

## Linus Pauling Institute

Micronutrient Research for Optimum Health



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### Manganese

Manganese is a mineral element that is both nutritionally essential and potentially toxic. The derivation of its name from the Greek word for magic remains appropriate, because scientists are still working to understand the diverse effects of manganese deficiency and manganese toxicity in living organisms [\(1\)](#).

#### Function

Manganese (Mn) plays an important role in a number of physiologic processes as a constituent of multiple [enzymes](#) and an activator of other enzymes [\(2\)](#).

#### Antioxidant function

Manganese superoxide dismutase (MnSOD) is the principal [antioxidant](#) enzyme in the [mitochondria](#). Because mitochondria consume over 90% of the oxygen used by cells, they are especially vulnerable to [oxidative stress](#). The superoxide radical is one of the [reactive oxygen species](#) produced in mitochondria during [ATP](#) synthesis. MnSOD [catalyzes](#) the conversion of superoxide radicals to hydrogen peroxide, which can be reduced to water by other antioxidant enzymes [\(3\)](#).

#### Metabolism

A number of manganese-activated [enzymes](#) play important roles in the [metabolism](#) of [carbohydrates](#), [amino acids](#), and [cholesterol](#) [\(4\)](#). Pyruvate carboxylase, a manganese-containing enzyme, and phosphoenolpyruvate carboxykinase (PEPCK), a manganese-activated enzyme, are critical in [gluconeogenesis](#)— the production of glucose from non-carbohydrate precursors. Arginase, another manganese-containing enzyme, is required by the liver for the urea cycle, a process that detoxifies ammonia generated during amino acid metabolism [\(3\)](#). In the brain, the manganese-activated enzyme, glutamine synthetase, converts the amino acid glutamate to glutamine. Glutamate is an [excitotoxic](#) neurotransmitter and a precursor to an inhibitory neurotransmitter, gamma-aminobutyric acid (GABA) [\(5, 6\)](#).

#### Bone development

Manganese deficiency results in abnormal skeletal development in a number of animal species. Manganese is the preferred [cofactor](#) of [enzymes](#) called glycosyltransferases; these enzymes are required for the synthesis of [proteoglycans](#) that are needed for the formation of healthy [cartilage](#) and bone [\(7\)](#).

#### Wound healing

Wound healing is a complex process that requires increased production of [collagen](#). Manganese is required for the activation of prolylase, an [enzyme](#) that functions to provide the [amino acid](#), proline, for collagen formation in human skin cells [\(8\)](#). A genetic disorder known as prolylase deficiency results in abnormal wound healing among other problems, and is characterized by abnormal manganese [metabolism](#) [\(7\)](#). Glycosaminoglycan synthesis, which requires manganese-activated glycosyltransferases, may also play an important role in wound healing [\(9\)](#).

## Nutrient interactions

### **Iron**

Although the specific mechanisms for manganese absorption and transport have not been determined, some evidence suggests that iron and manganese can share common absorption and transport pathways [\(10\)](#). Absorption of manganese from a meal decreases as the meal's iron content increases [\(7\)](#). Iron supplementation (60 mg/day for four months) was associated with decreased blood manganese levels and decreased MnSOD activity in white blood cells, indicating a reduction in manganese nutritional [status](#) [\(11\)](#). Additionally, an individual's iron status can affect manganese [bioavailability](#). Intestinal absorption of manganese is increased during iron deficiency, and increased iron stores (ferritin levels) are associated with decreased manganese absorption [\(12\)](#). Men generally absorb less manganese than women; this may be related to the fact that men usually have higher iron stores than women [\(13\)](#). Further, iron deficiency has been shown to increase the risk of manganese accumulation in the brain [\(14\)](#).

### **Magnesium**

Supplemental magnesium (200 mg/day) has been shown to slightly decrease manganese [bioavailability](#) in healthy adults, either by decreasing manganese absorption or by increasing its excretion [\(15\)](#).

### **Calcium**

In one set of studies, supplemental calcium (500 mg/day) slightly decreased manganese [bioavailability](#) in healthy adults. As a source of calcium, milk had the least effect, while calcium carbonate and calcium phosphate had the greatest effect [\(15\)](#). Several other studies have found minimal effects of supplemental calcium on manganese [metabolism](#) [\(16\)](#).

## Deficiency

Manganese deficiency has been observed in a number of animal species. Signs of manganese deficiency include impaired growth, impaired reproductive function, skeletal abnormalities, [impaired glucose tolerance](#), and altered [carbohydrate](#) and [lipid metabolism](#). In humans, demonstration of a manganese deficiency syndrome has been less clear [\(2, 7\)](#). A child on long-term [total parenteral nutrition](#) (TPN) lacking manganese developed bone demineralization and impaired growth that were corrected by manganese supplementation [\(17\)](#). Young men who were fed a low-manganese diet developed decreased serum [cholesterol](#) levels and a transient skin rash [\(18\)](#). Blood calcium, phosphorus, and alkaline phosphatase levels were also elevated, which may indicate increased [bone remodeling](#) as a consequence of insufficient dietary manganese. Young women fed a manganese-poor diet developed mildly abnormal glucose tolerance in response to an intravenous (IV) infusion of glucose [\(16\)](#). Overall, manganese deficiency is not common, and there is more concern for toxicity related to manganese overexposure (see [Safety](#)).

## The Adequate Intake (AI)

Because there was insufficient information on manganese requirements to set a Recommended Dietary Allowance ([RDA](#)), the Food and Nutrition Board (FNB) of the Institute of Medicine set an adequate intake level ([AI](#)). Since overt manganese deficiency has not been documented in humans eating natural diets, the FNB based the AI on average dietary intakes of manganese determined by the Total Diet

Study—an annual survey of the mineral content of representative American diets (4). AI values for manganese are listed in the table below in milligrams (mg)/day by age and gender. Manganese requirements are increased in pregnancy and lactation (4).

<b>Adequate Intake (AI) for Manganese</b>			
<b>Life Stage</b>	<b>Age</b>	<b>Males (mg/day)</b>	<b>Females (mg/day)</b>
Infants	0-6 months	0.003	0.003
Infants	7-12 months	0.6	0.6
Children	1-3 years	1.2	1.2
Children	4-8 years	1.5	1.5
Children	9-13 years	1.9	1.6
Adolescents	14-18 years	2.2	1.6
Adults	19 years and older	2.3	1.8
Pregnancy	all ages	-	2.0
Breast-feeding	all ages	-	2.6

### **Disease Prevention**

Low dietary manganese or low levels of manganese in blood or tissue have been associated with several chronic diseases. Although manganese insufficiency is not currently thought to cause the diseases discussed below, more research may be warranted to determine whether suboptimal manganese nutritional [status](#) contributes to certain disease processes.

#### **Osteoporosis**

Women with [osteoporosis](#) have been found to have decreased [plasma](#) or [serum](#) levels of manganese and also an enhanced plasma response to an oral dose of manganese (19, 20), suggesting they may have lower manganese status than women without osteoporosis. Yet, a more recent study in postmenopausal women with and without osteoporosis did not find any differences in plasma levels of manganese (21). A study in healthy postmenopausal women found that a [supplement](#) containing manganese (5 mg/day), copper (2.5 mg/day), and zinc (15 mg/day) in combination with a calcium supplement (1,000 mg/day) was more effective than the calcium supplement alone in preventing spinal bone loss over a two-year period (22). However, the presence of other trace elements in the supplement makes it impossible to determine whether manganese supplementation was the beneficial agent for maintaining [bone mineral density](#).

#### **Diabetes mellitus**

Manganese deficiency results in [glucose](#) intolerance similar to [diabetes mellitus](#) in some animal species, but studies examining the manganese [status](#) of diabetic humans have generated mixed results. In one study, whole blood manganese levels did not differ significantly between 57 diabetics and 28 non-diabetic controls (23). However, urinary manganese [excretion](#) tended to be slightly higher in 185 diabetics compared to 185 non-diabetic controls (24). A case-control study of 250 diabetic and non-diabetic individuals found that type 2 diabetic individuals had higher serum manganese levels than non-diabetics (25). However, a more recent study in 257 type 2 diabetics and 166 non-diabetic controls found lower blood levels of manganese in the diabetic patients (26). Additionally, a study of functional manganese status found the activity of the [antioxidant enzyme](#), MnSOD, was lower in the white blood cells of diabetics than in non-diabetics (27). Neither 15 mg nor 30 mg of oral manganese improved glucose tolerance in diabetics or non-diabetic controls when given at the same time as an oral glucose

challenge (28). Although manganese appears to play a role in glucose [metabolism](#), there is little evidence that manganese supplementation improves glucose tolerance in diabetic or non-diabetic individuals.

## Epilepsy (seizure disorders)

Manganese deficient rats are more susceptible to [seizures](#) than manganese sufficient rats, and rats that are genetically prone to [epilepsy](#) have lower than normal brain and blood manganese levels. Certain subgroups of humans with epilepsy reportedly have lower whole blood manganese levels than non-epileptic controls. One study found blood manganese levels of individuals with epilepsy of unknown origin were lower than those of individuals whose epilepsy was induced by [trauma](#) (e.g., head injury) or disease, suggesting a possible genetic relationship between epilepsy and abnormal manganese metabolism. While manganese deficiency does not appear to be a cause of epilepsy in humans, the relationship between manganese metabolism and epilepsy deserves further research (7, 29).

## Sources

### Food sources

In the U.S., estimated average dietary manganese intakes range from 2.1-2.3 mg/day for men and 1.6-1.8 mg/day for women. People eating vegetarian diets and Western-type diets may have manganese intakes as high as 10.9 mg/day (4). Rich sources of manganese include whole grains, nuts, leafy vegetables, and teas. Foods high in phytic acid, such as beans, seeds, nuts, whole grains, and soy products, or foods high in oxalic acid, such as cabbage, spinach, and sweet potatoes, may slightly inhibit manganese absorption. Although teas are rich sources of manganese, the [tannins](#) present in tea may moderately reduce the absorption of manganese (15). Intake of other minerals, including iron, calcium, and phosphorus, have been found to limit retention of manganese (4). The manganese content of some manganese-rich foods is listed in milligrams (mg) in the table below. For more information on the nutrient content of foods, search the [USDA food composition database](#) (30).

Food	Serving	Manganese (mg)
Pineapple, raw	1/2 cup, chunks	0.77
Pineapple juice	1/2 cup (4 fl. oz.)	0.63
Pecans	1 ounce (19 halves)	1.28
Almonds	1 ounce (23 whole kernels)	0.65
Peanuts	1 ounce	0.55
Instant oatmeal (prepared with water)	1 packet	0.99
Raisin bran cereal	1 cup	0.78-3.02
Brown rice, cooked	1/2 cup	1.07
Whole wheat bread	1 slice	0.60
Pinto beans, cooked	1/2 cup	0.39
Lima beans, cooked	1/2 cup	0.49
Navy beans, cooked	1/2 cup	0.48
Spinach, cooked	1/2 cup	0.84
Sweet potato, cooked	1/2 cup, mashed	0.44
Tea (green)	1 cup (8 ounces)	0.41-1.58
Tea (black)	1 cup (8 ounces)	0.18-0.77

## Breast Milk and Infant Formulas

Infants are exposed to varying amounts of manganese depending on their source of nutrition. Manganese concentrations in breast milk, cow-based formula, and soy-based formula range from 3-10 mcg/liter, 30-50 mcg/liter, and 200-300 mcg/liter, respectively. However, [bioavailability](#) of manganese from breast milk is higher than from infant formulas, and manganese deficiencies in breast-fed infants or toxicities in formula-fed infants have not been reported [\(31\)](#).

## Water

Manganese concentrations in drinking water range from 1 to 100 micrograms (mcg)/liter, but most sources contain less than 10 mcg/liter [\(32\)](#). The U.S. Environmental Protection Agency (EPA) recommends 0.05 mg (50 mcg)/liter as the maximum allowable manganese concentration in drinking water [\(33\)](#).

## Supplements

Several forms of manganese are found in supplements, including manganese gluconate, manganese sulfate, manganese ascorbate, and amino acid [chelates](#) of manganese. Manganese is available as a stand-alone supplement or in combination products [\(34\)](#). Relatively high levels of manganese ascorbate may be found in a bone/joint health product containing chondroitin sulfate and glucosamine hydrochloride (see [Safety](#)).

## Safety

### Toxicity

#### Inhaled manganese

Manganese toxicity may result in multiple [neurologic](#) problems and is a well-recognized health hazard for people who inhale manganese dust, such as welders and smelters [\(1, 4\)](#). Unlike ingested manganese, inhaled manganese is transported directly to the brain before it can be metabolized in the liver [\(35\)](#). The symptoms of manganese toxicity generally appear slowly over a period of months to years. In its worst form, manganese toxicity can result in a permanent neurological disorder with symptoms similar to those of [Parkinson's disease](#), including [tremors](#), difficulty walking, and facial muscle spasms. This [syndrome](#), often called manganism, is sometimes preceded by psychiatric symptoms, such as irritability, aggressiveness, and even hallucinations [\(36, 37\)](#). Additionally, environmental or occupational inhalation of manganese can cause an inflammatory response in the lungs [\(38\)](#). Clinical symptoms of effects to the lung include cough, acute bronchitis, and decreased lung function [\(39\)](#).

#### Methylcyclopentadienyl manganese tricarbonyl (MMT)

MMT is a manganese-containing compound used in gasoline as an anti-knock additive. Although it has been used for this purpose in Canada for more than 20 years, uncertainty about adverse health effects from inhaled exhaust emissions kept the U.S. EPA from approving its use in unleaded gasoline. In 1995, a U.S. court decision made MMT available for widespread use in unleaded gasoline [\(35\)](#). A study in Montreal, where MMT had been used for more than ten years, found airborne manganese levels to be similar to those in areas where MMT was not used [\(40\)](#). A more recent Canadian study found higher concentrations of respirable manganese in an urban versus a rural area, but average concentrations in both areas were below the safe level set by the U.S. EPA [\(41\)](#). The impact of long-term exposure to low levels of MMT combustion products, however, has not been thoroughly evaluated and will require additional study [\(42\)](#).

#### Ingested manganese

Limited evidence suggests that high manganese intakes from drinking water may be associated with neurological symptoms similar to those of Parkinson's disease. Severe neurological symptoms were reported in 25 people who drank water contaminated with manganese, and probably other

contaminants, from dry cell batteries for two to three months (43). Water manganese levels were found to be 14 mg/liter almost two months after symptoms began and may have already been declining (1). A study of older adults in Greece found a high prevalence of neurological symptoms in those exposed to water manganese levels of 1.8-2.3 mg/liter (44), while a study in Germany found no evidence of increased neurological symptoms in people drinking water with manganese levels ranging from 0.3-2.2 mg/liter compared to those drinking water containing less than 0.05 mg/liter (45). Manganese in drinking water may be more [bioavailable](#) than manganese in food. However, none of the studies measured dietary manganese, so total manganese intake in these cases is unknown. In the U.S., the EPA recommends 0.05 mg/liter as the maximum allowable manganese concentration in drinking water (33).

Additionally, more recent studies have shown that children exposed to high levels of manganese through drinking water experience cognitive and behavioral deficits (46). For instance, a cross-sectional study in 142 10-year old children, who were exposed to a mean manganese water concentration of 0.8 mg/liter, found that children exposed to higher manganese levels had significantly lower scores on three tests of intellectual function (47). Another study associated high levels of manganese in tap water with hyperactive behavioral disorders in children (48). These and other recent reports have raised concern over the neurobehavioral effects of manganese exposure in children (46).

A single case of manganese toxicity was reported in a person who took large amounts of mineral [supplements](#) for years (49), while another case was reported as a result of a person taking a Chinese herbal supplement (36). Manganese toxicity resulting from foods alone has not been reported in humans, even though certain vegetarian diets could provide up to 20 mg/day of manganese (4, 32).

### Intravenous manganese

Manganese [neurotoxicity](#) has been observed in individuals receiving [total parenteral nutrition](#), both as a result of excessive manganese in the solution and as an incidental contaminant (50). Neonates are especially vulnerable to manganese-related neurotoxicity (51). Infants receiving manganese-containing TPN can be exposed to manganese concentrations about 100-fold higher than breast-fed infants (31). Because of potential toxicities, some argue against including manganese in parenteral nutrition (52).

### Individuals with increased susceptibility to manganese toxicity

- **Chronic liver disease:** Manganese is eliminated from the body mainly in [bile](#). Thus, impaired liver function may lead to decreased manganese excretion. Manganese accumulation in individuals with [cirrhosis](#) or liver failure may contribute to neurological problems and [Parkinson's disease](#)-like symptoms (1, 34).
- **Newborns:** The newborn brain may be more susceptible to manganese toxicity due to a greater expression of [receptors](#) for the manganese transport protein (transferrin) in developing nerve cells and the immaturity of the liver's [bile](#) elimination system (4).
- **Children:** Compared to adults, infants and children have higher intestinal absorption of manganese, as well as lower [biliary](#) excretion of manganese (46). Thus, children are especially susceptible to any negative, neurotoxic effects of manganese. Indeed, several recent studies in school-aged children have reported deleterious cognitive and behavioral effects following excessive manganese exposure (47, 48, 53).
- **Iron-deficient populations:** Iron deficiency has been shown to increase the risk of manganese accumulation in the brain (14).

Due to the severe implications of manganese [neurotoxicity](#), the Food and Nutrition Board (FNB) of the Institute of Medicine set very conservative tolerable upper intake levels (UL) for manganese; the ULs are listed in the table below according to age (4).

Tolerable Upper Intake Level (UL) for Manganese	
Age Group	UL (mg/day)

Infants 0-12 months	Not possible to establish*
Children 1-3 years	2
Children 4-8 years	3
Children 9-13 years	6
Adolescents 14-18 years	9
Adults 19 years and older	11

\*Source of intake should be from food and formula only.

## Drug interactions

Magnesium-containing antacids and laxatives and the antibiotic medication, tetracycline, may decrease the absorption of manganese if taken together with manganese-containing foods or supplements ([34](#)).

## High levels of manganese in supplements marketed for bone/joint health

Two studies have found that supplements containing a combination of glucosamine hydrochloride, chondroitin sulfate, and manganese ascorbate are beneficial in relieving pain due to mild or moderate [osteoarthritis](#) of the knee when compared to a [placebo](#) ([54, 55](#)). The dose of elemental manganese supplied by the supplements was 30 mg/day for eight weeks in one study ([55](#)) and 40 mg/day for six months in the other ([54](#)). No adverse effects were reported during either study, and blood manganese levels were not measured. Neither study compared the treatment containing manganese ascorbate to a treatment containing glucosamine hydrochloride and chondroitin sulfate without manganese ascorbate, so it is impossible to determine whether the supplement would have resulted in the same benefit without high doses of manganese.

## Linus Pauling Institute Recommendation

The adequate intake ([AI](#)) for manganese (2.3 mg/day for adult men and 1.8 mg/day for adult women) appears sufficient to prevent deficiency in most individuals. The daily intake of manganese most likely to promote [optimum health](#) is not known. Following the Linus Pauling Institute recommendation to take a multivitamin/multimineral supplement containing 100% of the daily values (DV) of most nutrients will generally provide 2 mg/day of manganese in addition to that in foods. Because of the potential for toxicity and the lack of information regarding benefit, manganese supplementation beyond 100% of the DV (2 mg/day) is not recommended. There is presently no evidence that the consumption of a manganese-rich plant-based diet results in manganese toxicity.

## Adults over the age of 50

The requirement for manganese is not known to be higher for older adults. However, liver disease is more common in older adults and may increase the risk of manganese toxicity by decreasing the elimination of manganese from the body (see [Toxicity](#)). Manganese supplementation beyond 100% of the DV (2 mg/day) is not recommended.

## References

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