

# L-Methionine

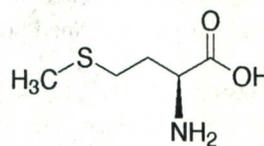
## DESCRIPTION

L-methionine is a protein amino acid. It is classified as an essential amino acid for humans and therefore must be supplied in the diet. According to the Food and Agriculture Organization of the United Nations (FAO) and World Health Organization (WHO), recommended daily L-methionine intake is 13 mg per kg or about one gram daily for adults. Actual intake is higher. This is principally derived from dietary proteins. Rich sources of L-methionine include cheeses, eggs, fish, meat and poultry. L-methionine is also found in fruits and vegetables, but not as abundantly. Small amounts of free L-methionine occur in vegetables, vegetable juices and fermented foods.

In addition to its role as a precursor in protein synthesis, L-methionine participates in a wide range of biochemical reactions, including the production of S-adenosylmethionine (SAM or S-AdoMet), L-cysteine, glutathione, taurine and sulfate. SAM itself, as a methyl donor (see S-AdoMet), is involved in the synthesis of creatine, epinephrine, melatonin and the polyamines spermine and spermidine, among several other substances.

L-methionine is also a glycogenic amino acid and may participate in the formation of D-glucose and glycogen. The ability of L-methionine to reduce the liver-toxic effects of such hepatotoxins as acetaminophen and methotrexate has led to the suggestion that methionine should be added to acetaminophen products. However, there is some recent research suggesting that elevated L-methionine intake may promote intestinal carcinogenesis. This is unclear. Further, one of the metabolites of L-methionine, L-homocysteine, has been implicated as a significant factor in coronary heart disease and other vascular diseases.

L-methionine is a sulfur-containing amino acid that is minimally soluble in water. Its molecular formula is  $C_5H_{11}NO_2S$ , and its molecular weight is 149.21 daltons. L-methionine is also known as 2-amino-4-(methylthio)butyric acid, alpha-amino-gamma-methylmercaptobutyric acid, (S)-2-amino-4-(methylthio)butanoic acid and gamma-methylthio-alpha-aminobutyric acid. It is abbreviated as Met and its one-letter abbreviation is M. The terms L-methionine and methionine are used interchangeably. The D-stereoisomer, D-methionine, does not possess biological activity with regard to protein synthesis and the biochemical reactions mentioned above. However, D-methionine, as well as L-methionine, may possess antioxidant activity. L-methionine is represented by the following chemical structure:



L-methionine

## ACTIONS AND PHARMACOLOGY

### ACTIONS

L-methionine may protect against the toxic effects of hepatotoxins, such as acetaminophen. Methionine may have antioxidant activity.

### MECHANISM OF ACTION

The mechanism of the possible anti-hepatotoxic activity of L-methionine is not entirely clear. It is thought that metabolism of high doses of acetaminophen in the liver lead to decreased levels of hepatic glutathione and increased oxidative stress. L-methionine is a precursor to L-cysteine. L-cysteine itself may have antioxidant activity. L-cysteine is also a precursor to the antioxidant glutathione. Antioxidant activity of L-methionine and metabolites of L-methionine appear to account for its possible anti-hepatotoxic activity. Recent research suggests that methionine itself has free-radical scavenging activity by virtue of its sulfur, as well as its chelating ability.

### PHARMACOKINETICS

Following ingestion, L-methionine is absorbed from the lumen of the small intestine into the enterocytes by an active transport process. Some metabolism of L-methionine takes place within the enterocytes. That which is not metabolized is transported to the liver via the portal circulation. In the liver, L-methionine, along with other amino acids, participates in protein biosynthesis. It may also participate in a wide variety of metabolic reactions, including the formation of S-AdoMet, L-homocysteine, L-cysteine, taurine and sulfate. It can also be metabolized to produce D-glucose and glycogen. L-methionine not metabolized in the liver is transported to the various tissues of the body where it is involved in reactions similar to those described above.

### INDICATIONS AND USAGE

There are no indications for the use of supplemental methionine unless specifically recommended by a physician. It is effective as an antidote in some cases of acetaminophen poisoning. But, because some research suggests that it may promote some cancers, its use as a supplement is inadvisable.

### RESEARCH SUMMARY

When given within 10 hours of acetaminophen poisoning, oral methionine has been found to be as effective as N-acetylcysteine in preventing severe liver damage and death. There is preliminary evidence that methionine might also

help protect against some of the adverse side effects of methotrexate and gentamicin, among others.

On the other hand, high intake of methionine can lead to increased levels of the oxidant homocysteine. There is some fear that high intake of dietary methionine can promote some cancers, and there is some very preliminary experimental data to support that fear. There is also some epidemiological data suggesting a link between increased dietary methionine and increased risk of gastric cancer. More research is needed.

#### CONTRAINDICATIONS, PRECAUTIONS, ADVERSE REACTIONS

##### CONTRAINDICATIONS

L-methionine is contraindicated in those with the genetic disorder homocystinuria. It is also contraindicated in those who are hypersensitive to any component of a methionine-containing product.

##### PRECAUTIONS

L-methionine supplements should be avoided by pregnant women and nursing mothers unless they are prescribed by a physician.

L-methionine supplementation should be avoided by those with neoplastic disease. It should also be avoided by those with elevated homocysteine levels and used with caution in those with coronary heart disease.

Supplemental L-methionine should be used with great caution in those with schizophrenia and those with hepatic and renal failure. In any case, L-methionine supplements should only be used if recommended and monitored by a physician.

##### ADVERSE REACTIONS

Doses of L-methionine of up to 250 mg daily are generally well tolerated. Higher doses may cause nausea, vomiting and headache. Healthy adults taking 8 grams of L-methionine daily for four days were found to have reduced serum folate levels and leucocytosis. Healthy adults taking 13.9 grams of L-methionine daily for five days were found to have changes in serum pH and potassium and increased urinary calcium excretion. Schizophrenic patients given 10 to 20 grams of L-methionine daily for two weeks developed functional psychoses. Single doses of 8 grams precipitated encephalopathy in patients with cirrhosis.

#### INTERACTIONS

##### DRUGS

*Acetaminophen and methotrexate:* L-methionine may decrease hepatic toxicity in those with acetaminophen overdose or in those taking methotrexate. Theoretically, it may decrease hepatic toxicity in the case of other potential hepatotoxic drugs, as well.

*Gentamicin:* Methionine may protect against the ototoxic effects of gentamicin.

#### NUTRITIONAL SUPPLEMENTS

Dietary supplementation with L-methionine was found to decrease glycine levels when given to healthy women on a low-protein diet.

High L-methionine intake in a diet high in salt and nitrites/nitrates may increase the risk of stomach cancer.

#### OVERDOSAGE

There are no reports of overdose.

#### DOSAGE AND ADMINISTRATION

L-methionine supplements should only be taken with a physician's recommendation.

#### LITERATURE

Bellone J, Farelo G, Bartoletta E, et al. Methionine potentiates both basal and GHRH-induced GH secretion in children. *Clin Endocrinol (Oxf)*. 1997; 47:61-64.

Breillot F, Hadida F, Echinard-Darin P, et al. Decreased rat rhabdomyosarcoma pulmonary metastases in response to low methionine diet. *Anticancer Res*. 1986; 76:6299-639.

Duranton B, Freund JN, Galluser M, et al. Promotion of intestinal carcinogenesis by dietary methionine. *Carcinogenesis*. 1999; 20:493-497.

Hladovec J, Sommerova Z, Pisarikova A. Homocysteinemia and endothelial damage after methionine load. *Thrombo Res*. 1997; 88:361-364.

Jones AL, Hayes PC, Proudfoot AT, Vale JA, Prescott LF, Krenzelok EP. Should methionine be added to every paracetamol tablet? *BMJ*. 1997; 315:301-304.

Kroger H, Hauschild A, Ohde M, et al. Nicotinamide and methionine reduce the liver toxic effects of methotrexate. *Gen Pharmacol*. 1999; 33:203-206.

La Vecchia C, Negri E, Franceschi S, Decarli A. Case-control study on influence of methionine, nitrite, and salt on gastric carcinogenesis in northern Italy. *Nutr Canc*. 1997; 27:65-68.

Meakins TS, Persaud C, Jackson AA. Dietary supplementation with L-methionine impairs the utilization of urea-nitrogen and increases 5-L-oxoprolinuria in normal women consuming a low protein diet. *J Nutr* 1998; 128:720-727.

Sha S-H, Schacht J. Antioxidants attenuate gentamicin-induced free radical formation *in vitro* and ototoxicity *in vivo*: D-methionine is a potential protectant. *Hearing Res*. 2000; 142:34-40.

Vale JA, Meredith TJ, Goulding R. Treatment of acetaminophen poisoning. The use of oral methionine. *Arch Int Med*. 1981; 141(3 Spec No):394-396.