

## Risk Assessment

## Magnesium

### General information

#### Chemistry

Magnesium is a metallic element of group 2 of the periodic table and has an atomic weight of 24.3.

#### Natural occurrence

Magnesium is the eighth most abundant element in the earth's crust. It does not occur as a pure metal in nature, but it is found in large deposits as magnesite, dolomite and other minerals. In this risk assessment the word 'magnesium' refers to ionic magnesium, except where specific magnesium salts are described.

#### Occurrence in food, food supplements and medicines

Magnesium is ubiquitous in foods, but the content varies substantially. Leafy vegetables, as well as grains and nuts, generally have a higher magnesium content (60-2700 mg/kg) than meats and dairy products (less than 280 mg/kg). A number of magnesium salts are used as food additives. Magnesium salts are also used in food supplements at levels providing up to 750 mg/day, and licensed medicines to treat malabsorption, as a perioperative nutritional support or in special diets, and are included in antacid and laxative formulations.

#### Other sources of exposure

The magnesium content of water is variable. The concentration depends on the region of its source and its manner of storage. 'Hard' water has a higher concentration of magnesium salts.

#### Recommended amounts

COMA has calculated a RNI of 300 mg/day for adult males and 270 mg/day for adult females (COMA, 1991). The RNI for infants and children ranges from 55 to 280 mg/day. An RNI for magnesium during pregnancy was not calculated by COMA.

#### Analysis of tissue levels and magnesium status

Tissue levels of magnesium are determined by atomic spectroscopy.

#### Brief overview of non-nutritional beneficial effects

Dietary magnesium has been claimed to benefit bone health, but further studies are necessary to confirm this suggestion.

There have been clinical trials and case reports of the therapeutic effects of magnesium in potentially life-threatening conditions, such as the cardiac arrhythmia 'torsade de pointes', digitalis toxicity, bronchospasm, alcohol withdrawal syndrome, ischaemic heart disease and myocardial infarction. It has also been suggested that magnesium possibly plays a role in the regulation of blood pressure.

Magnesium salts are effective cathartic agents and are also used in some antacid preparations.

### Function

Magnesium is required as a cofactor for many enzyme systems. It is required for protein synthesis and for both anaerobic and aerobic energy generation and for glycolysis, either indirectly as a part of magnesium-ATP complex, or directly as an enzyme activator. Magnesium plays a multifunctional role in cell metabolism, (particularly at the level of key phosphorylations), and has a critical role in cell division. It has been suggested that magnesium is necessary for the maintenance of an adequate supply of nucleotides for the synthesis of RNA and DNA. Magnesium regulates the movement of potassium in myocardial cells and is also known to act as a calcium channel blocker.

Magnesium is an important element in the metabolism and/or action of vitamin D, and is essential for the synthesis and secretion of parathyroid hormone.

### Deficiency

Magnesium deficiency has been linked to cardiovascular, skeletal, gastrointestinal and central nervous system disorders and to the use of loop diuretics.

Magnesium is essential for the normal function of the parathyroid gland and for vitamin D metabolism. Magnesium depletion markedly disturbs calcium homeostasis, and hypocalcaemia is a common manifestation of moderate to severe magnesium deficiency.

### Interactions

Calcium homeostasis is controlled in part by a magnesium-requiring mechanism, which releases parathyroid hormone. Several magnesium-activated enzymes are inhibited by calcium.

### Absorption and bioavailability

The net absorption of magnesium from the diet is typically approximately 50 percent. High levels of dietary fibre from fruits, vegetables, and grains decrease magnesium absorption. Dietary protein is also known to influence intestinal magnesium absorption.

Magnesium is absorbed along the entire intestinal tract, but the sites of maximal absorption appear to be the distal jejunum and ileum. It has been suggested that absorption occurs by both an unsaturable passive and saturable active transport system. Thus, in both adults and children, the fractional absorption of magnesium is inversely proportional to the amount ingested.

## Distribution

Magnesium is abundant in the body with the largest amounts found in bone. It is also found in a variety of other tissues including muscle, liver, heart and kidneys. In plasma, half of magnesium present is in the ionised form. About 20% is bound to proteins, the remaining 80% is unbound. Most intracellular magnesium is found bound to the endoplasmic reticulum.

## Excretion

Magnesium is excreted primarily in the urine. The extent of urinary excretion, and thereby the homeostasis of magnesium, is influenced by a wide variety of hormones, including calcitonin, thyroxine, glucocorticoids, glucagons and angiotensin. Under normal conditions, the kidney tubule reabsorbs 95% of the filtered load of magnesium and about 5% is excreted in urine.

## Toxicity

### Human data

No adverse effects have been associated with the ingestion of magnesium as a naturally occurring substance in foods. However, adverse effects have been seen with excessive magnesium intake as a consequence of the use of various magnesium salts for pharmacological/medicinal purposes.

The primary manifestation of excessive ingestion of magnesium from non-food sources is osmotic diarrhoea, which is reversible. Magnesium has a well-known cathartic effect and is used in medicines for this purpose.

### Animal data

There are only a limited number of studies on the toxicity of magnesium in animals. Studies on the short-term toxicity of magnesium administered by the intravenous route demonstrated that the LD<sub>50</sub> value in rats is 174 mg/kg bw in females and 206 mg/kg bw in males, and in dogs is in excess of 1200 mg/kg bw, but such data are of no value for this risk assessment. High doses (1000 mg/kg bw/day three times daily) of magnesium sulphate administered subcutaneously in reproductive studies in rats resulted in lower food consumption and decreased body weight gains in the dams and produced delayed differentiation in their pups.

### Carcinogenicity and genotoxicity

Mice given magnesium chloride in the diet for 96 weeks (2% in diet, equivalent to approximately 3000 mg/kg bw/day) exhibited no evidence of compound-related carcinogenicity.

*In vitro* genotoxicity tests were negative for magnesium chloride and magnesium sulphate.

**Dose response**

No relevant data have been identified.

**Mechanism of toxicity**

No relevant data have been identified.

**Vulnerable groups**

No vulnerable groups have been identified.

**Genetic variations**

No genetic variations have been identified.

## Studies of particular importance in the risk assessment

(For full review see <http://www.food.gov.uk/science/ouradvisors/vitandmin/evmpapers> or the enclosed CD)

*Nagy et al., 1988*

No adverse effects were reported in this study in which 20 patients with duodenal ulcers received up to 1200 mg of magnesium per day in the form of an aluminium-magnesium-hydroxycarbonate antacid over a 6-week trial period in a randomised, prospective cross-over clinical trial.

*Marken et al., 1989*

Diarrhoea and other gastrointestinal effects were reported in a number of individuals participating in this randomised double-blind placebo-controlled cross-over study. The dose of magnesium in this study was 470 mg/day (given as 800 mg/day magnesium oxide) for 60 days.

*Zemel et al., 1990*

This study investigated the effect of magnesium supplementation on blood pressure, erythrocyte cation metabolism and serum lipid levels in 13 patients with mild hypertension. The study employed a 3-week placebo run-in period and no adverse effects were reported following a dose of 486 mg magnesium twice daily for three months (given as magnesium aspartate).

*Paolisso et al., 1992*

In this double-blind cross-over study, doses of 393 mg/day magnesium (as magnesium pidolate) were well tolerated by 12 older subjects (mean age 77.8 years) over a 4-week period.

*Bashir et al., 1993*

This was a randomised double-blind placebo-controlled cross-over trial, in which 21 patients with stable congestive heart failure, secondary to coronary heart disease, received 384 mg magnesium/day (as magnesium chloride) for 6 weeks. Gastrointestinal effects, including diarrhoea, were reported in 6 out of the 21 subjects receiving magnesium.

*Stendig-Lindberg et al., 1993*

No diarrhoea or gastrointestinal effects were reported in a long-term study in which a group of 31 post-menopausal women received daily supplements of magnesium hydroxide (providing up to 750 mg/day magnesium) for 6 months followed by 226 mg/day of magnesium for 18 months.

*Altura et al., 1994*

No adverse effects were reported in 18 healthy 18-38 year old males who were given diets enriched with magnesium oxide for 6 days, providing a daily dose of 452 mg magnesium.

## Exposure assessment

Food:	Mean: 280 mg/day (NDNS 1986/7) 97.5th percentile: 510 mg/day
Drinking water:	100 mg/day (assuming an intake of 2 L/day, estimated from 50 mg/L – EC directives)
Supplements:	750 mg/day (Annex 4)
Estimated maximum intake:	$510 + 100 + 750 = 1400$ mg/day

No potential high intake groups have been identified.

## Risk assessment

The common effect of excessive ingestion of magnesium is osmotic diarrhoea. However, this effect was only observed in a limited number of studies of variable quality.

There are only limited data on the oral and general toxicity of magnesium in animals. The available data suggest a lack of carcinogenicity at doses of up to 3000 mg/kg bw/day. Mutagenicity tests on magnesium salts have also been negative.

### ESTABLISHMENT OF GUIDANCE LEVEL

There are insufficient data to establish a Safe Upper Level for magnesium. Although a few studies reported mild and reversible diarrhoea in a small percentage of patients and healthy volunteers at levels of 384 to 470 mg/day, these symptoms were not observed in the majority of studies using similar or higher doses. For guidance purposes only, 400 mg/day supplemental magnesium would not be expected to result in any significant adverse effects. This is equivalent to 6.7 mg/kg bw/day in a 60 kg adult. An uncertainty factor for human variability is not needed because the value is derived from a number of studies in humans, some of which reported no adverse effects at considerably higher doses. Guidance has not been given for total magnesium since the reported adverse effects are not associated with magnesium in food. The potential implications of this dose range for vulnerable groups such as infants and older people needs to be addressed by further studies.

### References

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