitro bioenergetic aspects of exposure to manganese.

4) Experimental animal toxicological inhalation studies are being conducted using automotive emissions resulting from fuels containing organic manganese compound additives.

5) Additional research and development of fine particulate control devices and demonstration of improved particulate control systems, including the removal of trace metals.

Recommendations for Additional Research

1) Develop standard methods of sampling and measurement for inorganic and organic manganese compounds.

2) Establish and conduct a quality control program on environmental sample analyses to ensure monitoring comparability.

3) Develop a stationary source test program for particulate emissions by particle size and chemical element analysis of the sized fractions. Determine source to receptor relationships.

4) Conduct a fuel/fuel additive surveillance program to monitor trace element composition; characterize products of combustion, their impact upon the environment and their biological effects.

5) Conduct a toxicological screening test system for particulate emissions including perimeter monitoring to evaluate toxic effects of ambient air particulates attributed to a known source.

6) Investigate the catalytic role of manganese in the conversion of sulfur dioxide to sulfate in the atmosphere.

7) Determine the nutritional requirement of manganese for man and acceptable general population and occupational exposure levels.