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Project Summary

Health Assessment Document for Manganese

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The Office of Health and Environmental Assessment of the Office of Research and Development, Environmental Protection Agency (EPA), has prepared a Health Assessment Document (HAD) for manganese at the request of the Office of Air Quality Planning and Standards (OAQPS). Manganese is one of several metals and associated compounds emitted to the ambient air that are currently being studied by the EPA to determine whether they should be regulated as hazardous air pollutants under the Clean Air Act. This HAD is designed to be used by OAQPS for decision making.

In the development of the current assessment document, the scientific literature has been inventoried, key studies have been evaluated and summaries and conclusions have been directed at qualitatively identifying the toxic effects of manganese. Observed effect levels and dose-response relationships are discussed in order to identify the critical effect and to place adverse health responses in perspective with observed environmental levels.

This Project Summary was developed by EPA's Office of Health and Environmental Assessment, Environmental Criteria and Assessment Office, Cincinnati, OH, to announce key findings of the research project that is fully documented in a separate report of the same title (see Project Report ordering information at back).

Introduction

This assessment document is based on original publications, although the overall knowledge covered by a number of reviews and reports was also considered. The references cited were selected to reflect current knowledge on those issues that are most relevant for a health assessment of manganese in the environment.

The rationale for structuring this document is based primarily on two major issues, exposure and response. The first portion of the document is devoted to manganese in the environment: physical and chemical properties, the monitoring of manganese in various media, natural and human-made sources, the transport and distribution of manganese within environmental media, and the levels of exposure. The second part is devoted to biological responses in laboratory animals and humans, including metabolism, pharmacokinetics, mechanisms of toxicity, as well as toxicological effects of manganese.

General Properties and Background Information

Manganese is a ubiquitous element in the earth's crust, in water and in particulate matter in the atmosphere. In the ground state, manganese is a gray-white metal resembling iron, but harder and more brittle. Manganese metal forms numerous alloys with iron, aluminum and other metals.

There are numerous valence states for manganese, with the divalent form giving the most stable salts and the tetravalent form giving the most stable oxide. The chlorides, nitrates and sulfates of manganese are highly soluble in water, but the oxides, carbonates and hydroxides are only sparingly soluble. The divalent compounds are stable in acid solution but are readily oxidized in alkaline conditions. The heptavalent form is found only in oxy-compounds.

Sources of Manganese in the Environment

Manganese is the twelfth most abundant element and fifth most abundant metal in the earth's crust. While manganese does not exist free in nature, it is a major constituent in at least 100 minerals and an accessory element in >200 others. Its concentration in various crustal components and soils ranges from near zero to 7000 μg/g, depending on the nature of the rock or soil. Crustal materials are an important source of atmospheric manganese due to natural and anthropogenic activities (e.g., agriculture, transportation, earth-moving), which generate suspended dusts and soils. The resulting aerosols consist primarily of coarse particles (>2.5 μm).

Manganese is also released to the atmosphere by manufacturing processes. Ferromanganese furnace emissions are composed mainly of fine particulate (<2.5 μm) with a high manganese content (15-25%). Ferroalloy manufacture was the largest manganese emission source in 1968. Control technology has improved and production volume has diminished, so, although current estimates are not available, levels are probably lower. Iron and steel manufacture is also an important manganese source. Manganese content of emitted particles is lower (0.5-8.7%), but overall production volume is greater than for manganese-containing ferroalloys.

Fossil fuel combustion also results in manganese release. The manganese content of coal is 5-80 μg/g. Fly ash is about equal to soil in manganese content (150-1200 μg/g) but contains particles finer in size. This is an important manganese source because of the volume of coal burned each year. Combustion of residual oil is less important because of its lower manganese content. About 15-30% of manganese derivatives combusted in gasoline are emitted from the tailpipe.

The relative importance of emission sources influencing manganese concentration at a given monitoring location can be estimated by chemical mass balance studies. Studies in St. Louis and Denver suggest that crustal sources are more important in the coarse than in the fine aerosol fraction. Conversely, combustion sources such as refuse incineration and vehicle emissions predominantly affect the fine fraction. In an area of steel manufacturing, the influence of this process is seen in both the fine and coarse fractions.

Another means of determining the influence of noncrustal sources is to compare the ratio of manganese and aluminum in an aerosol with that in soils. The derived enrichment factor (EF) indicates the magnitude of influences from noncrustal sources. In most areas, the EF for coarse aerosols in near unity, indicating crustal origin, but the EF for the fine fraction is substantially higher, indicating a greater influence from noncrustal sources of emission.

Environmental Fate and Transport Processes

A general overview of man's impact on the geochemical cycling of manganese shows a nearly doubled flux from the land to the atmosphere due to industrial emissions, and a tripled flux from land to oceans, by rivers, due to soil loss from agriculture and deforestation.

Atmospheric manganese is present in several forms. Coarse dusts contain manganese as oxides, hydroxides, or carbonates at low concentrations ($\leq$ 1 mg Mn/g). Manganese from smelting or combustion processes is often present in fine particles with high concentrations of manganese as oxides (up to 250 mg/g). Organic manganese usually is not present in detectable concentrations.

Oxides of manganese are thought to undergo atmospheric reactions with sulfur dioxide or nitrogen dioxide to give the divalent sulfate or nitrate salts. Manganous sulfate has been shown to catalyze SO_2 transformation to sulfuric acid, but the manganese concentration necessary for a significant catalytic effect has been disputed.

In water or soil, manganese is usually present as the divalent or tetravalent form. Divalent manganese (present as the hexaquo ion) is soluble and relatively stable in neutral or acidic conditions. Chemical oxidation to the insoluble tetravalent form takes place only at a pH above 8 or 9, and chemical reduction of the tetravalent form occurs only at pH <5.5. At intermediate pH, interconversion occurs only by microbial mediation.

Manganese tends to be mobile in oxygen-poor soils and in the groundwater environment. Upon entering surface water, manganese is oxidized and precipitated, primarily by bacterial action. If the sediments are transported to a reducing environment such as a lake bottom, however, microbial reduction can occur, causing re-release of divalent manganese to the water column.

Environmental Levels and Exposures

Nationwide air sampling has been conducted in some form since 1953. Analytical methodology has improved and monitoring stations have changed, complicating any analysis of trends in manganese concentration. However, it is evident that manganese concentrations in ambient air have declined during the period of record. The arithmetic mean manganese concentration of urban samples was 0.11 $\mu g/m^3$ in 1953-1957, 0.073 $\mu g/m^3$ in 1966-1967, and decreased to 0.033 $\mu g/m^3$ by 1982. In 1953-1957, the percentage of urban stations with an annual average of >0.3 $\mu g/m^3$ was ~10%. By 1969 these had dropped to <4%, and since 1972 the number has been <1%.

The highest manganese concentrations, with some observations exceeding 10 $\mu g/m^3$, were seen in the 1960s in areas of ferromanganese manufacture. More recent measurements in these areas indicated that decreases of at least an order of magnitude had occurred, although definitive studies were not available.

In most cases where comparable data on total suspended particulate (TSP) were available, decreases in TSP also occurred but were usually smaller in magnitude than those for manganese. This would suggest that the observed reductions in manganese were more than a simple reflection of TSP improvements, indicating specific reductions of manganese emissions.

Biological Role

Although manganese has been shown to be essential for many species of animals, as yet there are no well-defined occurrences of manganese deficiency in humans. Manganese deficiency has been demonstrated in mice, rats, rabbits and guinea pigs. The main manifestations of manganese deficiency are those associated with skeletal abnormalities, impaired growth, ataxia of the newborn, and defects in lipid and carbohydrate metabolism. Although the daily requirement of manganese for development and growth has not been adequately studied, it was accepted that diets containing 50 mg/kg manganese are adequate for most of the laboratory animals.

Synergistic/Antagonistic Factor

It is generally accepted that under normal conditions 3-4% of orally ingested manganese is absorbed in man and other mammalian species. Gastrointestinal absorption of manganese and iron may be competitive. This interaction has a limited relevance to human risk assessment under normal conditions. However, it does lead to the hypothesis that iron-deficient individuals may be more sensitive to manganese than the normal individual.

Evidence is accumulating that during mammalian development manganese absorption and retention are markedly increased giving rise to increased tissue accumulation of manganese.

Manganese does penetrate the blood-brain barrier and the placental barrier. Studies in animals indicate a higher manganese concentration in suckling animals, especially in the brain.

Acute Exposure

The average LD_{50} observed in different animal experiments indicates that the oral dose values range from 400-830 mg Mn/kg of soluble manganese compounds, much higher than the 38-64 mg Mn/kg for parenteral injection. The toxicity of manganese varies with the chemical form in which it is administered to animals. Acute poisoning by manganese in humans is very rare. It may occur following accidental or intentional ingestion of large amounts of manganese compounds. Along with a number of other metals, freshly formed manganese oxide fumes have been reported to cause metal fume fever.

Chronic Exposure

Chronic manganese poisoning, a neurologic syndrome also known as manganism, results from occupational exposures to manganese dusts, sometimes after only a few months of exposure. Manganism begins with a psychiatric disturbance followed by a neurologic phase resembling Parkinson's disease, and has been well described in the literature with clinical details. It has been reported in workers in ore crushing and packing mills, in the production of ferroalloys, in the use of manganese alloys in the steel industry and in the manufacture of dry cell batteries and welding rods. Very high concentrations of manganese have been found in mines where cases of manganism were reported. The manganese air concentration in the immediate vicinity of rock drilling in Moroccan mines was ~450 mg/m³ in one mine and ~250 mg/m³ in another. In two reports from Chilean mines, the air concentrations of manganese varied from 62.5-250 mg/m³ and from 0.5-46 mg/m³, respectively. Earlier studies in miners reported advanced cases of manganism, but more recent studies report neurological symptoms and a few signs where the exposure was at much lower concentrations. This may reflect either a different chemical form and particle size of the inhaled manganese or a straight dose-response effect. The inconsistencies in clinical examination make it difficult to compare across studies.

The full clinical picture of chronic manganese poisoning is reported less frequently at exposure levels below 5 mg/m³. Studies reporting effects at the above levels describe signs or symptoms that cannot be definitely attributed to manganese. Tremor at rest has been reported as the major effect on workers in an electrode plant exposed to 2-30 µg/m³ (0.002-0.03 mg/m³), although duration of exposure was not fully detailed. The prevalence of a few signs in workers exposed to 0.3-5 mg/m³ and 0.4-2.6 mg/m³ suggest that the effects may occur at exposures as low as 0.3 mg/m³ (300 µg/m³). The data available for identifying effect levels below this level is equivocal or inadequate. There is no clear-cut evidence of chronic manganese poisoning under 5 mg/m³. This is further complicated by the fact that good biological indicators of manganese exposure are not presently available. Consequently, studies directed toward clearly defining the dose-effect relationship will undoubtedly facilitate a more realistic estimate of the risk to developing manganism.

A high incidence of pneumonia and other respiratory ailments has been reported in workers with occupational exposure to manganese and in inhabitants living around factories manufacturing ferromanganese or manganese alloys. The increased incidence of pulmonary disease found in exposure to low concentrations of manganese is not necessarily directly attributable to manganese itself. Manganese exposure may increase susceptibility to pneumonia or other acute respiratory diseases by disturbing the normal mechanism of lung clearance.

Some reported animal studies imply a carcinogenic potential for manganese, but the data are inadequate to support this conclusion. No epidemiologic information relating manganese exposure to cancer occurrence in humans has been located. Using the International Agency for Research in Cancer criteria, the available evidence for manganese carcinogenicity would be rated inadequate for animals and "no data available" for humans.

The broad exposure ranges, the incomplete descriptions of chemical form and particle size are insufficient to relate response to exposure characteristics. In order to obtain definitive dose response data, a cohort study is needed, including documented clinical examinations, more accurate exposure characterization, and exposure data on individuals. All members of the cohort should be followed for neurological signs for at least 20 years with clear reporting of any lost data.

Existing Guidelines, Recommendations and Standards

In the United States, the American Conference of Governmental and Industrial Hygienists has recommended a 5 mg/m³ as both the time-weighted average threshold limit value (TWA-TLV) and the short-term exposure limit for manganese in air. This value is based on observations of poisoning in humans at concentrations near or above the recommended TLV. The National Institute for Occupational Safety and Health has not recommended an occupational criterion for exposure to airborne manganese, and the Occupational Safety and Health Administration has not promulgated a standard for manganese exposure. Occupational air standards in some other countries, as summarized by the International Labor Office, are as follows:

Country	mg/Mn/m³	Comment
Belgium	5	Ceiling value
Czechoslovakia	2	Ceiling value
	6	
Japan	5	
Poland	0.3	
Roumania	1	Ceiling value
	3	
Switzerland	5	Ceiling value
USSR	0 3	

The World Health Organization (WHO) recommends a criterion of 0.3 mg/m³ for respirable manganese in occupational exposures.

No toxicity-based criteria for standards for manganese in freshwater have been proposed. The WHO, the U.S. Public Health Service, and the U.S. EPA recommended a concentration of 0.05 mg/l in water to prevent undesirable taste and discoloration. In the USSR, the recommended maximum permissible concentrations is 0.1 mg/l. The recommendation is intended to prevent the discoloration of water.

For marine waters, the U.S. EPA has recommended a criterion for manganese of 0.1 mg/l for the protection of consumers of marine mollusks. Although the rationale for this criterion is not detailed, it is partially based on the observation that manganese can bioaccumulate by factors as high as 12,000 in marine mollusks.

Summary and Conclusions

Manganese is an essential element for humans and animals. The concentration of manganese present in individual tissues, particularly in the blood, is controlled after ingestion by homeostatic mechanisms and remains remarkably constant despite rapid fluctuations in intake. The main routes of absorption are the gastrointestinal and respiratory tracts. Acute poisoning by manganese may occur in exceptional circumstances where large amounts of manganese compounds are ingested or inhaled. Freshly formed manganese oxide fumes of respirable particle size can cause metal fume fever but are not believed to cause permanent damage. The most pronounced toxic effects of manganese are a central nervous system syndrome known as chronic manganese poisoning (manganism) and manganese pneumonitis.

While manganism and its association with manganese has been well described, a dose-response relationship in man cannot be evaluated because duration of exposure is not well documented. Also, early signs of the disease were sought in only a few studies in humans and none of the reported studies employed a standard cohort design (e.g., there was no follow-up or comprehensive characterization of the exposed populations).

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The complete report entitled "Health Assessment Document for Manganese," (Order No. PB 84-229954; Cost: $30.95, subject to change) will be available only from:

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