

EXPERT GROUP ON VITAMINS AND MINERALS

REVIEW OF MAGNESIUM

The attached review of magnesium is a slightly revised version of the paper presented to the Expert Group on Vitamins and Minerals at the meetings in June 2001 and in October 2001.

The following annexes are also included:

- Annex 1 Figures and tables referred to in the review paper
- Annex 2 Intakes of magnesium from foods in the UK
- Annex 3 Summary table of selected nutrition related information and existing guidance on intakes

Expert Group on Vitamins and Minerals Secretariat
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MAGNESIUM

Chemistry and Geochemistry

1. Magnesium is a metallic element of group 2 of the periodic table and has an atomic weight of 24.3. Magnesium salts are generally soluble in water.

Natural occurrence

2. 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.

Occurrence in food, food supplements and medicines

Food

3. Magnesium is ubiquitous in foods, particularly those of plant origin, being an essential constituent of chlorophyll; however the magnesium content varies substantially. Leafy vegetables as well as grains and nuts generally have higher magnesium content (6-270 mg/100 g) than meats and dairy products (less than 28 mg/100 g). A number of magnesium salts are used as food additives (JECFA, 1994). These include magnesium chloride, magnesium sulphate, magnesium acetate, magnesium carbonate, magnesium citrate and magnesium hydroxide.

4. Magnesium in multi-vitamin and mineral supplements occurs at levels of 10 to 150 mg (OTC, 2001).

Drinking water

5. Water is a variable source of intake; water with increased "hardness" has a higher concentration of magnesium salts. Since this varies depending on the area from which water comes and the manner in which it is stored, magnesium intake from water is only estimated in controlled diet studies. It has been suggested that magnesium intake can be increased by up to 20% in areas where the domestic water supply is hard (Anderson *et al.*, 1969).

Licensed medicinal products for oral use

6. Magnesium is present in very many products but is only used as a mineral supplement in 15, all of which are multinutrient products. Three may be sold in supermarkets and other retail outlets as dietary supplements, without the supervision of a pharmacist. The highest daily dose of magnesium authorised in General Sales List products is 100 mg. Twelve products can only be sold under the supervision of a pharmacist (without a doctor's prescription). The recommended daily doses for these are up to 360 mg when used in malabsorption, as perioperative nutritional support and for those on special diets. The magnesium is usually the form of the carbonate, sulphate, oxide or hydroxide.

7. Magnesium is also present in many antacids as the hydroxide, carbonate or trisilicate, and in many laxatives as the hydroxide or sulphate.

Intake and exposure

Food

8. Intakes of magnesium in the UK from food and supplements have been provided (see table 3 in Annex 3). Mean intakes in adults aged 16-64 years from all sources are 323 mg/d for males and 237 mg/d for females.

Water

9. The Natural Mineral Water, Spring Water and Bottled Drinking Water (Amendment) (England) Regulations 2001 and The Water Supply (Water Quality) Regulations 2000 will transpose provisions from Directive 98/83/EC, but will not come in to effect until 25 December 2003. These regulations will remove statutory limits for magnesium in all waters (drinking, bottled, mineral and spring). Currently, the limit for magnesium will be 50 mg/l in Drinking Water. On this basis, the consumption of 2 litres of drinking water by an adult as a worst case estimate would provide 100 mg magnesium.

Recommended amounts

10. The Committee on Medical Aspects of Food and Nutrition Policy (COMA) calculated a Reference Nutrient Intake (RNI) of 300 mg/day for adult males and 270 mg/d for adult females. These figures are compatible with recommended dietary intakes in other countries (Dreosti, 1995). COMA derived an increased increment of 50 mg/d for lactation. The RNI for infants and children ranges from 55 to 280 mg/d. A RNI for magnesium during pregnancy was not calculated by COMA.

Analysis of tissue levels and magnesium status

11. Tissue levels of magnesium are determined by atomic spectroscopy. The total body content of magnesium in an average adult is 25 grams; approximately 60% of that is present in bone, 20% is localised to muscle and the remaining 20% is present in soft tissue and liver (Kelepouris and Agus, 1998). It has been estimated that 99% of total body magnesium is present intracellularly. Of the extracellular fluid magnesium, 75% to 80% is unfilterable and 20% is protein bound.

12. Normal plasma concentration of magnesium ranges between 1.7 and 2.1 mg/dl (0.70 to 0.85 mmol/l).

Bioavailability

13. The intestinal absorption of magnesium from food and supplements was studied by Fine *et al.* (1991a). They reported that magnesium from a high-magnesium-containing food source, almonds, was just as bioavailable as from soluble magnesium acetate. In contrast, magnesium absorption from commercially available enteric-coated magnesium chloride was much less than from magnesium acetate, suggesting that enteric coating can impair bioavailability (Ricci *et al.*, 1991).

Interactions

Calcium

14. Magnesium is intimately involved with calcium in metabolism. Calcium homeostasis is controlled in part by a magnesium-requiring mechanism which releases parathyroid hormone. Several magnesium activated enzymes are inhibited by calcium. Hypomagnesaemia induced by starvation, malabsorption syndromes, alcoholism and prolonged diarrhoea is almost always accompanied by hypocalcaemia.

15. In contrast to the marked inhibition of phosphorus absorption Fine *et al.* (1991a) reported that increasing magnesium intake had no effect on the absorption of calcium. However, there was an increase in urinary calcium excretion with increasing magnesium intake and absorption.

16. Intakes of calcium in excess of 2600 mg/day have been reported to decrease magnesium balance (Seeling, 1993). Other studies have reported that high sodium and calcium intakes may result in increased renal magnesium excretion (Kesteloot and Joossens, 1990).

Protein

17. Dietary protein is also known to influence intestinal magnesium absorption; higher protein intakes have been shown to increase renal magnesium excretion (Mahalko *et al.*, 1983). Magnesium absorption is lower when protein intake is less than 30 g/day (Hunt and Schofield, 1969).

Manganese

18. A study where young pigs (N = 8) deficient in magnesium were fed a diet high in manganese (0.95 ± 0.10 mmol Mn/kg) for 5 weeks died following convulsive seizures. This study would suggest that manganese could exacerbate magnesium deficiency and is potentially responsible for a decrease in heart muscle magnesium concentrations. This reduction of magnesium concentrations in the heart may therefore be a contributing factor in the deaths of the pigs fed high manganese (Miller, 1999).

Absorption

Human

18. Magnesium transport into or out of cells appears to require the presence of carrier-mediated transport systems (Romani *et al.*, 1993). The efflux of magnesium from the cell is coupled to sodium transport and requires energy.

19. Magnesium influx also appears to be linked to sodium and bicarbonate transport but by a different mechanism. The molecular characteristics of the magnesium transport proteins have not been fully described.

20. Magnesium transport is influenced by hormonal and pharmacological factors including β -agonists, growth factors and insulin (Romani *et al.*, 1993). The net absorption of dietary magnesium in a typical diet is approximately 50 percent. High levels of dietary fibre from fruits, vegetables, and grains decrease magnesium absorption (Siener and Hesse, 1995).

21. Magnesium is absorbed along the entire intestinal tract, but the sites of maximal magnesium absorption appear to be the distal jejunum and ileum (Kayne and Lee, 1993).

22. In both children and adults, fractional intestinal magnesium absorption is inversely proportional to the amount of magnesium ingested (Kayne and Lee, 1993). Both an unsaturable passive and saturable active transport system for magnesium absorption may account for the higher fractional absorption at low dietary intakes (Fine *et al.*, 1991a).

Animal

23. Absorption of magnesium from the gastrointestinal tract of rats is reported to be in the region of 50% (Verbeek *et al.*, 1993). In Fischer 344 rats, magnesium and calcium absorption were affected by changes in dietary fibre and calcium, but not fat (Watkins *et al.*, 1992).

Distribution and metabolism

24. The administration of radiolabelled magnesium to rats and dogs revealed that the isotope was incorporated in all organs (Ebel and Gunther, 1990). The highest amounts are found in the heart and skeletal muscle. One half of the magnesium content of the body is located in the bones.

25. Magnesium is an important element in vitamin D metabolism and/or action. The secretion of parathyroid hormone is stimulated by low concentrations of magnesium (Targovnik *et al.*, 1971). Magnesium causes hypocalcaemia which also raises parathyroid hormone secretion, but as adequate magnesium is required for parathyroid hormone synthesis and secretion, alterations in parathyroid hormone levels are not consistent (Ryan, 1991).

26. A wide variety of hormones have been implicated in magnesium homeostasis by affecting urinary magnesium excretion, including calcitonin, thyroxine, glucocorticoids, glucagon and angiotensins (Ryan, 1991; Ebel and Gunther, 1980).

Excretion

Human

27. The kidney is the principal organ involved in magnesium homeostasis. Approximately 80% of plasma magnesium is unbound and available for glomerular filtration by the kidney (Kelepouris and Agus, 1998).

28. Under normal conditions, 95% of the filtered load of magnesium is reabsorbed by the kidney and about 5% is excreted in urine. Considerable reabsorption of filtered magnesium is known to occur in the proximal and distal tubules of the kidney.

Animal

29. Animal studies have shown that the recovery of filtered magnesium was 15% in the rat and 8% in dogs; it has been suggested that the main part of reabsorption (55% in rats, 63% in dogs) is localised within the ascending limb of loop of Henle (Ebel and Gunther, 1980)

Function

30. Magnesium is a required 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 (Bronzetti *et al.*, 1995; Food and Nutrition Board, 1997).

31. Magnesium plays a multifunctional role in cell metabolism, particularly at the level of key phosphorylations. The role of magnesium in cell division is also well recognised and it has been suggested that cell division of various cell types is highly dependent on the availability of extracellular magnesium (Rubin, 1975).

32. It has also been suggested that the presence of magnesium is important for maintaining an adequate supply of purine and pyrimidine nucleotides for RNA and DNA synthesis (Rubin, 1975). It is also necessary for sodium potassium-ATPase activity, which is responsible for active transport of potassium (Dørup, and Clausen, 1993). Magnesium regulates the movement of potassium in myocardial cells (Matsuda, 1991) and is also known to act as a calcium channel blocker (Iseri and French, 1984). Thus magnesium depletion is linked to muscle cramps, hypertension and coronary and cerebral vasospasms.

Deficiency

33. Magnesium deficiency has been linked to several disease states involving the cardiovascular, skeletal, gastrointestinal and central nervous systems. The most frequent causes of hypomagnesemia are reduced intake, impaired intestinal absorption, renal loss and genetic diseases.

34. In addition to patients with renal insufficiency, several studies have demonstrated that elderly people have relatively low dietary intakes of magnesium (Goren *et al.*, 1993). It has been suggested that their poor intake may be due to a variety of reasons including, poor appetite, loss of taste and smell, difficulties in shopping and preparing meals. Intestinal absorption of magnesium tends to decrease with ageing and urinary magnesium excretion increases (Lowik *et al.*, 1993)

35. Lowered serum magnesium levels have frequently been reported in athletes after physical activity (Dreosti, 1995). The mechanism underlying the sustained decrease in serum magnesium is unclear, but may involve the hormonal changes associated with prolonged physical activity, which include increased secretion of antidiuretic hormone, aldosterone, catecholamines, thyroid-stimulating hormone and corticosteroids.

36. Magnesium is essential for the normal function of the parathyroid gland, vitamin D metabolism and depletion markedly disturbs calcium homeostasis, and hypocalcemia is a common manifestation of moderate to severe magnesium deficiency (Martini, 1999).

37. Although magnesium deficiency has been linked with muscle weakness in infants, the evidence that this increases sudden infant death (SIDS) in prone sleeping infants is equivocal (Cadell, 2001).

Cardiovascular

37. Magnesium deficiency has been discussed as a possible contributory factor in the development of atherosclerosis, cardiac arrhythmias, myocardial damage and arterial hypertension (Douban and Brodsky, 1995; Tso and Barish, 1992). A number of epidemiological studies have investigated the role of magnesium levels from food and drinking water in relation to cardiovascular disease (reviewed by Marx and Neutra, 1997; Singh *et al.*, 1997; Altura and Altura, 1985; Durlach *et al.*, 1985).

38. Arterial and ventricular premature systoles, arterial fibrillation, and ventricular tachycardia and fibrillation have been reported in magnesium deficient patients (Hollifield, 1987; Rude, 1993).

Skeletal growth and Osteoporosis

39. Magnesium plays a major role in bone and mineral homeostasis and can also directly affect bone cell function as well as influence hydroxyapatite crystal formation and growth (Cohen, 1988). Magnesium influences both matrix and mineral metabolism in bone, and magnesium depletion causes cessation of bone growth, decreased osteoblastic and osteoclastic activity, osteopenia and bone fragility (Sojka, 1995).

40. Recent dietary restriction studies of magnesium in rats have shown reductions in bone magnesium content as well as in aberrant bone turnover (Creedon *et al.*, 1999). This finding was in agreement with other studies which examined the effect of moderate and severe magnesium deprivation on femoral magnesium concentration in the rat (Lerma *et al.*, 1993; Vormann *et al.*, 1997).

41. Significant reductions in the serum magnesium and bone mineral content have been described in several studies of postmenopausal women with osteoporosis (Cohen, 1988; Cohen *et al.*, 1983, Reginster *et al.*, 1989; Cohen and Laor, 1990; Stending-Linberg *et al.*, 1993).

Diabetes Mellitus

42. Magnesium depletion has been shown to result in insulin resistance as well as impaired insulin secretion and thus may make the control of diabetes difficult (Paolisso *et al.*, 1990). One possible cause for the magnesium depletion seen in diabetes is glycosuria-induced renal magnesium wasting (Rude, 1993). However more research is needed to establish whether there is a link between the prevalence of diabetes as a function of magnesium levels.

Overview of reported non-nutritional beneficial effects

43. Magnesium salts are effective cathartic agents (Fine *et al.*, 1991b) and are also used in certain antacid tablets (Ratzan *et al.*, 1980).
44. Dietary magnesium has been observed to be positively associated with bone mineral density in a community-based study in elderly men and women (Tucker *et al.*, 1999). The beneficial effects of supplementation with magnesium have also been studied in women with osteoporosis (Stending-Lindberg *et al.*, 1993; Sojka, 1995). However the rate of bone turnover was not affected in other studies in which dietary magnesium intake was increased by supplementation in healthy young adult females (Doyle *et al.*, 1999).
45. The effect of magnesium supplementation on bone turnover has been investigated in a number of other studies with conflicting findings (reviewed in Martini, 1999). It has been proposed that additional studies are needed to establish whether there is a link between supplementation with magnesium and bone health (Martini, 1999).
46. Clinical trials and case reports have suggested that magnesium is an effective therapeutic agent for potentially life threatening problems such as torsade de pointes, digitalis toxicity, bronchospasm, and alcohol withdrawal (Tso and Barish, 1992). Woods and Fletcher (1994) reported that the mortality rate from ischaemic heart disease was reduced by 21% and all-cause mortality rate reduced by 16% in magnesium (intravenous) treated patients with suspected myocardial infarction.
47. Epidemiologic evidence suggests that magnesium may play an important role in regulating blood pressure (Witteman *et al.*, 1994; Wynn and Wynn, 1987). However, some intervention studies with magnesium therapy for hypertensive patients have produced conflicting results. Several studies have shown a positive blood-pressure-lowering effect of magnesium supplements (Widman *et al.*, 1993; Witteman *et al.*, 1994); others have not (Zemel *et al.*, 1990; Doyle *et al.*, 1999).
48. It has been suggested that magnesium may have anti-carcinogenic effects by enhancing the fidelity of DNA replication (Blondell, 1980; Schalk *et al.*, 1986).
49. There is some evidence that magnesium supplementation may have an effect on asthma control in stable asthmatics. In a study of 18 stable subjects with asthma, oral magnesium supplementation of 300 mg/d was administered over 30 days and was found to decrease bronchial reactivity. Whilst a randomised placebo cross-over study of 17 stable asthmatic subjects exposed to 400 mg/d for 3 weeks while on a low magnesium diet showed no evidence of improvement of symptoms (Fogarty, 2000).

Toxicity

Human toxicity

49. Magnesium, when ingested as a naturally occurring substance in foods, has not been demonstrated to exert any adverse effects. However, adverse effects of excess magnesium

intake have been observed with various magnesium salts used for pharmacological/medicinal purposes.

Acute toxicity

50. The primary manifestation of excessive ingestion of magnesium from non-food sources is reversible osmotic diarrhoea. Magnesium has a well known cathartic effect and is used in medicines for this purpose (Fine *et al.*, 1991b). Osmotic diarrhoea has not been reported with normal dietary intakes of magnesium from food.

51. Urkabe *et al.* (1975) reported that a female adult suffered from metabolic alkalosis and hypokalaemia from the repeated daily ingestion of 30 grams of magnesium oxide (providing 18 grams of magnesium).

52. Ashton *et al.* (1990) reported the onset of severe magnesium toxicity after 32.5 grams of magnesium sulphate (providing 7 grams magnesium) given as an enema in a chronically constipated 25-month old girl. In addition to raised blood magnesium levels and hypokalaemia, cardiological changes typical of magnesium toxicity were diagnosed.

53. Several cases of paralytic ileus were encountered in adult patients who had taken large cathartic doses of magnesium; in the one case, two bottles of magnesium citrate and several doses of milk of magnesia, and in the other case, several doses of magnesium sulphate in a patient with mild renal impairment were taken (Golzarian *et al.*, 1994).

54. Smilkstein *et al.* (1988) reported the onset of cardiorespiratory arrest in a suicidal patient who was given a total of 465 grams of magnesium sulphate (providing approximately 46 grams magnesium) as a cathartic to counteract an intentional drug overdose.

55. More recently McGuire *et al.* (2000) reported a case of fatal hypermagnesemia resulting from the use of high doses of magnesium oxide administered as part of a megavitamin and megamineral therapy to a 2-year old child with mental retardation. A dose of between 800 and 2400 mg magnesium oxide per day had been administered by the mother of the child prior to admission.

56. Sullivan *et al.* (2000) reported that a 4-week old breast-fed baby developed hypotonia and lethargy after receiving a dose of 7 mmol magnesium every other day (in the form of Milk of Magnesia). After allowing for magnesium intake from breast milk (0.95 mmol per day), it was estimated that the child received an average total daily dose of 4.5 mmol magnesium.

57. Deaths from very large exposures to magnesium as magnesium sulphate or magnesium oxide have been reported following cardiac arrest, especially in individuals with renal insufficiency (Randall *et al.*, 1964; Thatcher and Rock, 1928).

Neurotoxicity

58. No human data available.

Carcinogenicity

59. No human data available

Human supplementation studies

60. Magnesium salts have been used in the treatment of different conditions including, constipation, pre-term labour and pregnancy-induced hypertension. The onset of diarrhoea and other gastrointestinal symptoms seems to be the most critical manifestation of higher intakes of magnesium.

61. The effects of oral magnesium supplementation were investigated in a randomised, double-blind, cross-over trial involving 21 patients with stable congestive heart failure secondary to coronary artery disease (Bashir *et al.*, 1993). All subjects were receiving diuretics and had normal renal function and low or normal serum magnesium concentrations. Although magnesium supplementation reduced the frequency of asymptomatic ventricular arrhythmia, gastrointestinal symptoms, including diarrhoea, developed in 6 out of 21 patients receiving magnesium at levels of 360 mg/day for 6 weeks.

62. A prospective randomised trial was conducted to assess the efficacy of oral enterically-coated magnesium chloride supplements (termed SLOW MAG) for the prevention of pre-term delivery (Ricci *et al.*, 1991). Gastrointestinal disturbances developed in 5 of 25 patients treated with magnesium at a dose of 384 mg. Therapy with magnesium chloride was found to be effective in prolonging pregnancy and preventing recurrent pre-term labour. Enteric coating of magnesium salts apparently reduced the onset of gastrointestinal effects.

63. Marken *et al.* (1989) conducted a randomised, double-blind, placebo-controlled cross-over study to determine if supplemented magnesium in the form of magnesium oxide (400 mg capsules given twice a day for 60 days) would produce changes in serum lipid profiles of healthy individuals. Diarrhoea was noted in 18 out of 50 subjects ingesting the magnesium supplement which provided a dose of 470 mg magnesium. Magnesium supplements did not produce any changes in lipid profiles.

64. A large majority of other studies using similar or even higher levels of supplemental magnesium reported no diarrhoea or other gastrointestinal complaints. For instance, healthy 18-38-year-old males given diets enriched with magnesium oxide, which provided a daily dose of 452 mg magnesium for 6 days did not report the occurrence of any gastrointestinal symptoms (Altura *et al.*, 1994).

65. Diarrhoea or other gastrointestinal complaints were not observed in patients with duodenal ulcers receiving 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 (Nagy *et al.*, 1988). The patients were also being treated with cimetidine.

66. In a longer-term study, a group of 31 postmenopausal women received daily supplements of magnesium hydroxide which provided up to 750 mg magnesium for 6 months followed by 226 mg of magnesium for 18 months without any gastrointestinal complaints

being observed (Stendig-Lindberg *et al.*, 1993). It was found that magnesium therapy prevented fractures and resulted in significant increase of bone density in 71% of subjects and arrested bone loss in 16% of patients.

67. Doses of 372 mg magnesium in elderly subjects over a 4-week period were not associated with any diarrhoea or gastrointestinal effects (Paolisso *et al.*, 1992). The authors concluded that the correction of low erythrocyte magnesium concentration may allow an improvement of glucose handling.

68. A number of studies investigating the role of magnesium supplementation on exercise metabolism and physical performance have been reviewed by Lukaski 1999; no diarrhoea or gastrointestinal symptoms were reported in studies that employed doses of 360 to 390 mg magnesium for four weeks in long-distance runners and other athletes.

69. Dimai *et al.* (1998) evaluated 12 healthy males with a mean age of 27-36, and 12 age-matched controls during 30 consecutive days of magnesium supplementation (365 mg) in the form of magnesium carbonate plus magnesium oxide. Supplementation with magnesium gave rise to a transient suppression of bone turnover. No gastrointestinal disturbances were reported in this study (Dimai *et al.*, 1998).

70. Zemel *et al.* (1990) investigated the effect of magnesium supplementation on blood pressure, erythrocyte cation metabolism and serum lipid in 13 patients with mild hypertension. After randomisation and a 3-week placebo run-in period, seven patients received 486 mg magnesium twice a day for three months. No effects on blood pressure and serum lipids were found. Again, no gastrointestinal disturbances were reported by the authors.

71. In contrast to the findings of Zemel *et al.* (1990), Widman *et al.* (1993) reported dose-dependent reduction in blood pressure through administration of magnesium in a double-blind placebo-controlled cross-over study. Seventeen hypertensive subjects received 365 mg/d magnesium for three weeks, followed by 729 mg/d for another 3 weeks and finished with a further dose of 972 mg for the final three weeks. No diarrhoea or gastrointestinal effects were reported.

Adverse drug reactions

72. Suspected adverse reactions to medicinal products are reported to the Committee on Safety of Medicines/Medicines Control Agency. Many factors influence the number of reports received, and in most situations there is considerable "under-reporting" of reactions. Very few adverse reactions have been reported for nutritional products containing magnesium, and as all are multiconstituent products the reactions may not be attributable to magnesium. There was no trend or pattern to indicate any particular problem.

Vulnerable groups

73. No data identified

Animal toxicity

74. There are only a limited number of studies on the oral toxicity of magnesium and its salts in experimental animals.

Acute toxicity

75. Mochizuki *et al.* (1998) studied the single dose toxicity of magnesium sulphate by intravenous administration in rats and dogs; the compound was administered at dose levels of up to 450 mg/kg bw in rats and up to 1200 mg/kg to female beagle dogs.

76. There were deaths at 200 mg/kg bw and above in the study with rats in both sexes. An LD₅₀ value of 206 mg/kg bw was proposed for males and 174 mg/kg for female rats. Convulsions and abnormal gait were reported in rats dosed at 130 mg/kg bw.

77. There were no deaths in dogs and the LD₅₀ in this species was proposed to be in excess of 1200 mg/kg bw.

78. Akagi *et al.* (1998a) investigated the toxicity of magnesium sulphate administered by a 24-hour intravenous infusion at doses of up to 200 mg/kg bw/h in female beagle dogs for two weeks with a two week recovery period. One dog receiving magnesium sulphate at 200 mg/kg bw/h died after 32 hours and the other dog in the same group was sacrificed as it was in a moribund state. Dogs receiving the compound at 100 mg/kg bw/h had a lowered food consumption and body weight gain and showed abnormalities in electrocardiographic measurements; basophilia was also reported in the kidneys. Decreased calcium levels were reported in animals receiving the compound at 50 mg/kg bw and above. These changes were found to be reversible and thus the authors proposed a no-effect level (NOEL) of 50 mg/kg bw in dogs.

79. Akagi *et al.* (1998b) also studied the 4-week toxicity of magnesium sulphate in dogs. The compound was administered by 24-hour intravenous infusion at doses of up to 100 mg/kg/h for 4 weeks. The symptoms observed in the animals and the NOEL were similar to those found in the above-mentioned 2-week study by the same group.

Sub-chronic toxicity

80. Tanaka *et al.* (1994) studied the toxicity of magnesium chloride that was administered in the diet at 0.6, 1.25, 2.5 or 5% (equivalent to approximately 900, 1875, 3750 and 7500 mg/kg bw/day) to groups of 10 mice for thirteen weeks. A lowering in body weight was noted in both sexes in the high dose groups. There were no treatment-related effects on haematological parameters and in blood biochemistry. Vacuolation of kidney tubular cells was noted in males in the 2.5 and 5% diet groups.

Neurotoxicity

81. No data identified.

Reproductive Toxicology

82. The developmental toxicity of magnesium sulphate in rats was investigated by Katsumata *et al.* (1998). The compound was administered subcutaneously at doses of 250, 500 and 1000 mg/kg bw three times daily to CD female rats from gestation day 15, through to gestation day 20. Dams in the middle- and high-dose groups had a lowered food consumption. Animals in the high-dose group had a lowered body weight gain and were less active. Lower body weights were also observed in F1 pups born to the high-dose group animals, which exhibited signs of delays in differentiation. The effect in pups may have been due to maternal toxicity at higher doses. The dose of 500 mg/kg bw administered three times daily was proposed as the NOEL for developmental effects; the NOEL for toxicity to the dams was 250 mg/kg bw (3 times daily).

Carcinogenicity

83. There was no evidence of compound-related carcinogenicity when magnesium chloride was administered up to 2% in the diet (equivalent to approximately 3000 mg/kg bw/day) of mice for 96 weeks in a limited study (Kurata *et al.*, 1989). A lowering in body weight was noted in the females of the high dose group although, survival was not affected. With the exception of a significant decrease in the incidence of liver tumours among males of the high-dose group, no difference was noted in the tumour incidence between the treated and control animals.

84. Extensive searching of the literature did not reveal any other carcinogenicity studies on magnesium.

Genotoxicity

In vitro

85. Shidate *et al.* (1984) investigated the mutagenicity of a range of food additives and reported that both magnesium chloride and magnesium sulphate were negative in the Ames Salmonella mutagenicity test and chromosome aberration assay in Chinese hamster fibroblast cells.

86. The *in vitro* mutagenicity of magnesium sulphate was also studied more recently by Oguma *et al.* (1998); negative activities were reported in both the Ames test in bacteria and chromosomal aberration tests in Chinese hamster fibroblast cells

In vivo

87. No *in vivo* mutagenicity data on magnesium was identified in the literature.

Regulatory considerations

88. JECFA has evaluated a number of magnesium salts for their use as food additives (JECFA, 1994). In view of the low order toxicity of the more common salts of magnesium (e.g. magnesium carbonate, magnesium chloride, magnesium hydroxide), an acceptable daily intake (ADI) was not set by JECFA. However, an ADI of 6 mg/kg bw/day for magnesium

fumarate, 50 mg/kg bw/day for magnesium gluconate, 25 mg/kg bw/day for magnesium sorbate and 0.7 mg/kg bw/day for magnesium sulphite has been set by JECFA.

Existing recommendations on maximum intake levels

Food

89. COMA (1991) noted that there was no evidence to suggest that large intakes of magnesium from the diet are harmful to humans with normal renal function. However, when taken at doses of 3 to 5 grams, magnesium salts have a cathartic effect (Goodman, 1965) and prolonged usage for this reason can be very toxic or even fatal (Outerbridge *et al.*, 1973). The Infant Formula and Follow-on Formula Regulations (1995) state a maximum magnesium content of 15 mg/100kcal. Foods intended for Use in Energy Restricted Diets for Weight Reduction Regulations (1997) state a level of 150 mg in whole diet products and 50 mg for a meal replacement.

Drinking water

90. The current maximum level for magnesium in drinking water is 50 mg/L (see paragraph 9).

Existing recommendations on maximum supplementation levels

91. The Consumers for Health Choice (1998) quote an upper safe level of 700 mg for a 70 kg adult. The Council for Responsible nutrition, a UK trade association recommend a safe upper limit of 300 mg/day magnesium for long term supplementation and 400 mg/day for short term supplementation (CRN, 1999).

Summary

92. Magnesium does not exist naturally in the pure metallic state, but is found as large deposits as magnesite, dolomite and other minerals. Magnesium in the diet is found in leafy vegetables as well as grains and nuts.

93. Magnesium is a required cofactor in many enzyme systems and plays a key role in protein synthesis, energy production, cell metabolism and RNA and DNA synthesis. Magnesium deficiency has been linked to several disease states involving the cardiovascular, skeletal, gastrointestinal and central nervous systems.

94. The net absorption of magnesium from the diet is estimated at 50 percent in humans. Calcium homeostasis is linked to magnesium metabolism. The absorption of magnesium has been shown to be influenced by high intakes of protein. Magnesium occurs both intra- and extracellularly and is found in bone, muscle and other tissues. Approximately 20% of extracellular magnesium is protein bound. Magnesium is primarily excreted in the urine.

95. There is no data to link high dietary intakes of magnesium with toxicity in humans; adverse effects have only been reported following therapeutic uses at very high doses. The

primary effect of excessive ingestion of magnesium from non-dietary sources is osmotic diarrhoea. Cardiological changes typical of magnesium toxicity have been reported following the use of extremely high therapeutic doses.

96. There is limited data on the oral toxicity of magnesium in animals. Studies on the short-term toxicity of magnesium by the intravenous route demonstrated that the LD₅₀ value in rats is between 174 to 206 mg/kg bw/day and in dogs is in excess of 1200 mg/kg bw/day. There was no evidence of compound-related carcinogenicity identified when magnesium chloride was administered in the diet of mice for 96 weeks.

97. Magnesium chloride and magnesium sulphate were negative in *in vitro* genotoxicity tests. Higher doses of magnesium sulphate administered subcutaneously in reproductive studies resulted in lower food consumption and decreased body weight gains in the dams. Pups born to dams receiving high doses of magnesium sulphate showed signs of delayed differentiation.

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NNEX 1 TO EVM/01/13

Table 1. Human Supplementation Studies

Subjects	Endpoint/findings	Dose mg/day	NOAEL/LOAEL for Gastrointestinal effects.	Duration	Comment	Reference
21 patients with congestive heart failure, aged 55+ years	Supplementation reduced frequency of asymptomatic ventricular arrhythmia-diarrhoea and gastrointestinal symptoms developed in 6 out of 21 patients	360	LOAEL= 360 mg	6 weeks	This study employed a randomised, double-blind cross-over design. The subjects were also receiving diuretics and had normal renal function.	Bashir <i>et al.</i> (1993)
74 patients between 24 and 34 weeks gestation with pre-term labour, mean age 21.36 (\pm 5.79) years	Enteric-coated magnesium chloride was as effective as ritodrine in prolonging pregnancy and preventing pre-term labour. Gastrointestinal symptoms developed in 5 out of 25 patients.	384	LOAEL = 384 mg	Patients received a dose of magnesium every 4 hours until delivery or completion of 36 weeks.	This study was a prospective randomised clinical trial. Magnesium preparation (SLOW MAG) was enterically coated for delayed release.	Ricci <i>et al.</i> , 1991
50 healthy volunteers of 18 - 32 years	No changes in lipid profiles as a result of treatment. Diarrhoea was noted in 18 out of 50 subjects	470	LOAEL = 470 mg	60 days	This investigation was a double-blind, placebo-controlled cross-over study	Marken <i>et al</i> (1989)
18 healthy volunteers of 18 to 38 years	Serum ionised magnesium levels were altered by dietary intakes of magnesium	452	NOAEL = 452mg	6 days	This study employed a randomised, triple cross-over design. The absorption of different magnesium oxide preparations (i.e. hard v soft gel) were compared and the role of phosphate on serum magnesium was investigated	Altura <i>et al</i> (1994)

Subjects	Endpoint/findings	Dose mg/day	NOAEL/LOAEL for gastrointestinal effects.	Duration	Comment	Reference
20 patients with duodenal ulcers, aged 20-46 years	TISACID tablets (Al-Mg-hydroxy-carbonate) was effective in healing duodenal ulcers by reducing the acidity of gastric content	1200	NOAEL=1200mg	6 weeks	This study was prospective and employed a cross-over design. Patients were also receiving cimetidine	Nagy <i>et al</i> (1988)
31 postmenopausal patients with osteoporosis, mean age 31 ± SD 10.6 years)	Magnesium therapy prevented fractures and gave rise to increases in bone density in 71 %, and led to arrest of bone loss in 16% of patients (31 in total)	750 mg for 6 months then 224 mg for a further 18 months	NOAEL= 224-750 mg	24 months	The mean bone density increased significantly after the first year and remained stationary after the second.	Stendig-Lindberg <i>et al</i> (1993)
12 elderly diabetic patients, mean age 77.8 ± 2.1 years	Chronic magnesium administration increased erythrocyte magnesium concentration and improved insulin response and action in 12 elderly subjects	372	NOAEL=372 mg	4 weeks	This was a randomised, double-blind cross-over study. 25 young healthy subjects were used as controls.	Paolisso <i>et al</i> (1992)
24 healthy male subjects, aged 27-36 years	Transient suppression in bone turnover was noted in a study employing 12 healthy males and 12 age-matched controls	365	NOAEL=365 mg	30 days	It was suggested that the suppressive effect on bone turnover may be mediated by a reduction in serum ionised magnesium levels.	Dimai <i>et al</i> (1998)
7 hypertensive patients, aged 53 ± 5 years	Magnesium supplementation in seven patients did not affect blood pressure or lipid profiles.	486	NOAEL=486 mg	3 months	The subjects were randomised and were subjected to a 3-week placebo run-in period. The patients were magnesium repleted	Zemel <i>et al</i> (1990)

ANNEX 2 TO EVM/01/13.REVISED AUG 2001

INTAKES OF MAGNESIUM FROM FOOD AND SUPPLEMENTS

The data presented on magnesium intakes are obtained from dietary surveys of specific population age groups in Britain carried out over the last 15 years¹²³⁴⁵. In each survey food consumption data were collected by means of a dietary record (usually weighed) kept for 4 or 7 consecutive days. Nutrient intakes were calculated using a set of nutrient composition data contemporaneous with the time of the survey. Therefore some apparent differences in intakes between population age groups may be due to changes in the nutrient composition data and reflect changes in the nutrient composition of manufactured foods over time.

Total intakes of magnesium

Table 1 provides information on the absolute intakes of magnesium by the British population, classified by age and sex. Mean and median intake, and the upper and lower end of the intake distribution (defined as upper and lower 2.5 percentiles, respectively), are given.

Average intakes of magnesium were lowest for infants aged 6-12 months and highest for males aged 16-64 years. Pre-school children, boys (but not girls) aged 3½-4½ years had a significantly higher mean intake than the youngest group of boys and girls (1½-2½ years). For young people aged 4-18 years, average magnesium intakes increased significantly with age, while in adults, intakes were significantly lower among the youngest group of men and women compared with the overall means. Average magnesium intakes decreased significantly with age for older people free-living in the community.

Mean and median magnesium intakes were below Reference Nutrient Intakes (RNIs) for young people aged 7 to 18, females aged 16-64, and older people free-living in the community or in institutions, aged 65 years and over. Significant proportions of young people, adults and older adults had intakes below the LRNI (Lower Reference Nutrient Intake). In girls aged 11-18 years around 50% had intakes below the LRNI. Intakes at the 97.5%ile were about 1.4 to 2 times the median in all groups.

Table 2 provides information on magnesium intakes from food adjusted for body weight and classified by age and sex. Body weight adjusted magnesium intakes are highest in infants and show a trend to decrease with age for children and young people.

¹ Food and nutrient intakes of British infants. 1986

² National Diet and Nutrition Survey of children aged 1½-4½ years. 1992/3

³ National Diet and Nutrition Survey of young people aged 4-18 years. 1997/8

⁴ Dietary and nutritional survey of British adults. 1986/7

⁵ National Diet and Nutrition Survey of people aged 65 years and over. 1994/5

Sources of magnesium in the diet

Table 3 indicates the contribution made by different types of food to average intakes of magnesium by young people aged 15-18 years. This dataset was collected in 1997 and so most closely reflects current eating habits and fortification practices.

The main food source of magnesium in this age group is cereals and cereal products (29%), of which over a third came from bread (12%) and nearly a quarter (7%) came from breakfast cereals. Vegetables, potatoes and savoury snacks provided 23% of magnesium intake, of which over half came from potatoes. Meat and meat products provided 13% of total intake and milk and milk products 12%.

The main sources of magnesium were similar in other age groups except that the contribution from milk tended to be higher in young children (27% of total intake for 1½-4½ year olds). In adults the contribution from beverages was also higher, mainly due to beer and lager, which provided 11% of intake for males aged 16-64 years.

Magnesium intakes from supplements

There were few consumers of magnesium-containing supplements and their contribution to mean intakes was zero or negligible.

Of course, the proportion of intake from supplements is higher if supplement consumers are considered separately.

Table 4 shows the number of consumers of dietary supplements containing magnesium in each age group, together with the mean, median and range of intakes from supplements for those who consumed them. No more than 2% of any group studied used supplements containing magnesium. The range of intakes from supplements was wide with the maximum intake from this source at 300 mg per day in females aged 65 years and over free-living in the community.

Diet and Nutrition Surveys Branch
Nutrition Division
Food Standards Agency
May 2001

Table 1: Total intakes of Magnesium

Age/sex	Absolute Magnesium intake (mg/day)			
	Intakes from food			
	2.5%ile	Mean	Median	97.5%ile
Infants (1986) 6-12mths/M&F	54	124	125	212
Pre-school children (1992/3)⁶				
1½-2½ yrs/M/F	62	132	130	221
2½-3½ yrs/M/F	73	137	133	223
3½-4½ yrs/M	81	146	141	228
3½-4½ yrs/F	77	137	134	207
Young people (1997/8)⁷				
4-6 yrs/M	67	172	170	264
4-6 yrs/F	92	155	145	244
7-10 yrs/M	117	194	187	302
7-10 yrs/F	98	177	176	261
11-14 yrs/M	97	218	214	351
11-14 yrs/F	102	182	176	290
15-18 yrs/M	145	256	254	390
15-18 yrs/F	84	191	189	314
Adults (1986/7)⁷				
16-24 yrs/M	148	304	298	516
16-24 yrs/F	104	215	208	395
25-34 yrs/M	157	325	317	527
25-34 yrs/F	99	232	225	413
35-49 yrs/M	165	336	321	576
35-49 yrs/F	116	250	233	473
50-64 yrs/M	170	317	308	540
50-64 yrs/F	117	238	226	437
Older people free-living in the community (1994/5)⁸				
65-74yrs/M	112	263	255	423
65-74yrs/F	103	207	195	337
75-84 yrs/M	125	241	226	413
75-84 yrs/F	91	186	177	303
85 and over/M	98	217	218	375
85 and over/F	73	177	173	315
Older people living in institutions (1994/5)⁹				
65-84 yrs/M	106	214	205	332
65-84 yrs/F	97	200	202	290
85 and over/M	99	217	205	376
85 and over/F	103	178	170	285

⁶ None of the dietary supplements taken in this survey provided any magnesium

⁷ Intakes from all sources

⁸ Dietary supplements provided negligible magnesium for participants in this survey

Table 2: Bodyweight adjusted Magnesium intake

Age/sex	Bodyweight adjusted Magnesium intake (mg/kg bwt /day)⁹		
	<i>Intakes from food</i>		
	Mean	Median	97.5%ile
Infants (1986) 6-12mths/M&F	12.93	12.64	21.68
Pre-school children (1992/3) 1½-2½ yrs/M&F 2½-3½ yrs/M&F 3½-4½ yrs/M 3½-4½ yrs/F	10.81 9.41 8.82 8.40	10.38 9.10 8.56 8.29	17.71 14.99 13.55 12.40
Young people (1997/8) 4-6 yrs/M 4-6 yrs/F 7-10 yrs/M 7-10 yrs/F 11-14 yrs/M 11-14 yrs/F 15-18 yrs/M 15-18 yrs/F	8.12 7.65 6.54 5.75 4.82 3.89 3.91 3.28	7.91 7.34 6.49 5.49 4.78 3.81 3.90 3.20	12.29 11.81 10.41 9.10 7.93 6.64 6.14 5.42
Adults (1986/7)¹⁰ 16-24 yrs/M 16-24 yrs/F 25-34 yrs/M 25-34 yrs/F 35-49 yrs/M 35-49 yrs/F 50-64 yrs/M 50-64 yrs/F	4.40 3.64 4.35 3.82 4.42 3.97 4.13 3.75	4.38 3.61 4.28 3.76 4.21 3.72 3.93 3.56	7.48 6.96 7.22 6.97 7.79 7.75 7.24 7.09
Older people free-living in the community (1994/5) 65-74 yrs/M 65-74 yrs/F 75-84 yrs/M 75-84 yrs/F 85 and over/M 85 and over/F	3.43 3.22 3.31 2.98 3.21 3.06	3.26 3.00 3.19 2.74 3.11 2.88	5.53 5.70 6.02 5.22 5.59 6.09
Older people living in institutions (1994/5) 65-84 yrs/M 65-84 yrs/F 85 and over/M 85 and over/F	3.21 3.40 3.25 3.12	3.05 3.31 3.22 2.88	5.70 5.36 5.62 5.62

⁹ Body weights measured for each subject for all age groups except infants aged 6-12 months where reported body weights were used.

¹⁰ Intakes for adults aged 16-64 are from all sources.

Table 3¹¹: Sources of Magnesium in the diet

Food Type	Contribution of food types to average daily intake of magnesium	
	mg/day	% of total
Cereal and cereal products	65.9	29
- of which breakfast cereals	14.9	7
- of which bread	27.2	12
Milk and milk products	27.1	12
Egg and egg dishes	1.6	1
Fat spreads	0.2	0
Meat and meat products	28.9	13
Fish and fish dishes	4.4	2
Vegetables, potatoes and savoury snacks	51.6	23
- of which roast/fried potatoes and chips	19.4	9
- of which boiled, mashed, baked potatoes	8.9	4
Fruits and nuts	7.5	3
Sugar, confectionery and preserves	9.8	4
Beverages	22.3	10
- of which beers and lagers	7.4	3
Miscellaneous	5.0	2
Total intake from food	224.5*	100*
<i>Intake from dietary supplements</i>	<i>0</i>	<i>0</i>
Total intake from food and supplements	224.5*	100*

*Total allows for rounding

¹¹ NDNS: Young people aged 4-18 years. 1997/8. 15-18 year group.

Table 4: Magnesium intake from supplements

<i>Age/sex</i>	Consumers of magnesium supplements		Magnesium intake from supplements (consumers only) (mg/day)		
	<i>Number</i>	<i>%</i>	<i>Mean</i>	<i>Median</i>	<i>Range</i>
<i>Infants (1986)</i> 6-12 mths/M&F	*	*	*	*	*
<i>Pre-school children (1992/3)</i> 1½-4½ yrs/M&F	1	<1	6.0	6.0	6.0
<i>Young people (1997/8)</i> 4-6 yrs/M&F	1	<1	0.2	0.2	0.2
7-10 yrs/M&F	3	<1	17.2	0.4	0.3-50.0
11-14 yrs/M	-	-	-	-	-
11-14 yrs/F	-	-	-	-	-
15-18 yrs/M	2	1	17.0	4.0	4.0-35.7
15-18 yrs/F	2	1	19.4	16.1	7.1-25.0
<i>Adults (1986/7)</i> 16-64 yrs/M	15	1	14.7	5.2	0.1-71.4
16-64 yrs/F	17	2	21.7	1.0	0.1-124.3
<i>Older people free-living in the community (1994/5)</i> 65 and over/M	9	1	17.7	8.8	0.7-45.0
65 and over/F	13	2	64.8	10.1	0.3-300.0
<i>Older people living in institutions (1994/5)</i> 65 and over/M	3	1	42.5	32.9	7.5-75.0
65 and over/F	5	2	21.8	12.9	10.8-43.3

* Data unavailable

- Zero intake

ANNEX 3 TO EVM/01/13.REVISED AUG2001

Magnesium: Summary table of selected nutrition related information and existing guidance on regulations

Unit of usage	mg/day		mg/100 kcal
	Male	Female	
UK DRV's ¹²			
Adults			
LRNI	190	150	
RNI	300	270	
EAR	250	200	
Infants			
LRNI	45	45	
RNI	75-80	75-80	
EAR	60	60	
Mean adult UK dietary intake from all sources			
Adults (16-64) ¹³	323	237	
65 years and over ¹⁴			
free living	254	197	
institutionalised	205	188	
EU labelling RDA ¹⁵	300mg		
Supplemental doses	150-750mg		
Regulations			
Infant formula ¹⁶			5 – 15mg
Infant foods ¹⁷			
Weight reduction ¹⁸			
whole daily diet replacement			Maximum 40mg
meal replacement			
		150	
		50	
Maximum total safe daily intake ¹			
COMA 1991 ¹	Up to 3g		
EHPM 1997 ¹⁹	Upper safe level 700mg (Long-term consumption)		

¹² Committee on Medical Aspects of Food and Nutrition Policy (1991). Dietary Reference Values for Food Energy and Nutrients for the United Kingdom. Report on Health and Social Subjects 41. London: HMSO.

¹³ Dietary and nutritional survey of British adults. 1986/7

¹⁴ National Diet and Nutrition Survey of people aged 65 years and over. 1994/5

¹⁵ The Food Labelling Regulations 1996

¹⁶ The Infant Formula and Follow-on Formula Regulations 1995

¹⁷ The Processed Cereal-based Foods and Baby Foods for Infants and Young Children Regulations 1999 (amended)

¹⁸ The Foods Intended for Use in Energy Restricted Diets for Weight Reduction Regulations 1997.

¹⁹ Vitamins and Minerals A Scientific Evaluation of the Range of Safe Intakes. European Federation of Health Product Manufacturers 1997.