6
Magnesium

BACKGROUND INFORMATION

Overview

Total body magnesium (Mg) content is approximately 25 g (1,000 mmol), of which 50 to 60 percent resides in bone in the normal adult. One-third of skeletal magnesium is exchangeable, and it is this fraction that may serve as a reservoir for maintaining a normal extracellular magnesium concentration (Elin, 1987). Extracellular magnesium accounts for about 1 percent of total body magnesium. The normal serum magnesium concentration is 0.75 to 0.95 mmol/liter (1.8 to 2.3 mg/dl).

Magnesium is a required cofactor for over 300 enzyme systems (Wacker and Parisi, 1968). It is required for both anaerobic and aerobic energy generation and for glycolysis, either indirectly as a part of the Mg-ATP complex or directly as an enzyme activator (Garfinkel and Garfinkel, 1985). Magnesium has also been shown to be required for mitochondria to carry out oxidative phosphorylation (Wacker and Parisi, 1968). The mitochondrial enzymes utilize the magnesium chelate of ATP and ADP as the actual substrates for phosphate transfer reactions.

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

Magnesium transport in mammalian cells may be influenced by hormonal and pharmacological factors including β-agonists, growth factors, and insulin (Gunther, 1993; Hwang et al., 1993; Romani et al., 1993). It has been suggested that a hormonally regulated magnesium uptake system controls intracellular magnesium concentration in cellular compartments. The magnesium concentration in these compartments would then serve to regulate the activity of magnesium-sensitive enzymes.

Magnesium presence is important for maintaining an adequate supply of purine and pyrimidine nucleotides required for the increased DNA and RNA synthesis that occurs during cell proliferation (Rubin, 1975; Switzer, 1971). Replicating cells must be able to synthesize new protein, and this synthesis has been reported to be highly sensitive to magnesium depletion. Many hormones, neurotransmitters, and other cellular effectors regulate cellular activity via the adenylate cyclase system, and the activation of adenylate cyclase requires the presence of magnesium. There is also evidence for magnesium binding through which magnesium directly increases adenylate cyclase activity (Maguire, 1984).

Magnesium is necessary for sodium, potassium-ATPase activity, which is responsible for active transport of potassium (Dorup and Clausen, 1993). Magnesium regulates the outward movement of potassium in myocardial cells (Matsuda, 1991). The arrhythmogenic effect of magnesium deficiency may be related to magnesium's role in maintaining intracellular potassium.

Magnesium has been called "nature's physiological calcium channel blocker" (Iseri and French, 1984). During magnesium depletion, intracellular calcium rises. Since calcium plays an important role in skeletal and smooth muscle contraction, a state of magnesium depletion may result in muscle cramps, hypertension, and coronary and cerebral vasospasms. Magnesium depletion is found in a number of diseases of cardiovascular and neuromuscular function, in malabsorption syndromes, in diabetes mellitus, in renal wasting syndromes, and in alcoholism (Ma et al., 1995). These observations have led to studies regarding the role of inadequate magnesium intake in the development of disease, as opposed to abnormal handling of magnesium caused by the disease process. It is important to ensure that such evaluations are undertaken in apparently normal individuals for whom dietary intake is the primary independent variable.

Physiology of Absorption, Metabolism, and Excretion

In both children and adults, fractional intestinal magnesium absorption is inversely proportional to the amount of magnesium ingested (Kayne and Lee, 1993). In balance studies, under controlled dietary conditions in healthy older men, an average of 380 mg (15.8 mmol)/day of ingested magnesium resulted in net absorption of approximately 40 to 60 percent; true absorption ranged from 51 to 60 percent for various foodstuffs when subjects were on a constant diet (Schwartz et al, 1984). Net absorption has been estimated to be 15 to 36 percent at higher daily intakes (550 to 850 mg [22.9 to 35.4 mmol]) and with varying levels of dietary bran and oxalate (Schwartz et al., 1986). 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). Both an unsaturable passive and saturable active transport system for magnesium absorption may account for the higher fractional absorption at low dietary magnesium intakes (Fine et al., 1991a).

A principal factor that regulates intestinal magnesium transport has not been described. Vitamin D and its metabolites 25-hydroxyvitamin D (25(OH)D) and 1,25-dihydroxyvitamin D ($1,25(OH)_2D$) enhance intestinal magnesium absorption to a small extent (Hardwick et al., 1991; Krejs et al., 1983). Recently, a low magnesium diet in rats was shown to increase intestinal calbindin-D_{9k}. Although these preliminary data suggest a role for this vitamin D-dependent, calcium-binding protein in intestinal magnesium absorption, the severe magnesium deficiency imposed may have resulted in renal damage (not described) (Hemmingsen et al., 1994).

The kidney is the principal organ involved in magnesium homeostasis (Quamme and Dirks, 1986). The renal handling of magnesium in humans is a filtration-reabsorption process; there is no tubular secretion of magnesium. Approximately 65 percent of filtered magnesium is reabsorbed in the loop of Henle and 20 to 30 percent in the proximal convoluted tubule (Quamme and Dirks, 1986). Magnesium reabsorption in the proximal convoluted tubule appears to be passive; it follows changes in salt and water reabsorption and is associated with the rate of fluid flow. In the loop of Henle, there appears to be an additional active transport system: a decrease in magnesium reabsorption in this segment is independent of sodium chloride transport in either hypermagnesemia or hypercalcemia (Quamme, 1989). In vivo studies in animals and humans, however, have demonstrated a tubular maximum for magnesium that probably reflects a composite of these tubular reabsorptive processes (Quamme and Dirks, 1986).

During experimental magnesium depletion in humans, magnesium decreases in the urine to very low levels (< 20 mg [1 mmol]/day) within 3 to 4 days (Fitzgerald and Fourman, 1956; Heaton, 1969; Shils, 1969). Despite the close regulation of magnesium by the kidney, no one has described a hormone or factor that is responsible for renal magnesium homeostasis. Because patients with either primary hyper- or hypoparathyroidism usually have normal serum magnesium concentrations and a normal tubular maximum for magnesium, it is probable that parathyroid hormone (PTH) is not an important regulator of magnesium homeostasis (Rude et al., 1980). Glucagon, calcitonin, and ADH affect magnesium transport in the loop of Henle in a manner similar to PTH, but the physiological relevance of these actions is unknown (Quamme and Dirks, 1986). Little is known about the effect of vitamin D on renal magnesium handling.

Excessive alcohol intake has been shown to cause renal magnesium wasting, which, if a diet is marginal in magnesium content, could place an individual at risk for magnesium depletion. Indeed, nearly all chronic alcoholics have symptoms of magnesium depletion (Abbott et al., 1994). However, the evidence does not substantiate the suggestion that alcoholism is due to magnesium deficiency.

A growing list of medications has been found to result in increased renal magnesium excretion. Diuretics commonly used in the treatment of hypertension, heart failure, and other edematous states may cause hypermagnesuria (Ryan, 1987).

Factors Affecting the Magnesium Requirement

Bioavailability

As mentioned previously, net absorption of dietary magnesium in a typical diet is approximately 50 percent. High levels of dietary fiber from fruits, vegetables, and grains decrease magnesium absorption and/or retention (Siener and Hesse, 1995; Wisker et al., 1991). Men consuming 355 mg (14.8 mmol)/day of magnesium were in positive magnesium balance on a low-fiber (9 g/day) diet but in negative balance on a high-fiber (59 g/day) diet (Kelsay et al., 1979). Similar trends were observed in young women consuming 243 to 252 mg (10.0 to 10.5 mmol)/day of magnesium and receiving a lower fiber (23 g/day) versus higher fiber (39 g/day) diet (Wisker et al., 1991).

Nutrient-Nutrient Interactions

Phosphorus. Many foods high in fiber contain phytate, which may decrease intestinal magnesium absorption, probably by binding magnesium to phosphate groups on phytic acid (Brink and Beynen, 1992; Franz, 1989; Wisker et al., 1991). The ability of phosphate to bind magnesium may explain decreases in intestinal magnesium absorption seen in subjects on high phosphate diets (Franz, 1989; Hardwick et al., 1991; Reinhold et al., 1991).

Calcium. Most human studies of effects of dietary calcium on magnesium absorption have shown no effect (Fine et al., 1991a; Hardwick et al., 1991; Spencer et al., 1978b), but one has reported decreased magnesium absorption rates (Greger et al., 1981). Perfusion of the jejunum of normal subjects with 0 to 800 mg (0 to 20 mmol) calcium had no effect on magnesium absorption (Brannan et al., 1976). Increased calcium intake did not affect magnesium balance when as much as 2,000 mg (50 mmol)/day of calcium was given to adult men (Spencer et al., 1978b, 1994), or when an additional 1,000 mg (25 mmol)/day of calcium was given to adolescents (Andon et al., 1996). Magnesium intake ranging from 241 to 826 mg (10 to 34.4 mmol)/day did not alter calcium balance at either 241 mg (10 mmol) or 812 mg (20.3 mmol)/day of calcium (Spencer et al., 1994). However, intakes of calcium in excess of 2,600 mg (65 mmol)/day have been reported to decrease magnesium balance (Greger et al., 1981; Seelig, 1993). Several studies have found that high sodium and calcium intake may result in increased renal magnesium excretion (Kesteloot and Joossens, 1990; Martinez et al., 1985; Quamme and Dirks, 1986), which may be secondary to the interrelationship of the proximal tubular reabsorption of filtered sodium, calcium, and magnesium (Quamme and Dirks, 1986). Overall, at the dietary levels recommended in this report, the interaction of magnesium with calcium is not of concern.

Protein. Dietary protein may also influence intestinal magnesium absorption; magnesium absorption is lower when protein intake is less than 30 g/day (Hunt and Schofield, 1969). A higher protein intake (94 g/day) may increase renal magnesium excretion (Mahalko et al., 1983), presumably because an increased acid load increases urinary magnesium excretion (Wong et al., 1986). However, the increased urinary magnesium excretion did not change overall magnesium retention, which indicates an ability of subjects to adapt to this level of protein given the level of magnesium provided (258 mg [10.8 mmol]/day). Other studies in adolescents have shown improved magnesium absorption and retention when protein intakes were higher (93 versus 43 g protein/day) (Schwartz et al., 1973).

Special Populations

Physical Activity. Dietary magnesium intake in athletes has been reported to be at or above recommended intakes (Clarkson and Haymes, 1995; Kleiner et al., 1994; Niekamp and Baer, 1995), presumably due to their higher food intake. Plasma/serum magnesium concentrations have been reported to fall with chronic endurance exercise activity, while red blood cell values appear to rise (Deuster and Singh, 1993). Although the decrease in plasma magnesium has been suggested to reflect magnesium depletion in athletes (Clarkson and Haymes, 1995), no clear demonstration of magnesium depletion directly related to exercise has been shown. Magnesium supplements did not enhance performance in a study of marathon runners (Terblanche et al., 1992).

Intake of Magnesium

The U.S. Department of Agriculture Continuing Survey of Food Intakes by Individuals (CSFII) in 1994, adjusted by the method of Nusser et al. (1996), indicated that the mean daily magnesium intake in males aged 9 and older was 323 mg (13.5 mmol) (fifth percentile = 177 mg [7.4 mmol]; fiftieth percentile = 310 mg [12.9 mmol]; ninety-fifth percentile = 516 mg [21.5 mmol]) (Cleveland et al., 1996) (see Appendix D for data tables). The mean daily intake for females aged 9 and older was 228 mg [9.5 mmol] (fifth percentile = 134 mg [5.6 mmol]; fiftieth percentile = 222 mg [9.3 mmol]; ninety-fifth percentile = 342 mg [14.3 mmol]). In both sexes, intake decreased at age 70 and older. These intakes were similar to those found in the National Health and Nutrition Examination Survey (NHANES) III from l988–1991 (Alaimo et al., 1994). National survey data for Canada are not currently available. Other surveys have reported lower intakes in both men and women (Hallfrisch and Muller, 1993).

The NHANES III study demonstrated ethnic differences in intake. In that report, non-Hispanic black subjects were found to consume less than either non-Hispanic white or Hispanic subjects. Another study demonstrated that elderly Hispanic males consumed a mean of 237 ± 62 mg (9.9 ± 2.6 mmol)/day, while Hispanic females consumed a mean of 232 ± 71 mg (9.7 ± 3.0 mmol)/day (Pluckebaum and Chavez, 1994).

Food and Water Sources of Magnesium

Magnesium is ubiquitous in foods, but the magnesium content of foods varies substantially. Because chlorophyll is the magnesium chelate of porphyrin, green leafy vegetables are rich in magnesium. Foods such as unpolished grains and nuts also have high magnesium content, whereas meats, starches, and milk are more intermediate. Analyses from the 1989 Total Diet Study of the U.S. Food and Drug Administration indicated that approximately 45 percent of dietary magnesium was obtained from vegetables, fruits, grains, and nuts, whereas about 29 percent was obtained from milk, meat, and eggs (Pennington and Young, 1991). Refined foods generally have the lowest magnesium content. With the increased consumption of refined and/or processed foods, dietary magnesium intake in the United States appears to have decreased over the years (Marier, 1986). Total magnesium intake is usually dependent on caloric intake, which explains the higher intake levels seen in the young and in adult males and the lower levels seen in women and in the elderly.

Water is a variable source of intake; typically, water with increased "hardness" has a higher concentration of magnesium salts. Since this varies depending on the area from which water comes, much like fluoride, and the manner in which it is stored, magnesium intake from water is usually not estimated except in controlled diet studies. This omission may lead to underestimating total intake and its variability.

Intake from Supplements

Based on a national survey in 1986, 14 percent of men and 17 percent of women in the United States took supplements containing magnesium (Moss et al., 1989). Approximately 8 percent of young children (2 to 6 years of age) used magnesium-containing supplements. Women and men who use magnesium supplements took similar doses, about 100 mg (4.2 mmol)/day, although the ninety-fifth percentile of intake was somewhat higher for women, 400 mg (16.7 mmol)/day, than for men, who were taking 350 mg (14.6 mmol)/day. Children who took magnesium had a median daily intake of 23 mg (1 mmol) and a ninety-fifth percentile daily supplemental intake of 117 mg (4.9 mmol).

Effects of Inadequate Magnesium Intake

Severe magnesium depletion leads to specific biochemical abnormalities and clinical manifestations that can be easily detected. Hypocalcemia is a prominent manifestation of magnesium deficiency in humans (Rude et al., 1976). Magnesium deficiency must become moderate to severe before symptomatic hypocalcemia develops. Even mild degrees of magnesium depletion, however, may result in a significant fall in the serum calcium concentration, as demonstrated in a 3-week study of dietary-induced experimental human magnesium depletion (Fatemi et al., 1991).

Magnesium is also important in vitamin D metabolism and/or action. Patients with hypocalcemia and magnesium deficiency are resistant to pharmacological doses of vitamin D, 1α hydroxyvitamin D, and $1{,}25(OH)_2D$ (for a review, see Fatemi et al. [1991]).

Neuromuscular hyperexcitability is the initial problem cited in individuals who have or are developing magnesium deficiency (Rude and Singer, 1980). Latent tetany, as elicited by a positive Chvostek's and Trousseau's sign, or spontaneous carpal-pedal spasm may be present. Frank, generalized seizures may also occur. Although hypocalcemia may contribute to the neurological signs, hypomagnesemia without hypocalcemia may result in neuromuscular hyperexcitability.

There is emerging evidence that habitually low intakes of magnesium and resulting abnormal magnesium metabolism are associated with etiologic factors in various metabolic diseases. In considering data from such studies, it is important to separate the identification of associations between the effect of the disease on magnesium status from the effect of inadequate intake on magnesium status and subsequent risk of disease. The specific disease states in which magnesium status is implicated are discussed in the following sections.

Cardiovascular

In normal subjects, experimental magnesium depletion results in increased urinary thomboxane concentration, angiotensin II-induced plasma aldosterone levels, and blood pressure—indicating a potential effect of magnesium deficiency on vascular function (Nadler et al., 1993; Rude et al., 1989). Magnesium depletion is associated with cardiac complications, including electrocardiographic changes, arrhythmias, and increased sensitivity to cardiac glycosides (Rude, 1993). Atrial and ventricular premature systoles, atrial fibrillation, and ventricular tachycardia and fibrillation have been reported in hypomagnesemic patients (Hollifield, 1987; Rude, 1993). Significantly higher retention rates after magnesium load tests have been reported in patients with ischemic heart disease compared to normal controls (Rasmussen et al., 1988). This suggests that a low magnesium concentration may also play a role in cardiac ischemia. However, the extent to which the disease modifies the indicators of magnesium deficiency rather than the deficiency resulting in the disease manifestations varies with the symptom and the individual studied.

The development of atheromatous disease has been associated with magnesium in epidemiological observational studies. Areas with increased water hardness (which is due to high calcium and magnesium content) tend to have lower cardiovascular death rates (Altura et al., 1990; Hammer and Heyden, 1980; Leoni et al., 1985; Luoma et al., 1983; Neri and Johansen, 1978; Neri et al., 1985; Rubenowitz et al., 1996). Problems with evaluating epidemiological studies have been identified (Comstock, 1979), and some studies have not found such an association (Hammer and Heyden, 1980; Leoni et al., 1985). However, as presented by Tucker (1996) and Beaton (1996), a congruence of positive studies may suggest an association of dietary intake and disease. Animals on low magnesium diets develop arterial wall degeneration and calcification as well as hypertriglyceridemia, hypercholesterolemia, and atherosclerosis (Altura et al., 1990; Orimo and Ouchi, 1990). Controlled human studies that support this relationship are lacking.

Magnesium depletion in patients with cardiac diseases may be due to concomitant medications, such as diuretics, as well as to dietary magnesium depletion. Although cardiac arrhythmia may be associated with the primary cardiac disorders, magnesium depletion may further predispose to cardiac arrhythmias by decreasing intracellular potassium.

Accumulation of magnesium may reduce the morbidity and mortality of patients in the period following myocardial infarction. Two large, placebo-controlled, randomized, double-blind studies of patients with myocardial infarction have shown that intravenous magnesium therapy reduces the incidence of therapy-requiring arrhythmias to approximately one-half that seen in control patients (Antman, 1996; Seelig and Elin, 1996). In one study of patients with acute myocardial infarction, magnesium therapy given before thrombolytic therapy decreased mortality by 24 percent (Woods and Fletcher, 1994). Another large study of myocardial infarction did not find favorable effects of magnesium that was administered after thrombolytic therapy (ISIS-4, 1995). Debate currently centers over the time of administration of magnesium in terms of its favorable effects (for review see Antman [1996]). Evidence does not support the concept that the patients were magnesium deficient prior to onset of the acute attack, only that magnesium therapy was beneficial to outcome.

Blood Pressure

Epidemiologic evidence suggests that magnesium may play an important role in regulating blood pressure (Ascherio et al., 1992; Joffres et al., 1987; Ma et al., 1995; McCarron, 1983; Witteman et al., 1989). In these studies, populations that have low dietary intake of magnesium have been reported to have an increased incidence of hypertension. In one of the earlier studies, dietary intake of magnesium in 44 normotensive subjects was significantly greater than intake in 46 untreated hypertensive subjects (McCarron, 1983). In the Honolulu heart study, magnesium intake was the dietary variable that had the strongest association with blood pressure (Joffres et al., 1987). In another nutritional survey of 58,218 Caucasian women, those who reported intakes of less than 200 mg (8.33 mmol)/day of magnesium had a significantly higher risk of developing hypertension than did women whose intakes were greater than 300 mg (12.5 mmol)/day. In a large prospective study of 30,681 men without diagnosed hypertension, dietary magnesium intake was inversely related to systolic and diastolic blood pressure and to change in blood pressure during a 4-year follow-up period (Ascherio et al., 1992). In this study, however, only dietary fiber had an independent inverse association. Another study of 15,248 subjects found that dietary magnesium intake was inversely associated with systolic and diastolic blood pressure (Ma et al., 1995).

Intervention studies with magnesium therapy for hypertensive patients have led to conflicting results. Several studies have shown a positive blood-pressure-lowering effect of magnesium supplements (Dyckner and Wester, 1983; Geleijnse et al., 1994; Motoyamo et al., 1989; Widman et al., 1993; Witteman et al., 1994); others have not (Cappuccio et al., 1985; Sacks et al., 1995; Wallach and Verch, 1986; Yamamoto et al., 1995; Zemel et al., 1990). Other dietary factors may also play a role. A recent study demonstrated that a diet of fruits and vegetables, which increased magnesium intakes from an average of 176 mg (7.3 mmol)/day to 423 mg (17.6 mmol)/day, significantly lowered blood pressure in adults who were not classified as hypertensive (systolic blood pressure < 140 mm Hg; diastolic blood pressure < 95 mm Hg) (Appel et al., 1997). The addition of nonfat dairy products to the high fruit and vegetable diet, which increased calcium intake as well, resulted in further lowering of blood pressure. Potassium intake was also greatly increased in both dietary regimens studied.

One study of hypertensive patients revealed low serum magnesium concentrations (Albert et al., 1958). No difference was detected in serum magnesium levels in other studies, however (Gadallah et al., 1991; Tillman and Semple, 1988). In patients with essential hypertension, free magnesium levels in erythrocytes were inversely related to both the systolic and diastolic blood pressure (Resnick et al., 1984). It is unclear whether the decrease in serum magnesium concentration was due to magnesium depletion or to pathophysiological events that lead to hypertension.

The possible relationship between hypertension and magnesium depletion is an important consideration, as the two coexist in a high proportion of individuals with diabetes and alcoholism (Resnick et al., 1991). However, the role of long-term dietary intake of magnesium in the prevalence of hypertension seen in the United States and Canada has not been established.

Skeletal Growth and Osteoporosis

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 deficiency may be a risk factor for postmenopausal osteoporosis. Significant reductions in the serum magnesium and bone mineral content (BMC), but not red blood cell magnesium concentration or bone magnesium content, have been described in women with postmenopausal osteoporosis compared to age-matched controls (Reginster et al., 1989). No correlations were found in a 4-year clinical trial of magnesium intake and BMC in pre- and postmenopausal women consuming about 250 mg (10.4 mmol)/day of magnesium (Freudenheim et al., 1986), or in four of five skeletal sites measured in postmenopausal women also consuming an average of 253 mg ± 11 mg (10.5 ± 0.4 mmol)/day of magnesium (Angus et al., 1988).

In contrast, BMC of the radius in postmenopausal Japanese-American women was weakly positively correlated with magnesium intake (Yano et al., 1985), while elderly women who consumed less than 187 mg (7.8 mmol)/day had a significantly lower bone mineral density (BMD) compared with women whose average magnesium intake from diet was more than 187 mg (7.8 mmol)/day (Tucker et al., 1995).

Two studies are available on the effect of magnesium supplementation on osteoporosis. In women with documented osteoporosis, supplementation with 750 mg (31.3 mmol) of magnesium for the first 6 months followed by 250 mg (10.4 mmol) supplementation from the seventh to twenty-fourth month increased radial BMD after 12 months, but no further change was seen in BMD by the end of the second year (Stendig-Lindberg et al., 1993). Supplementation with 500 mg (20.8 mmol) of magnesium and 600 mg (15 mmol) of calcium in postmenopausal women who were receiving estrogen replacement therapy and daily multivitamin and mineral tablets resulted in increased calcaneous BMD in less than a year when compared with the postmenopausal women who received sex steroid therapy alone (Abraham and Grewal, 1990). These observations suggest that dietary magnesium may be related to osteoporosis and indicate a need for further investigation of the role of magnesium in bone metabolism (Sojka and Weaver, 1995).

Diabetes Mellitus

Magnesium depletion in a few studies has been shown to result in insulin resistance as well as impaired insulin secretion, and thereby may worsen control of diabetes (for review, see Paolisso et al. [1990]). An experimental magnesium depletion study was conducted to examine the development of insulin resistance. Normal male subjects were given a controlled diet for three weeks in a depletion metabolic study in which magnesium intake was 12 mg (0.5 mmol)/day. Intravenous glucose tolerance tests performed at the beginning and end of the 21-day depletion indicated a significant decrease in insulin sensitivity (Nadler et al., 1993). Such findings have raised the possibility that insulin resistance and abnormal glucose tolerance in individuals may be due to inadequate magnesium (Paolisso et al., 1992). Magnesium depletion in clinical observational studies has been defined by low serum magnesium concentrations as well as a reduction of total and/or ionized magnesium in red blood cells, platelets, lymphocytes, and skeletal muscle (Nadler et al., 1992), in spite of subjects consuming a level of magnesium similar to that in population studies (Schmidt et al., 1994).

Insulin resistance is commonly noted in the elderly (Fink et al., 1983; Rowe et al., 1983). Dietary magnesium supplements have been shown to improve glucose tolerance (Paolisso et al., 1992) and improve insulin response in elderly, non-insulin-dependent patients with diabetes (Paolisso et al., 1989). One possible cause for the magnesium depletion seen in diabetes is glycosuria-induced renal magnesium wasting (Rude, 1993). However, until magnesium depletion studies conducted in normal individuals can relate specific dietary intake levels with abnormal glucose tolerance testing or other indicators of glucose metabolism, it is premature to consider the prevalence of diabetes mellitus as a functional indicator of adequacy for magnesium.

Increased Risk in the Elderly

Several studies have demonstrated that elderly people have relatively low dietary intakes of magnesium (Goren et al., 1993; Lowik et al., 1993). Their lower intake may be due to a variety of reasons, including poor appetite, loss of taste and smell, poorly fitting dentures, and difficulty in shopping for and preparing meals (Mountokalakis, 1987). Meals in some long-term care facilities may provide less than the recommended levels of magnesium (Lipski et al., 1993). In addition, magnesium metabolism may change with aging. As mentioned earlier, intestinal magnesium absorption tends to decrease with aging, and urinary magnesium excretion increases (Lowik et al., 1993; Martin, 1990). A suboptimal diet in magnesium may therefore place this population at risk for magnesium depletion.

ESTIMATING REQUIREMENTS FOR MAGNESIUM

Selection of Indicators for Estimating the Magnesium Requirement

Serum Magnesium

The serum magnesium concentration may not reflect intracellular magnesium availability. Nevertheless, measurement of the serum magnesium concentration is the most available and commonly employed test to assess magnesium status. The serum magnesium level may be influenced by changes in serum albumin, other anionic ligands, and pH; however, correction for changes due to these factors is seldom made (Quamme, 1993). Normal values by age and gender have been derived from sampling the U.S. population in NHANES I (Lowenstein and Stanton, 1986). A serum magnesium concentration of less than 0.75 mmol/liter (1.8 mg/dl) is thought to indicate magnesium depletion (Elin, 1987).

Experimentally induced dietary magnesium depletion consistently leads to decreased serum magnesium values in otherwise healthy humans. This suggests that, under these circumstances, serum magnesium is a sensitive indicator of magnesium status (Fatemi et al., 1991). Hypomagnesemia (serum magnesium < 0.75 mmol/liter [1.8 mg/dl]) usually develops concurrently with moderate to severe magnesium depletion. However, in clinical studies in which concentrations of magnesium in blood cells, bone cells, or muscle cells are abnormally low (such as in diabetes mellitus, alcoholism, or malabsorption syndromes), serum magnesium values have been reported to be within the normal range (Abbott et al., 1994; Nadler et al., 1992; Rude and Olerich, 1996). These findings suggests that intracellular magnesium is a better guide to magnesium status in humans than is the concentration in serum (Reinhart, 1988; Ryzen et al. 1986). One recent longitudinal evaluation of 8,251 subjects who entered a study between 1971 and 1975 found 492 cardiovascular events when the subjects were reevaluated between 1982 and 1984 (Gartside and Glueck, 1995). Subjects with serum magnesium levels less than 0.81 mmol/liter (1.9 mg/dl) had greater risk of cardiovascular disease than did those with a serum magnesium level greater than 0.87 mmol/liter (2.1 mg/dl). Although both values were within what has been considered the normal range, 0.75 to 0.95 mmol/liter (1.8 to 2.3 mg/dl) (Elin, 1987), this variation in response questions the validity of serum magnesium levels as indicators of magnesium status (Gartside and Glueck, 1995). There are also reports that elderly subjects may have a decrease in magnesium status as determined by magnesium tolerance testing (see below) despite normal serum magnesium concentrations. Thus, serum magnesium concentration has not been validated as a reliable indicator of body magnesium status.

Plasma-Ionized Magnesium

Recently, ion-specific electrodes have become available for determining ionized magnesium in the plasma. Early results suggest that this may be a better index of magnesium status than the total serum magnesium concentration; however, further evaluation is necessary. Few studies have been conducted under varying conditions to assess its validity (Altura et al., 1992; Mimouni, 1996).

Intracellular Magnesium

The total magnesium contents of several tissues, including red blood cells, skeletal muscle, bone, and peripheral lymphocytes have been evaluated as indices of magnesium status. However, determination of intracellular magnesium concentration should be a more physiologically relevant measurement of magnesium status, as it is thought to play a critical role in enzyme activation within the cell. In general, poor correlation exists between the serum magnesium concentration and intracellular levels. Lymphocyte magnesium does not correlate well with serum or red blood cell magnesium levels (Elin and Hosseini, 1985; Ryzen et al., 1986) and serum magnesium concentration does not accurately reflect muscle magnesium content (Alfrey et al., 1974; Wester and Dyckner, 1980). In normal subjects lymphocyte and skeletal muscle magnesium did correlate well, however not in patients with congestive heart failure (Dyckner and Wester, 1985). Thus, further evaluation is needed before lymphocyte or muscle magnesium content can be utilized to assess magnesium status.

Red blood cell magnesium has been determined by nuclear magnetic resonance (Rude et al., 1991). The fluorescence probe has been utilized for determination of free magnesium in lymphocytes and platelets (Hua et al., 1995; Nadler et al., 1992). Red blood cell magnesium values fall within days following institution of a low-magnesium diet in normal subjects (Fatemi et al., 1991). The mean intracellular free magnesium was lower than normal in patients at high risk for magnesium depletion (for example, individuals with diabetes or alcoholism) (Hua et al., 1995; Nadler et al., 1992; Rude, 1991).

In one study, total red blood cell magnesium concentration was found to be lower in elderly subjects (77.8 ± 2.1 years), as compared with younger people (36.1 ± 0.4 years), when the mean magnesium consumption of both groups was 311 ± 21 mg (13.0 ± 0.9 mmol)/day (Paolisso et al., 1992). However, the evidence was not judged sufficient to use red blood cell magnesium as an indicator of status.

Magnesium Balance Studies

The principal measure of adequate dietary magnesium in the past has been the dietary balance study (Greger and Baier, 1983; Hunt and Schofield, 1969; Mahalko et al., 1983; Schwartz et al., 1984, 1986). Most balance studies were performed at clinical research centers where the diet was constant and controlled. However, this technique still presents several problems, including the measurement of magnesium intake and urine and stool magnesium excretion. In addition, sweat and dermal losses of magnesium have not usually been considered.

In adults, balance studies should be performed at magnesium intakes just below and above those at which zero balance is achieved to obtain the approximately linear dependence of loss and retention near balance (Beaton, 1996). The intake associated with zero balance from each individual studied can then be grouped and the variability of requirements estimated (Beaton, 1996). Since magnesium intake is related to energy intake (Clarkson and Haymes, 1995; Niekamp and Baer, 1995), balance studies may report the findings in relation to estimated energy requirements if the data are to be applied to the general population. Magnesium may be obtained from food, water, nutrient supplements, or pharmalogical agents, but the bioavailability may differ.

Although numerous magnesium balance studies have been performed, not all met the requirements of a well-designed study. Some provided for a period of adaptation but did not include magnesium intakes, which would have allowed average requirements to be estimated. Balance studies performed prior to 1960 utilized less accurate means to measure magnesium as compared with atomic absorption spectrophotometry. The minimum criteria used here for inclusion of balance studies for the development of recommendations for magnesium requirements included either an adaptation period of at least 12 days or a determination of balance while the subjects consumed self-selected diets. The disadvantage of using self-selected diets is that only one level is being evaluated. If the individual is in balance or nearly so, it is not possible to discern if this is just an adaptation to that level or if it truly represents the minimal level of adequacy. Similarly, if only one level of intake is provided, no matter how accurate, it is not possible to get the dose response data necessary to estimate the requirement. At least two levels need to be evaluated: one below and one near the required level.

When a study is not carried out in a metabolic unit or under close supervision, data are generally lacking on magnesium intake from water. This omission precludes the use of many of the earlier studies conducted in free-living environments or current studies in which intakes were calculated rather than analyzed.

Estimates of Tissue Accretion During Growth

In the absence of data regarding specific requirements for magnesium for growth during various life stages, accretion rates of magnesium have been estimated (Nordin, 1976; Widdowson and Dickerson, 1964). The rates of tissue accretion during childhood are derived from analysis of cadavers, and the utility of these data is limited. In some cases using data from cadavers, the estimates of whole body mineral retention must be calculated based on measurements from regional sites (Fomon and Nelson, 1993). Fomon and Nelson (1993) and Koo and Tsang (1997) used data from cadavers to estimate a net accretion of 10 mg (0.4 mmol)/day during the second year of life. However, further information is needed before this approach may be uniformly used to estimate magnesium needs throughout childhood.

The total magnesium content of an infant weighing 3.5 kg (7.7 lb) is approximately 220 mg (9.2 mmol)/kg or 760 mg (32 mmol). Magnesium as a percentage of fat-free body mass increases during gestation, but at birth the percentage is much less than that of an adult (Widdowson and Dickerson, 1964). The content of magnesium in an adult man is estimated to total 27.4 g (1,141.7 mmol), or about 390 mg (16.2 mmol)/kg (Widdowson and Dickerson, 1964).

In order to accumulate approximately 26.6 g (1,108.3 mmol) over the 20 years of growth from infancy to adulthood, an average daily accretion during this period of about 3.6 mg (0.2 mmol) would be necessary. However, the growth rate is not linear with age. It has been suggested that an adequate accretion rate (positive balance) for girls 10 to 12 years of age and weighing about 40 kg (88 lb) is 8.5 mg (0.3 mmol)/day (Andon et al., 1996). For older children who are heavier and experiencing greater growth in lean and bony tissue, a positive balance in the range of 10 mg (0.4 mmol)/day would be appropriate.

Magnesium Tolerance Test

The magnesium tolerance test, which is based on the renal excretion of a parenterally administered magnesium load, has been used for many years. It is considered by some to be an accurate means of assessing magnesium status in adults, but not in infants and children (Gullestad et al., 1992; Ryzen et al., 1985). However, the sensitivity of this method in detecting magnesium depletion may be different between subjects with and without hypomagnesemia. In 15 hypomagnesemic subjects, 85 ± 3 percent of a parenterally administered magnesium load was retained, compared to only 14 ± 4 percent in 23 normal controls (Ryzen et al., 1985). In a group of 24 chronic alcoholics at risk of magnesium deficiency, retention of 51 ± 5 percent was also significantly greater than the control group. While the magnesium tolerance test has been shown in this and other studies (Cohen and Laor, 1990; Costello et al., 1997; Gullestad et al., 1992) to detect magnesium depletion in both hypomagnesemic and normomagnesemic subjects at risk of magnesium depletion, the test was not sensitive to detect treatment effects of magnesium supplementation in otherwise healthy subjects (Costello et al., 1997). After 3 months of supplementation of 350 mg (14.5 mmol)/day of magnesium, the mean retention of 37 percent did not change significantly. Thus, the sensitivity of this method in normal subjects is not yet validated and so cannot be accepted as the primary indicator for assessing adequacy at this time.

One of the problems in using the magnesium tolerance test is that it requires normal renal handling of magnesium. Urinary magnesium loss (related to conditions such as diabetes or drug or alcohol use) may yield an inappropriate negative test. Moreover, impaired renal function may result in a false positive test (Martin, 1990). Age may also be a confounding variable, since older subjects (73 ± 6 years) have been reported to retain significantly more magnesium than younger subjects (33 ± 10 years), despite a comparable mean daily dietary magnesium intake of 5.1 mg (0.2 mmol)/kg of body weight (Gullestad et al., 1994). Supplements of 225 mg (9.4 mmol)/day of magnesium as magnesium lactate-citrate for 30 days to the elderly subjects turned the test results toward normal. Martin (1990) studied 30 elderly females (mean age of 82 years, range 72 to 93 years) who were stated to have "lower than recommended dietary magnesium intakes." Subjects with serum magnesium less than 0.59 ± 0.07 mmol/liter (1.4 ± 0.2 mg/dl) retained a higher percentage of the magnesium load (61 ± 12 percent) than subjects with mean serum magnesium levels of 0.72 ± 0.02 mmol/liter (1.7 ± 0.05 mg/dl) whose retention was 43 ± 16 percent. Both of these levels of retention, however, are high compared to that seen in younger age groups. Thus the influence of renal function in this test cannot be ignored. Of significant concern, even if this test is validated in future studies as a primary indicator of magnesium status, is the invasive procedure (intravenous administration) used.

Epidemiological Studies and Meta-analysis

As discussed in the previous section, epidemiologic studies have suggested that individuals or groups ingesting hard water that contains magnesium, consuming a diet higher in magnesium, or using magnesium supplements, have decreased morbidity from cardiovascular disease or less hypertension (Altura et al., 1990; Ascherio et al., 1992; Hammer and Heyden, 1980; Joffres et al., 1987; Leoni et al., 1985; Luoma et al., 1983; Ma et al., 1995; McCarron, 1983; Nadler et al., 1993; Neri and Johansen, 1978; Neri et al., 1985; Rubenowitz et al., 1996; Witteman et al., 1989). Low magnesium intake has also been linked to osteoporosis (Sojka and Weaver, 1995). Because of the difficulty of conclusively establishing that the lack of dietary magnesium was the primary causative factor in these chronic diseases, the basis for a claim is equivocal. Thus, based on the scientific literature currently available, these data can not serve as the indicators of adequacy in estimating magnesium requirements. However, as recently reviewed by Tucker (1996), the evidence from many studies, taken together, may lend confidence to the theory that dietary magnesium intake may indeed contribute to these disorders.

FINDINGS BY LIFE STAGE AND GENDER GROUP

Birth through 12 Months

No functional criteria of magnesium status have been demonstrated that reflect response to dietary intake in infants. Thus, recommended intakes of magnesium are based on an Adequate Intake (AI) that reflects the observed mean intake of infants fed principally with human milk.

Indicators Used to Set the AI

Human Milk. Human milk is recognized as the optimal milk source for infants throughout at least the first year of life and recommended as the sole nutritional milk source for infants during the first 4 to 6 months of life (IOM, 1991). Therefore, determination of the AI for magnesium for infants is based on data from infants fed human milk as the principal fluid during periods 0 through 6 and 7 through 12 months of age. The AI is set at the mean value for observed intakes as determined from studies in which intake of human milk was measured by test weighing volume, and intake of food was determined by dietary records for 3 days or more.

Balance Studies. The limited data on magnesium balance in infants were considered supportive evidence for the derived AI. Many of the magnesium balance studies involving human milk-fed infants have been performed on premature infants or infants in the first weeks of life. Net retention of magnesium in the studies of premature infants was 10 to 15 mg (0.4 to 0.6 mmol)/day with 45 percent absorption (Atkinson et al., 1987; Schanler et al., 1985). This level of retention was similar to that reported earlier in 10 breast-fed infants at 5 to 7 days of age, with repeat balance studies performed in three of these infants again at 4 to 6 weeks of age (Widdowson, 1965).

Differences in magnesium needs between infants fed human milk and those fed infant formula are described in the "Special Considerations" section.

AI Summary: Ages 0 through 6 Months

Based on data from a summary of recent studies in North America and the United Kingdom (Atkinson et al., 1995), the concentration of magnesium in human milk is about 34 mg (1.4 mmol)/liter, and the concentration remains relatively constant over the first year of lactation (Allen et al., 1991; Dewey et al., 1984). The AI is set based on a reported average intake of human milk of 780 ml/day (Allen et al., 1991; Butte et al., 1984; Heinig et al., 1993) and the average milk magnesium concentration of 34 mg (1.4 mmol)/liter. This gives an AI of 30 mg (1.3 mmol)/day. The balance data cited above support an AI of 30 mg (1.3 mmol)/day for this age range, as it would allow infants to maintain a positive magnesium balance of at least 10 mg (0.4 mmol)/day during early infancy.

AI Summary: Ages 7 through 12 Months

During the second 6 months of life, solid foods become a more important part of the infant diet and add a significant but poorly defined amount of magnesium. The absorption of magnesium from solid foods and the effects of solid foods on absorption of magnesium from human milk are unknown. To set an AI for infants from 7 through 12 months of age, the average magnesium intake from solid foods—55 mg (2.2 mmol)/day—for 9- to 12-month-old formula-fed infants (Specker et al., 1997) was used. This approach assumes that infants who are fed human milk have intakes of solid food similar to those fed formulas.

Based on the data of Heinig et al. (1993), the mean volume of human milk consumed between 7 and 11 months of age would be 600 ml/day. Thus, magnesium intake from human milk with an average magnesium concentration of 34 mg (1.4 mmol)/liter would be about 20 mg (0.8 mmol)/day. Summing the intake from human milk and from solid food, the AI for magnesium for infants 7 through 12 months of age is set at 75 mg (3.1 mmol)/day.

AI for Infants	**0 through 6 months**	**30 mg (1.1 mmol)/day**
	7 through 12 months	**75 mg (3.1 mmol)/day**

Special Considerations

Infant Formulas. Commercial infant formulas that are cow milk-based are generally higher in magnesium concentration, 40 to 50 mg (1.7 to 2.1 mmol)/liter, than human milk. Soy-based formulas may have even higher concentrations of magnesium, 50 to 80 mg (2.1 to 3.3 mmol)/liter (Fomon and Nelson, 1993; Greer, 1989). In a large series of studies (>300 balances), Fomon and Nelson (1993) reported approximately 40 percent net absorption of magnesium in infants fed soy or cow milk-based formulas with a net retention of 10 mg (0.4 mmol)/day based on total intakes of 53 to 59 mg (2.2 to 2.5 mmol)/day of magnesium.

Higher absorption values of 57 to 71 percent of magnesium intake from standard cow milk-based infant formulas have been reported (Kobayashi et al., 1975; Moya et al., 1992). A dietary fractional absorption rate of 64 ± 4 percent was reported in three infants aged 4 to 10 months. Magnesium intakes of the infants exceeded 150 mg (6.3 mmol)/day in the latter study.

Direct assessment of an AI for magnesium for formula-fed infants is not possible due to the lack of data comparing magnesium absorption from human milk and from infant formulas. Based on the current U.S. practices of infant formula manufacturers, the increase of 20 percent above the level of magnesium intake of human milk-fed infants allows for the possibility of a lower bioavailability of magnesium from formulas. This leads to an estimated intake of 35 mg (1.5 mmol)/day (human milk + 20 percent) for formula-fed infants. Similar absorption of magnesium from soy versus routine formulas (Fomon and Nelson, 1993) does not indicate a greater need for magnesium in soy formula-fed infants, but the practice of increasing magnesium intake in soy formulas relative to cow-milk formulas is widely followed by formula manufacturers.

Ages 1 through 3, 4 through 8, 9 through 13, and 14 through 18 Years

Indicators Used to Set the EAR

A possible approach to determining human magnesium requirements is to estimate the intake required to achieve a level of retention associated with a beneficial outcome. Although magnesium retention during growth should be positive, the desirable extent of retention for magnesium is unknown. As discussed earlier, there are inadequate data upon which to attribute a specific benefit to maximal retention of magnesium. This is unlike calcium, for which maximal retention can be associated with benefit to bone mass accretion. Since the criterion of maximal retention could not be used for magnesium, magnesium balance data were used as the basis for establishing Estimated Average Requirements (EARs) for these age groups.

As mentioned previously, an adequate accretion rate (positive balance) for girls 10 to 12 years of age and weighing about 40 kg (88 lb) may be 8.5 mg (0.3 mmol)/day (Andon et al., 1996). It is probable that for older children, who are heavier and experiencing greater growth in lean and bony tissue, a positive balance in the range of 10 mg (0.4 mmol)/day of magnesium would be appropriate. This would allow for the greater need for magnesium during the specific periods of faster growth during older childhood. In the absence of more definitive goals, a daily positive balance of 8 to 10 mg (0.3 to 0.4 mmol) of magnesium seems to be a reasonable goal upon which to base an EAR for growing children and adolescents.

Balance Studies. For children under 10 years of age, there is only one report of a balance study published since 1960 (Schofield and Morrell, 1960). For children between 10 and 15 years of age, seven studies were available for consideration (see Table 6-1). The amount of magnesium lost via other routes (dermal, sweat, menses, and other losses) was not measured or estimated in the calculations of any of these studies. Other balance studies performed in children prior to 1960 (see review by Seelig [1981]) were not considered because information regarding absorption over a range of intakes was not provided and results reported may not be reliable using the analytical methodology available at that time.

Given the information provided in the available balance studies, expression of magnesium requirements for children is probably more accurate on the basis of intake per day, rather than per unit of body weight or per amount of lean tissue. When expressed on a mg/kg/day basis, magnesium requirements determined by balance studies in subjects who were obese were much lower than those in subjects of normal weight (Jones et al., 1967), as fat contains less magnesium than other tissues and body fat increases with age. Expressing EARs and Recommended Dietary Allowances (RDAs) per kg ideal body weight or lean body mass would be more accurate than per kg total weight. However, since most reports of balance studies do not provide individual intake and body weight or height data, it is seldom possible to determine the response of individuals to specific levels of magnesium consumed on either an ideal or actual body weight basis. Future experiments might address requirements in relation to energy needs (Shils and Rude, 1996).

Because of the lack of studies in younger children, the data from children 10 to 15 years old (see Table 6-1) were extrapolated using reference body weights. Interpretation of the available balance data are confounded by the lack of information provided on individual body weights, varying age and weight ranges studied within and between studies, and variations in dietary protein (both in amount and source) and calcium (see "Calcium" and "Protein" below). In reviewing the details of the studies summarized in Table 6-1, it appears that, provided the diet has adequate protein for 9 through 13 year olds, group mean positive magnesium balance in the range of 10 mg (0.41 mmol)/day is achieved at intakes of approximately 5 mg (0.21 mmol)/kg/day. In the recent short-term study using multitracer stable isotope technique to assess magnesium balance in 13 adolescent girls (Abrams et al., 1997), the mean magnesium balance was slightly negative (–0.9 ± 41 mg [0.04 ± 1.7 mmol]/day) at comparatively high levels of average intake (6.4 mg [0.27 mmol]/kg/day of magnesium). Some of this may have been due to the amount of calcium in the diet (1,310 mg [33 mmol]/day); however, another recent study using multitracer stable isotopes (Sojka et al., 1997), did not show a significant difference in magnesium balance with two levels of dietary calcium (see "Calcium" below).

In the one balance study in which children 7 to 9 years old were evaluated, positive magnesium balance was achieved on daily dietary magnesium intakes that ranged from 121 to 232 mg (5.0 to 9.7 mmol)/day (Schofield and Morrell, 1960); a magnesium intake of 5 mg (0.21 mmol)/kg/day appeared to meet some but not all of the younger children's needs. Taken together with the data on older children, the available balance studies suggest that at a magnesium intake of 5 mg/kg body weight/day, some but not all children would be in magnesium balance. The extent to which this represents 50 percent of children in these age groups and pubertal stages meeting their needs is difficult to predict because of the confounding variables of other dietary components. For establishing the EARs for magnesium for children ages 1 through 3 and 4 through 8, for which balance studies are unavailable, the value of 5 mg/kg/day is adopted.

Additional Factors Considered for the Above Studies

Calcium. As stated earlier, increasing calcium intake may have a negative effect on magnesium balance (Greger et al., 1981). In two recent studies in this age group, however, little effect was noted. Compared with a calcium intake of 667 mg (16.7 mmol)/day, intakes of 1,667 mg (41.7 mmol)/day (the additional 1,000 mg [25 mmol] from two divided doses of a supplement) did not decrease magnesium retention in girls aged 10 to 12 years (Andon et al., 1996). In a magnesium kinetic study in which five girls aged 12 to 14 years were given two stable isotopes of magnesium at two levels of calcium, 800 mg (20 mmol) and 1,800 mg (45 mmol), no significant differences were seen in the magnesium balances measured or in the percentage of magnesium absorbed (Sojka et al., 1997). The calcium contents of the diets provided in the other two balance studies of adolescents were 1,200 mg (30 mmol) (which included supplements) (Schwartz et al., 1973) and 1,060 to 1,080 mg (26.5 to 27 mmol) from foods (Greger et al., 1978). Supplementation with 900 mg (22.5 mmol) of calcium to a controlled, food-based diet containing 300 to 350 mg (12.5 to 14.6 mmol) and 697 mg (17.4 mmol) calcium/day did not affect overall magnesium retention in eight adult male subjects (Lewis et al., 1989).

Protein. Magnesium requirements are influenced by the level of dietary protein, apparently in part related to effects on urinary magnesium excretion (Lakshmanan et al., 1984; Mahalko et al., 1983; Wisker et al., 1991). Magnesium intakes in male adolescents on lower protein intakes (50 g/day) were inadequate, but with higher protein diets (94 g/day), balances became positive (Schwartz et al., 1973). Some have suggested that the effect of protein may differ for animal and vegetable sources. However, in one study of adolescent girls, little difference was noted in this age group when soy was substituted for animal protein at a level of 30 percent of the total protein that was fed at a level of 46 to 49 g/day (Greger et al., 1978). The influence of protein intake on magnesium requirements needs additional study.

EAR Summary: Ages 1 through 3 and 4 through 8 Years

In the absence of adequate balance or usual accretion data in children aged 1 through 8 years, it is necessary to interpolate data from other age groups based on changes in body weight and linear growth.

TABLE 6-1 Magnesium (Mg) Balance Studies in Adolescents Aged 9 through 18 Years

Study, Year	n	Age (y)	Weight (kg)	Adaptation period (d)	Balance period (d)	Average Daily Mg Intake	Balance	Comments
Females								
Andon et al., 1996	13	10.5–12.5	39 ± 5	7	7	176 mg (4.45 mg/kg)	19 ± 25 mg/d	Intake >5.0 mg/kg/d resulted in positive balance in all subjects.
	13		42 ± 8	7	7	176 mg (4.45 mg/kg)	22 ± 15 mg/d	Half of subjects on 1,667 mg Ca/d; half on 1667 mg Ca/d.
Greger et al., 1978	5	12.5–14.5	34.5–58.5	9	21	190 ± 29 mg	–6.8 ± 10.4 mg/d	At intakes of 4.0 mg/kg/d, only 2 of the 26 girls were in positive balance.
	5			9	21	195 ± 29 mg	–6.8 ± 10.4 mg/d	At intakes of 4.0 mg/kg/d, only 2 of the 26 girls were in positive balance.
	4			9	21	195 ± 29 mg	–1.8 ± 2.2 mg/d	
Greger et al., 1979	11	12.5–14.2	52.5 ± 13.6	5	9	Avg. 276 mg	15 ± 18 mg/d	Diet contained 1,049 mg calcium; 11.3 mg zinc.
				5	9		2 ± 36 mg/d	Diet contained 1,049 mg calcium; 14.5 mg zinc.

Abrams et al., 1997	13	12.3 ± 1.6	48 ± 17.7	14	10	19–321 mg (6.4 ± 1.2 mg/kg/d)	–0.9 ± 41.2 mg/d	Six of 13 in negative balance; adapted to 1,310 mg calcium intake before entry.
Sojka et al., 1997	5	12–14	54.6	7	14	264–346 mg (305 ± 30 mg)	13 ± 35 mg/d	Diet contained 61 g protein; 823 mg calcium.
				7	14	272–294 mg (286 ± 9 mg)	–34 ± 48 mg/d	Diet contained 61 g protein; 1,824 mg calcium.
Males								
Schwartz et al., 1973	6	13.8–15	40.5–70.5*	15	15 2x/2 y	240 mg (4.3 + 0.21 mg/kg)	–0.62 ± .07 mg/kg/d	43 g/d protein.
					15 2x/2 y	240 mg (4.1 ± 0.16 mg/kg)	0.19 ± 0.08 mg/kg/d	93 g/d protein.
					15 2x/2 y	740 mg (13.1 ± 0.51 mg/kg)	1.25 ± 0.26 mg/kg/d	43 g/d protein.
					15 2x/2 y	740 mg (14.5 ± 0.61 mg/kg)	0.88 ± 0.48 mg/kg/d	93 g/d protein.
Abrams et al., 1997	12	10.9 ± 1.1	35.7 ± 7.0	14	10	194–321 (6.4 ± 1.2 mg/kg/d)	15.6 ± 36.8 mg/d	Five of 12 in negative balance; adapted to 1,310 mg calcium before entry.

* Weights at end of first balance study.

Based on studies in adolescents (Abrams et al., 1997; Andon et al., 1996; Greger et al., 1978, 1979; Schwartz et al., 1973) and the one study in 7- to 9- year-old children (Schofield and Morrell, 1960), a magnesium intake of 5 mg (0.21 mmol)/kg/day appears to have met some but not all the needs of those evaluated. This is the basis for the EAR for children ages 1 through 3 years and 4 through 8 years. For children ages 1 through 3 years with a reference weight of 13 kg (Table 1-3), the EAR is 65 mg (2.7 mmol)/day. For children ages 4 through 8 years with a reference weight of 22 kg, the EAR is 110 mg (4.6 mmol)/day. It is recognized that further studies specific to this age group are needed before more precise EARs can be assigned or distinctions made between males and females or between children of different racial or ethnic groups.

EAR for Children	**1 through 3 years**	**65 mg (2.7 mmol)/day**
	4 through 8 years	**110 mg (4.6 mmol)/day**

Based on the 1994 CSFII magnesium intake data, adjusted for day-to-day variation (Nusser et al., 1996), the first percentile of intake for children ages 1 through 3 years is 80 mg (3.3 mmol) (see Appendix D), which is above the EAR of 65 mg (2.7 mmol)/day. The median intake for magnesium for this age group is 180 mg (7.5 mmol). For children ages 4 through 8 years, the first percentile of intake is 103 mg (4.3 mmol)/day, slightly below the EAR of 110 mg (4.6 mmol)/day. The median magnesium intake is 206 mg (8.6 mmol)/day.

Determination of the RDA: Ages 1 through 3 and 4 through 8 Years

The variance in requirements cannot be determined from the available data. Thus, a coefficient of variation (CV) of 10 percent is assumed, which results in an RDA for magnesium of 80 mg (3.3 mmol)/day for children ages 1 through 3 years, and an RDA of 130 mg (5.4 mmol)/day for children ages 4 through 8 years.

RDA for Children	**1 through 3 years**	**80 mg (3.3 mmol)/day**
	4 through 8 years	**130 mg (5.4 mmol)/day**

EAR Summary: Ages 9 through 13 Years, Boys

The Abrams et al. (1997) study provides some data for boys ages 9 through 13 years that leads to the conclusion that boys, not yet into maximal growth at this age, appear to require about the same amount of magnesium as girls per kg per day. Thus, the EAR is estimated to be 5 mg (0.21 mmol)/kg/day for boys ages 9 through 13 years. Based on a reference weight of 40 kg (Table 1-3) for boys ages 9 through 13 years, their EAR is 200 mg (8.3 mmol)/day.

EAR for Boys 9 through 13 years 200 mg (8.3 mmol)/day

Based on the 1994 CSFII magnesium intake data adjusted for day-to-day variation (Nusser et al., 1996), the tenth percentile of intake for boys ages 9 through 13 years is 181 mg (7.5 mmol)/day, and the twenty-fifth percentile intake is 216 mg (9 mmol)/day (see Appendix D). Thus the EAR of 200 mg (8.3 mmol)/day for boys ages 9 through 13 years would fall between the tenth and twenty-fifth percentile of intake in this age category.

EAR Summary: Ages 9 through 13 Years, Girls

Because the protein intake of the younger girls in the Andon et al. (1996) study was not indicated, it is possible that one of the reasons that most of the girls were in positive magnesium balance on the 176 mg (7.3 mmol)/day intake was their higher intake of dietary protein. The second possible reason is their younger age and body size. In the absence of additional data and assuming a protein intake of 50 g/day, the EAR for girls ages 9 through 13 years is 5 mg (0.21 mmol)/kg/day, based primarily on the Andon et al. (1996) study, in which all girls who consumed this level or less were in positive balance. Their average weights were 41 kg (90 lb), and few had yet started menarche. In the Greger et al. study (1979), the average weight was 52.5 kg (115.7 lb), and 6 of the 11 girls had already started menarche. Their requirements reflect a greater lean body mass. Thus, based on the reference weight of 40 kg (Table 1-3) for girls ages 9 through 13 years, their EAR is 200 mg (8.3 mmol)/day.

EAR for Girls 9 through 13 years 200 mg (8.3 mmol)/day

Based on the 1994 CSFII intake data and adjusted for day-to-day variation (Nusser et al., 1996), the twenty-fifth percentile magnesium intake for girls ages 9 through 13 years is 194 mg (8.1 mmol), and the median intake is 224 mg (9.3 mmol)/day (see Appendix D). Thus, the magnesium EAR of 200 mg (8.1 mmol)/day would be between the twenty-fifth percentile and the median intake for girls ages 9 through 13 years.

Determination of the RDA for Magnesium: Ages 9 through 13 Years

The variance in requirements cannot be determined from the data available. Thus, a CV of approximately 10 percent is assumed for each EAR. This results in an RDA of 240 mg (10 mmol)/day for both boys and girls ages 9 through 13 years.

RDA for Boys	**9 through 13 years**	**240 mg (10 mmol)/day**
RDA for Girls	**9 through 13 years**	**240 mg (10 mmol)/day**

EAR Summary: Ages 14 through 18 Years

Given the available data, it seems appropriate to conclude that for older adolescents, the average magnesium requirement is greater than 5 mg (0.21 mmol)/kg/day. The average *additional* magnesium intake necessary to result in a net retention of about 8 mg (0.33 mmol)/day is about 16 mg (0.67 mmol) or 0.3 mg (0.12 mmol)/kg/day for a 55 kg adolescent based on an assumed absorption rate of 40 percent (range 30 to 50 percent) (Abrams et al., 1997). Less than 5 mg (0.21 mmol)/kg/day of magnesium resulted in negative balances in all boys when they consumed the lower protein intake in the Schwartz et al. (1973) study and in most of the older girls in the Greger et al. (1978) study. In the 2-year Schwartz et al. (1973) study, even for subjects on the high protein diet, average magnesium retention was 6 and 15 mg (0.25 and 0.63 mmol)/day for each year, respectively, at the 240 mg (10 mmol)/day intake level. Thus, the EAR is estimated to be 5.3 mg (0.22 mmol)/kg/day in 14- through 18-year-old boys and girls, given that the highest average level provided in any of the five long-term balance studies (Andon et al., 1996; Greger et al., 1978, 1979; Schwartz et al., 1973, Sojka et al., 1997) was 5.6 mg (0.23 mmol)/kg/day. This resulted in slightly negative nitrogen balances in the older children studied (Greger et al., 1978; Schwartz et al., 1973). An average intake of 6.4 mg (0.27 mmol)/kg/day resulted in net positive magnesium retention in the more recent stable isotope study of Abrams et al. (1997). Thus, for boys ages 14 through 18 years, with reference weight 64 kg (Table 1-3), the EAR for magnesium is 340 mg (14.2 mmol)/day, and for girls in this age range with reference weight of 57 kg, the EAR is 300 mg (12.5 mmol)/day.

EAR for Boys	**14 through 18 years**	**340 mg (14.2 mmol)/day**
EAR for Girls	**14 through 18 years**	**300 mg (12.5 mmol)/day**

Based on the 1994 CSFII intake data, adjusted for day-to-day variation (Nusser et al., 1996), the magnesium EAR of 345 mg (14.4 mmol)/day for boys ages 14 through 18 years is above the median intake of 301 mg (12.5 mmol)/day and below the seventy-fifth percentile of intake, 372 mg (15.5 mmol)/day (see Appendix D). For girls in this age range, the EAR for magnesium of 300 mg (12.5 mmol)/day is just above the ninetieth percentile of intake, 296 mg (12.3 mmol)/day.

Determination of the RDA: Ages 14 through 18 Years

The variance in requirements cannot be determined from the available data. Thus, a CV of approximately 10 percent is assumed for each EAR. This results in an RDA for magnesium of 410 mg (17.1 mmol)/day for boys ages 14 through 18 years and an RDA for magnesium of 360 mg (15.0 mmol)/day for girls ages 14 through 18 years when rounded.

RDA for Boys	**14 through 18 years**	**410 mg (17.1 mmol)/day**
RDA for Girls	**14 through 18 years**	**360 mg (15.0 mmol)/day**

Ages 19 through 30 Years

Indicators Used to Set the EAR for Men

Balance Studies. The results of studies that have looked at magnesium balance in men and women aged 19 through 30 years in various situations are included in Table 6-2. As with the balance studies conducted in adolescents, no estimates or measurements of other losses of magnesium (due to dermal, sweat, etc.) are included. Since few references are available to estimate these losses, gross balances are presented. In the controlled diet study (Greger and Baier, 1983), which was designed to look at the influence of aluminum on mineral balances, men (25 ± 3 years) were in positive balance on average intakes of 447 mg (18.6 mmol) from food and dietary supplements. This represents 6.4 mg (0.27 mmol)/kg/day for these subjects, but may overestimate requirements as only one level was given.

Another controlled study, this one designed to look at the effect of bran on mineral requirements, was conducted in seven men aged

TABLE 6-2 Magnesium (Mg) Balance Studies in Men and Women Aged 19 through 30 Years

Study, Year	*n*	Age (y)	Adaptation Period (d)	Balance Period (d)	Average Daily Mg Intake	Balance (mg/d)	Comments
Males							
Greger and Baier, 1983	8	25 ± 3	12	6	Avg. 447 mg (6.4 mg/kg)	–1 ± 8	6.4 mg/kg maintained balance but adaptation period was too short.
Lakshmanan et al., 1984	9	20–35	N/A	Four 1-wk periods over 1 y	Self-selected; 190–595 mg (avg. 333 ± 120 mg) (avg. 4.3 mg/kg)	–19 ± 48	Self-selected intakes (ranging from 204 to 595 mg) sufficient to maintain balance in 4 of 9 subjects.
Schwartz et al., 1986	7	22–32	28	21	Avg. 719 ± 105 mg	27 ± 19	Intakes greater than 597 mg/d were sufficient to maintain balance in all but one subject (who received 788 mg/d).
Females							
Lakshmanan et al., 1984	8	20–35	N/A	Four 1-wk periods over 1 y	Self-selected; 132–350 mg (avg. 239 ± 80 mg) (avg. 4.2 mg/kg)	–25 ± 40	Three of the 8 subjects in balance on average intakes self-selected (ranging from 213 to 304 mg).
Wisker et al., 1991	12	22–28	14	7	252 mg	7 ± 5	22.5 g/d fiber 71.8 g/d protein.
			14	7	243 mg	–12 ± 5	38.6 g/d fiber 55.7 g/d protein.
			14	7	245 mg	5 ± 2	38.6 g/d fiber 73.8 g/d protein.

22 to 32 years (Schwartz et al., 1986); dietary magnesium intake was 719 ± 105 mg (30 ± 4.4 mmol)/day. With one exception, all subjects were in magnesium equilibrium or positive balance after 48 days. These levels were thus not low enough to accurately estimate average requirements. In a year-long study of men aged 20 to 35 years, subjects kept daily food records for 1 year, and 1-week balance studies were conducted four times. The subjects continued to select their own diet but provided food and beverage samples for analysis (Lakshmanan et al., 1984). The assumption in this study was that each subject's average of the four weekly balances over the year would be representative of his typical intake and requirement. The average magnesium intake of 333 ± 120 mg (13.9 ± 5 mmol)/day resulted in a slight overall average negative balance. Again, since multiple levels were not evaluated, it is difficult to ascertain actual requirements from these data; however it appears that five of the nine subjects consuming this average intake of 333 mg (13.9 mmol)/day of magnesium were probably meeting their needs.

Indicators Used to Set the EAR for Women

Balance Studies. The results of two balance studies for women in this age range are also summarized in Table 6-2. The year-long study by Lakshmanan and coworkers (1984) included young women (20 to 35 years) on self-selected diets, with duplicates of week-long intakes analyzed four times during the year. The average magnesium intake of this age group of women was 239 ± 80 mg (10 ± 3.3 mmol); this intake resulted in positive magnesium balance or equilibrium in three of the eight subjects. A controlled food intake study in Germany tested a low-phytate barley fiber added to two levels of dietary protein to determine the effects of the fiber and protein on mineral balances (Wisker et al., 1991). Magnesium intake of 243 to 252 mg (10.1 to 10.5 mmol)/day (reported to be on the average 4.3 mg [0.18 mmol]/kg/day) in women resulted in the 12 subjects being close to equilibrium on the low-fiber, high-protein diet but not as close on the high-fiber, low-protein diet.

EAR Summary: Ages 19 through 30 Years, Men

Based primarily on the study of Lakshmanan et al. (1984) and the others cited above, the EAR for magnesium for males ages 19 through 30 years is estimated to be 330 mg (13.8 mmol)/day. This is based on the assumption that the best current indicator of adequacy, given the lack of supporting data for other outcomes, is for an individual to maintain total body magnesium over time as opposed to being in negative magnesium balance. The absence of confirmatory research providing causal relationships in human studies between magnesium intake and risk of cardiovascular disease precludes use of markers for cardiovascular disease in this age group at this time. This EAR also reflects the lack of data to support the concept that there is a need for continued accretion of magnesium during this life stage.

EAR for Men 19 through 30 years 330 mg (13.8 mmol)/day

Based on the 1994 CSFII intake data and adjusted for day-to-day variation (Nusser et al., 1996), the median magnesium intake for men ages 19 to 30 years is 331 (13.8 mmol)/day (see Appendix D), which is approximately the same magnesium intake as the EAR of 330 mg (13.8 mmol)/day.

EAR Summary: Ages 19 through 30 Years, Women

Based on the studies described above, and primarily on the overall negative balances of the Lakshmanan et al. (1984) study, which found average magnesium intakes of 239 mg (10 mmol)/day, the EAR for women ages 19 through 30 years is estimated to be above 239 mg (10.0 mmol)/day. The Wisker et al. (1991) study had somewhat more positive balances on a slightly higher overall intake of 255 mg (10.6 mmol)/day. This EAR is also based on the assumption that the best current indicator of adequacy, given the lack of supporting data for other outcomes, is for an individual to maintain total body magnesium over time as opposed to being in negative magnesium balance. This EAR also reflects the lack of data that there is a specific need for accretion of magnesium during this period.

EAR for Women 19 through 30 years 255 mg (10.6 mmol)/day

Based on the 1994 CSFII intake data and adjusted for day-to-day variation (Nusser et al., 1996), the median magnesium intake for women ages 19 through 30 years is 205 mg (8.5 mmol)/day, and the seventy-fifth percentile of magnesium intake is 250 mg (10.4 mmol)/day (see Appendix D), which is slightly below the EAR of 255 mg (10.6 mmol)/day.

Determination of the RDA: Ages 19 through 30 Years

The variance in requirements cannot be determined from the data available for either men or women. Thus, a CV of 10 percent is assumed in both cases. This results in an RDA for magnesium in men ages 19 through 30 years of 400 mg (16.7 mmol)/day, and for women ages 19 through 30 years of 310 mg (12.9 mmol)/day.

RDA for Men	**19 through 30 years**	**400 mg (16.7 mmol)/day**
RDA for Women	**19 through 30 years**	**310 mg (12.9 mmol)/day**

Ages 31 through 50 Years

Indicators Used to Set the EAR in Men

Balance Studies. The results of five balance studies in men aged 31 through 50 years, which met the criteria for inclusion, are shown in Table 6-3. Two controlled-intake studies which looked at the influence of dietary oxalate and fiber on mineral balances, included magnesium balances for men aged 34 to 58 years who were consuming either high-fiber (Kelsay et al., 1979) or high-oxalate (Kelsay and Prather, 1983) diets. Intakes ranged from 308 to 356 mg (12.8 to 14.8 mmol)/day. On a low, nondigestible fiber diet (4.9 g/day), average magnesium balance was positive; but the magnesium intake was not sufficient on the high-fiber or high-oxalate diets to maintain magnesium balance. Magnesium balance in male subjects aged 19 to 64 years given lower magnesium intakes (229 or 258 mg [9.5 or 10.8 mmol]) at two levels of dietary protein has also been estimated (Mahalko et al., 1983). Average magnesium balance at either protein level was at equilibrium for this wider-age-range group, indicating that, at least based on crude magnesium balance, dietary intake was near adequacy overall. However, in another study, magnesium intakes of 240 to 264 mg (10 to 11 mmol)/day resulted in net negative balances (–23 mg [1 mmol]/day and –26 mg [1.1 mmol]/day) in the five subjects studied (Spencer et al., 1994). Magnesium intakes of 789 to 826 mg (32.9 to 34.4 mmol)/day resulted in positive balances in these same subjects. Finally, in a year-long study of magnesium intakes by individuals on self-selected diets with periodic measurements of balance, average intake of seven male subjects aged 35 to 53 years, was 310 ± 88 mg (12.9 ± 3.7 mmol)/day (Lakshmanan et al., 1984). The individual averages of the four 1-week balance periods during the year resulted in a group mean negative magnesium balance, although three subjects had average

TABLE 6-3 Magnesium (Mg) Balance Studies in Men and Women Aged 31 through 50 Years

Study, Year	*n*	Age (y)	Adaptation Period (d)	Balance Period (d)	Average Daily Mg Intake (mean ± SEM)	Balance (mg/d) (mean ± SEM)	Comments
Males							
Kelsay et al., 1979	12	37–58	19	7	356 ± 10 mg	28 ± 17	4.9 g fiber from fruit and vegetable juices; Mg and iron added to be equivalent to higher fiber test diet.
			19	7	322 ± 12 mg	–32 ± 10	23.8 g fiber from fruits and vegetables.
Kelsay and Prather, 1983	12	34–58	21	7	308 ± 10 mg	20 ± 14	4.9 ± 0.4 g fiber including spinach.
			21	7	350 ± 7 mg	–10 ± 13	26.5 ± 0.6 g fiber with spinach.
			21	7	356 ± 10 mg	18 ± 13	24.0 ± 0.6 g fiber with cauliflower substituted for spinach.
Mahalko et al., 1983	10	19–64	16	12 (6 2x)	229 ± 24 mg[a]	13 ± 30[a]	65 g/d protein.
				12	258 ± 24 mg[a]	17 ± 36[a]	94 g/d protein.

Spencer et al., 1994	5	38–75	28	40	264 ± 26 mg	–23 ± 21	241 mg/d Ca.
				32	240 ± 24 mg	–26 ± 14	812 mg/d Ca.
				28	826 ± 37 mg	23 ± 24	241 mg/d Ca.
				39	798 ± 28 mg	48 ± 24	812 mg/d Ca.
Lakshmanan, 1984	7	35–53	N/A	Four 1-wk periods over 1 y	Self-selected; 157–418 mg	–48 ± 59	Three in equilibrium (intakes ranging from 286 to 418 mg); 4 subjects in average negative balance (intakes ranging from 157 to 344 mg) on self-selected average intakes.
Females							
Lakshmanan, 1984	10	35–53	N/A	Four 1-wk periods over 1 y	Self-selected; 164–301 mg (avg 231 ± 46 mg) (avg 4.2 mg/kg)	–25 ± 37	Four in positive balance or at equilibrium with intakes ranging from 182 to 258 mg; 6 were in negative balance with intakes ranging from 164 to 301 mg on self-selected average intakes.

[a] Mean ± SD.

positive balances or were in equilibrium and four were in negative balance.

Indicators Used to Set the EAR in Women

Balance Studies. The only study in females for this age group was part of the year-long study of dietary intakes of men and women, which included an estimation of magnesium balance in 10 women aged 25 to 53 years (Lakshmanan et al., 1984). The average magnesium intake was 231 ± 80 mg (9.6 ± 3.3 mmol)/day. Four subjects were in positive or zero balance, while six were in negative balance, which suggests that 231 mg (9.6 mmol)/day is probably less than is necessary to prevent magnesium loss in 50 percent of women ages 31 through 50 years. Thus, the average requirement for women ages 31 through 50 years appears to be somewhat higher than 231 mgs (9.6 mmol)/day.

EAR Summary: Ages 31 through 50 years, Men

Based on the studies described above, the average requirement for males ages 31 through 50 years does not appear to differ substantially from that of men ages 19 through 30 years. However, there are more instances of negative balance in the intake range of 300 to 350 mg (12.5 to 14.6 mmol)/day in the older subjects studied. The EAR is thus set at 350 mg (14.6 mmol)/day, with the expectation that with age, consumption of diets with higher fiber content increases. Since the two studies in which lower magnesium levels were consumed resulted in predominantly negative balances (Mahalko et al., 1983; Spencer et al., 1994), the data of the Lakshmanan et al. study (1984) raise a concern: the self-selected magnesium intake of the older men was more than 10 percent below that of the younger men in the same study.

This EAR is also based on the assumption that the best current indicator of adequacy, given lack of supporting data for other outcomes, is for an individual to maintain total body magnesium over time as opposed to being in negative magnesium balance. The observed change from average negative magnesium retention to positive retention or vice versa caused by changes in other factors in the diet (for example, fiber, protein) rather than the level of magnesium consumed provides two perspectives: (1) it gives some assurance that the dietary level being evaluated is within the range of the average requirement, and (2) it gives an indication of the many factors that affect magnesium requirements as evaluated by balance studies. Thus, it is the combination of balance studies that provides some assurance that the estimates of average requirements derived are of value as dietary reference intakes.

EAR for Men 31 through 50 years 350 mg (14.6 mmol)/day

Based on the 1994 CSFII magnesium intake data and adjusted for day-to-day variation (Nusser et al., 1996), the EAR of 350 mg (14.6 mmol)/day for men ages 31 through 50 years falls between the median magnesium intake of 327 mg (13.6 mmol)/day and the seventy-fifth percentile of magnesium intake of 397 mg (16.5 mmol)/day (see Appendix D).

EAR Summary: Ages 31 through 50 Years, Women

Based on the one study described above in which women aged 25 to 53 years were predominantly in negative magnesium balance at an average intake of 231 mg (9.6 mmol)/day (Lakshmanan et al., 1984), and comparing the information on younger women and on men, the EAR for women ages 31 through 50 years is estimated to be 265 mg (11.0 mmol)/day. This is quite close to the EAR for younger women, which was based on data from the same study. However, two pieces of evidence lead to the conclusion that the EAR is somewhat greater for this age group. Since renal function is critical to maintenance of magnesium status, and it has been shown to decline with age, it follows that an increased EAR is warranted. Also, a higher percentage of the older women were in negative balance compared to the younger women. This was also demonstrated when comparing the older men (31 through 50 years) with the younger men (19 through 30 years). This EAR is based on the assumption that the best current indicator of adequacy, given lack of supporting data for other outcomes, is for an individual to maintain total body magnesium over time.

EAR for Women 31 through 50 years 265 mg (11.0 mmol)/day

Based on the 1994 CSFII intake data and adjusted for day-to-day variation (Nusser et al., 1996), the median magnesium intake of women aged 31 through 50 years is 229 mg (9.5 mmol)/day (see Appendix D). This is below the EAR of 265 mg (11.0 mmol). The seventy-fifth percentile of intake is 277 mg (11.5 mmol)/day, which is above the EAR.

Determination of the RDA: Ages 31 through 50 Years

The variance in requirements cannot be determined from the available data for either men or women. Thus, a CV of 10 percent is assumed for both cases. This results in an RDA for men ages 31 through 50 years for magnesium of 420 mg (17.5 mmol) and for women, 320 mg (13.3 mmol)/day.

RDA for Men	**31 through 50 years**	**420 mg (17.5 mmol)/day**
RDA for Women	**31 through 50 years**	**320 mg (13.3 mmol)/day**

Ages 51 through 70 Years

Indicators Used to Set the EAR for Men

Balance Studies. The results of five balance studies for men aged 51 through 70 years are shown in Table 6-4. Balance studies cited in Table 6-3 (aged 31 through 50 years) by Kelsay et al. (1979), Kelsay and Prather (1983), Mahalko et al. (1983), and Spencer et al. (1994) included some male subjects in this age range, so these data are also included in this age group. Schwartz et al. (1984) assessed magnesium balance in eight males, mean age 53 ± 5 years and mean weight 67 ± 14 kg (148 ± 31 lb). A positive magnesium balance was found in the men who consumed an average intake of 381 mg (15.9 mmol)/day of magnesium (5.9 mg or 0.25 mmol/kg/day on the average).

Indicators Used to Set the EAR for Women

No studies have been reported for women in this age group.

EAR Summary: Ages 51 through 70 Years, Men

A mean daily magnesium intake of 381 mg (15.9 mmol) maintained balance in all eight subjects in the Schwartz et al. (1984) study, following a 30-day adaptation period. This would indicate that, in the absence of other studies that might demonstrate different results, the EAR should be less than 380 mg (15.8 mmol) in order to prevent magnesium loss. This study, along with those discussed above in the other adult age groups, indicates that the EAR can be expected to be somewhere between 330 and 380 mg (13.8 and 15.8 mmol)/day. Given the lower body weights in the Schwartz et al. (1984) study compared with those in the younger age groups, the magnesium intakes per kg body weight are greater (approxi-

TABLE 6-4 Magnesium (Mg) Balance Studies in Men and Women Aged 51 through 70 Years

Author, Year	*n*	Age (y)	Adaptation Period (d)	Balance Period (d)	Average Daily Mg Intake (mean ± SEM)	Balance (mg/d) (mean ± SEM)	Comments
Males							
Kelsay et al., 1979	12	37–58	19	7	356 ± 10 mg	28 ± 17	4.9 g fiber from fruit and vegetable juices; Mg and iron added to be equivalent to higher fiber test diet.
			19	7	322 ± 12 mg	–32 ± 10	23.8 g fiber from fruits and vegetables.
Kelsay and Prather, 1983	12	34–58	21	7	308 ± 10 mg	20 ± 14	4.9 ± 0.4 g fiber including spinach.
			21	7	350 ± 7 mg	–10 ± 13	26.5 ± 0.6 g fiber with spinach.
			21	7	356 ± 10 mg	18 ± 13	24.0 ± 0.6 g fiber with cauliflower substituted for spinach.
Mahalko et al., 1983	10	19–64	16	12 (6 2x)	229 ± 24 mg[b]	13 ± 30[b]	65 g/d protein.
				12	258 ± 24 mg[b]	17 ± 36[b]	94 g/d protein.
Spencer et al., 1994	5	38–75	28	40	264 ± 26 mg	–23 ± 21	241 mg/d Ca.
				32	240 ± 24 mg	–26 ± 14	812 mg/d Ca.
				28	826 ± 37 mg	23 ± 24	241 mg/d Ca.
				39	798 ± 28 mg	48 ± 24	812 mg/d Ca.
Schwartz et al., 1984	8	53 ± 5	30	6	381 ± 36 mg (5.7 mg/kg)	25 ± 15	Balance was positive in all subjects.
Females[a]							

[a] No studies have been reported in females in this age group.
[b] Mean ± SD.

mately 5.9 mg [0.25 mmol]/kg/day). Because the data for the age group 31 through 50 years reflect more instances of negative balance when dietary magnesium intakes were in the range of 300 to 350 mg (12.5 to 14.6 mmol)/day, it is appropriate to estimate the EAR to be 350 mg (14.6 mmol)/day, particularly in light of the importance of renal function to maintaining magnesium homeostasis. This EAR is based on the assumption that the best current indicator of adequacy, given lack of supporting data for other outcomes, is to maintain total body magnesium over time.

EAR for Men 51 through 70 years 350 mg (14.6 mmol)/day

Based on the 1994 CSFII intake data and adjusted for day-to-day variation (Nusser et al., 1996), the median intake of magnesium for men aged 51 through 70 years is 295 mg (12.3 mmol)/day, and the seventy-fifth percentile of intake is 362 mg (15.1 mmol)/day (see Appendix D), which is slightly above the EAR of 350 mg (14.6 mmol)/day.

EAR Summary: Ages 51 to 70 Years, Women

Because there are no studies in women in this age group, the EAR is based on the one study described in women aged 31 through 50 and on comparisons of the information in younger women and in men. There is no basis on which to change the EAR for this age group from that for women ages 31 through 50 years, which is estimated to be 265 mg (11.0 mmol)/day, other than a concern about the possible decline in renal function associated with aging. However, since an adjustment for declining renal function was included in the estimate of the 31- through 50-year-old women, no further adjustment is needed for this age group. Thus, the EAR is also 265 mg (11.0 mmol)/day for women ages 51 through 70 years. This EAR is also based on the assumption that the best current indicator of adequacy, given lack of supporting data for other outcomes, is to maintain total body magnesium over time.

EAR for Women 51 through 70 years 265 mg (11.0 mmol)/day

Based on the 1994 CSFII intake data and adjusted for day-to-day variation (Nusser et al., 1996), the median intake of magnesium for women aged 51 through 70 years is 230 mg (9.6 mmol)/day, and the seventy-fifth percentile of intake is 276 mg (11.5 mmol)/day (see Appendix D), which is slightly above the EAR of 265 mg (11.0 mmol)/day for women in this age range.

Determination of the RDA: Ages 51 through 70 Years

The variance in requirements cannot be determined from the data available for either men or women ages 51 through 70 years. Thus, a CV of 10 percent is assumed for both cases. This results in an RDA for men ages 51 through 70 years of approximately 420 mg (17.5 mmol)/day, and for women, 320 mg (13.3 mmol)/day.

RDA for Men	**51 through 70 years**	**420 mg (17.5 mmol)/day**
RDA for Women	**51 through 70 years**	**320 mg (13.3 mmol)/day**

Ages >70 Years

Indicators Used to Set the EAR

Studies in this age group have aggregated data from both men and women, and therefore the requirements will be considered together. The greater numbers of individuals with chronic diseases in this population, and the comparative lack of research studies carried out in healthy free-living individuals in this age category, make estimation of requirements problematic.

Balance Studies. No magnesium balance studies that meet the criteria previously described have been reported in subjects over 70 years of age.

Magnesium Tolerance Tests. One study with 36 healthy elderly subjects (8 males and 28 females) 65 years of age and older (average age 73 ± 6 years), used magnesium tolerance testing as the indicator of adequacy (Gullestad et al., 1994). The self-selected dietary magnesium intake was estimated from food frequency questionnaires to be 380 ± 94 mg (15.8 ± 3.9 mmol)/day in the males and 300 ± 61 mg (12.5 ± 2.5 mmol)/day in the females. When corrected for body weight, this intake was similar in both sexes, 5.1 mg (0.21 mmol)/kg/day. Magnesium retention from the load given was 28 ± 16 percent in the elderly and was significantly greater than the 3.6 percent retention in a reference group of 53 subjects aged 55 ± 12 years. However, no correlation was seen between estimated magnesium intake and magnesium retention from the load given. These data do not provide convincing evidence on which to base an estimated requirement.

Intracellular Studies. Intracellular magnesium was assessed in two studies in elderly subjects. Total red blood cell magnesium was measured in 381 institutionalized, elderly subjects aged 80 ± 9.5 years (Touitou et al., 1987). The mean dietary magnesium intake was 240 mg (10 mmol)/day. Abnormally low blood cell magnesium was found in 21 percent of the subjects (about 10 percent had low plasma magnesium concentrations as well). A large number of these subjects had conditions and/or had been on medications that contributed to the apparent poor magnesium status. After excluding these factors, the prevalence of low red blood cell magnesium in the remaining 198 subjects was not significantly different (19 percent). Again, no correlation was found between dietary intake and red blood cell magnesium values. In another study, red blood cell magnesium values in 12 nonobese elderly subjects (6 males, 6 females) aged 78 ± 2 years were compared with those of 25 young healthy subjects (13 males, 12 females) aged 36 ± 0.4 years (Paolisso et al., 1992). Self-selected dietary magnesium intakes of both groups were estimated to be 311 ± 21 mg (13.0 ± 0.9 mmol)/day. Red blood cell magnesium levels in the elderly were 1.86 mmol/liter (4.5 mg/dl), which was significantly less than that of the control subjects, with average levels of 2.18 mmol/liter (5.2 mg/dl). Magnesium therapy in the elderly resulted in a rise in red blood cell magnesium and an increase in insulin secretion and action, which suggests that the low red blood cell magnesium was physiologically relevant in this population.

EAR Summary: Ages > 70 Years

Because no balance studies meeting appropriate criteria are available, other possible indicators of magnesium requirements for this age group were reviewed. However, no conclusive studies were found. The methods used in the studies of magnesium tolerance testing and intracellular magnesium discussed above have yet to be validated sufficiently to serve as the basis for estimating average requirements.

The reported magnesium intakes from the three available studies using these methodologies, however, are consistent with balance studies in younger age groups. The study by Gullestad et al. (1994), using magnesium tolerance testing, found an estimated average dietary magnesium intake in males of 380 mg (15.8 mmol)/day and 300 mg (12.5 mmol)/day in females. The study of intracellular magnesium by Touitou and coworkers (1987) suggests that the average requirement would be approximately 240 mg [10 mmol]/day). The study by Paolisso and colleagues (1992) found that in elderly subjects, an average dietary magnesium intake of 311 mg (13.0 mmol)/day was accompanied by a lower mean red blood cell magnesium concentration, which was not found in younger controls.

Given the uncertainty in the above methods, and the lack of balance data in healthy, elderly individuals to support the intake levels that may appear to be warranted based on the above analysis, estimates of magnesium requirements are suggested to remain at the level established for the other older adult age groups. These estimates would be within the range identified above as estimating the average requirement for elderly. It must be remembered, though, that urinary magnesium excretion has been shown to increase with age (Lowik et al., 1993, Martin, 1990), indicating a decrease in renal function.

EAR for Men	**> 70 years**	**350 mg (14.6 mmol)/day**
EAR for Women	**> 70 years**	**265 mg (11.0 mmol)/day**

Based on the 1994 CSFII intake data and adjusted for day-to-day variation (Nusser et al., 1996), the median magnesium intake for men aged > 70 years is 274 mg (11.4 mmol)/day (see Appendix D). The EAR of 350 mg (14.6 mmol)/day falls between the seventy-fifth percentile of magnesium intake of 334 mg (13.9 mmol)/day and the ninetieth percentile of intake of 394 mg (16.4 mmol)/day. For women in this same age range, the median magnesium intake is 205 mg (8.5 mmol)/day. As for men ages > 70 years, the magnesium EAR for women of 265 mg (11.0 mmol)/day falls between the seventy-fifth percentile of intake of 248 mg (10.3 mmol)/day and the ninetieth percentile of intake of 290 mg (12.1 mmol)/day.

Determination of the RDA for Magnesium: Ages > 70 Years

The variance in requirements could not be determined from the available data for either men or women ages > 70 years. Thus, a CV of 10 percent is assumed for the > 70 years age group. This results in an RDA for men ages > 70 years for magnesium of approximately 420 mg (17.5 mmol)/day and for women ages > 70 years of 320 mg (13.3 mmol)/day.

RDA for Men	**> 70 years**	**420 mg (17.5 mmol)/day**
RDA for Women	**> 70 years**	**320 mg (13.3 mmol/day**

Pregnancy

Indicators Used to Set the EAR

Serum Magnesium Concentrations. Because serum magnesium concentration is reduced during pregnancy (Kurzel, 1991; Weissberg et al., 1992), the use of magnesium sulfate as a tocolytic agent has led some investigators to study the possible role of magnesium status in determining pregnancy and infant outcome, including the incidence of preterm labor and pregnancy-induced hypertension and fetal growth retardation, mental retardation, and cerebral palsy in the newborn (Conradt et al., 1984; Rudnicki et al., 1991; Schendel et al., 1996). However, the reduction in serum magnesium concentration during pregnancy is thought to be due, in part, to hemodilution, and this decrease parallels the decrease seen in serum protein (Seydoux et al., 1992). Serum ionized magnesium has also been reported to decrease late in pregnancy (Bardicef et al., 1995; Handwerker et al., 1996). Therefore, serum magnesium concentrations do not appear to be adequate indicators of magnesium status.

Intracellular Magnesium. Inconsistent findings have been reported on changes in lymphocyte magnesium concentrations during pregnancy. Some investigators report no change (Seydoux et al., 1992), while others find intracellular magnesium depletion (Bardicef et al., 1995). Such indicators of magnesium status have not been adequately assessed during pregnancy and thus are not used here as the basis for determining requirements.

Balance Studies. Few magnesium balance studies have been performed in pregnant subjects. One study of 48 magnesium balances conducted in 10 subjects for 7-day periods at various stages of pregnancy has been reported (Ashe et al., 1979). The balances, which were not carried out in a metabolic unit setting, demonstrated an average negative magnesium balance of –40 mg (–1.7 mmol)/day on a mean daily magnesium intake of 269 ± 55 mg (11.2 ± 2.3 mmol) (Ashe et al., 1979).

Magnesium Tolerance Tests. Parenteral magnesium load tests in postpartum American and Thai women have been conducted to evaluate the methodology (Caddell et al., 1973, 1975). In 185 American women, the mean magnesium retention was 51 percent. Higher magnesium retention was associated with lower serum magnesium concentrations as well as with diets low in magnesium-rich foods (Caddell et al., 1975). In Thai women, who consumed a diet containing more magnesium-rich foods, a mean retention of 23 percent was observed (Caddell et al., 1973).

Pregnancy Outcome. Several cross-sectional studies have investigated whether magnesium status is altered in women with gestational diabetes, preterm labor, pregnancy-induced hypertension, or preeclampsia (Bardicef et al., 1995; Kurzel, 1991; Seydoux et al., 1992; Weissberg et al., 1992). The results of these studies are not consistent, possibly due to the control groups that were used or the inability to distinguish whether altered magnesium status precedes the outcome or the outcome influences magnesium status.

In one cross-sectional study, lower serum magnesium concentrations were observed in women during preterm labor ($n = 71$) compared with normal pregnant women in labor ($n = 128$) (Kurzel, 1991). Although this study found no difference in serum magnesium concentrations between the two groups, others have observed reduced serum magnesium during labor (Weissberg et al., 1992). Therefore, it is not clear whether hypomagnesemia induces uterine irritability and leads to preterm labor or whether labor results in a reduction in serum magnesium concentration.

Longitudinal studies have an advantage over cross-sectional studies in that changes in magnesium intake or status can be determined prior to knowing the final outcome of pregnancy. A prospective observational study of 965 women who were followed from 30 weeks gestation found no effect of magnesium intake on birthweight, as determined by a self-administered questionnaire and a structured interview (Skajaa et al., 1991). The mean reported daily magnesium intake was relatively high at 445 mg (18.5 mmol) for the entire population, with a 95 percent range of 256 to 631 mg (10.7 to 26.3 mmol). The subgroups of women who gave birth to a small-for-gestational age infant, had preterm labor, or who later developed preeclampsia all had similar mean magnesium intakes and serum magnesium concentrations during their third trimester compared with women who had normal pregnancies. There were no differences in tissue magnesium concentrations determined from either abdominal rectus or myometrial muscle biopsies among women delivering by cesarean section because of intrauterine growth retardation ($n = 5$), preeclampsia ($n = 12$), or labor difficul-

TABLE 6-5 Magnesium (Mg) Supplementation Trials During Pregnancy

Criteria	Magnesium Dose (mg/d)	Mg Supplement		Placebo		Significance (p value)
		n	%	*n*	%	
Serum Magnesium						
Sibai et al., 1989	365	105	1.68 mg/dl[a]	112	1.56 mg/dl[a]	<0.01
Preeclampsia						
Sibai et al., 1989	365	4/185	2.2	7/189	3.7	NS
Spatling and Spatling, 1988	365	2/278	0.7	2/290	1.0	NS
Preterm Labor						
Sibai et al., 1989	365	13/185	7.0	14/189	7.4	NS
Spatling and Spatling, 1988	365	12/278	4.3	26/290	9.0	<0.05
Preterm Delivery						
Sibai et al., 1989	365	19/185	10.2	18/189	9.5	NS
Spatling and Spatling, 1988	365	4/278	1.4	8/290	2.8	NS
Kuti et al., 1981	127–202	2/111	1.8	50/365	7.9	<0.05
Intrauterine Growth Retardation						
Sibai et al., 1989	365	9/187	4.9	12/190	6.3	NS
Spatling and Spatling, 1988	365	5/278	1.8	6/290	2.1	NS
Kuti et al., 1981	127–202	1/111	1.0	2/635	0.3	NS
Infants Admitted to Special Care Unit						
Sibai et al., 1989	365	14/187	7.5	13/190	6.8	NS
Spatling and Spatling, 1988	365	20/278	7.2	36/290	12.4	<0.01

[a] Mean serum magnesium level.
NS = non-significant.

ties (n = 14). The results of this study appear to indicate that intrauterine growth retardation, preterm labor, and preeclampsia are not associated with daily magnesium intakes around 445 mg (18.5 mmol) or with serum magnesium concentrations at approximately 30 weeks gestation; and in a small number of women with adverse outcomes, tissue concentrations of magnesium were not abnormal at the time of delivery (Skajaa et al., 1991).

A retrospective study by Conradt and coworkers (1984) found that magnesium supplementation had a beneficial effect on pregnancy outcome. Pregnancy outcomes were studied during a period when the practice of magnesium supplementation changed. Women with high-risk pregnancies were routinely supplemented with 36 to 72 mg (1.5 to 3 mmol)/day magnesium throughout the study (n = 660), whereas during the previous 2 years women were routinely supplemented with 360 to 480 mg (15 to 20 mmol)/day magnesium (n = 264). Unfortunately, the study groups were not randomized, and baseline estimates of magnesium intakes were not determined. Pregnancy outcomes among these two groups were compared with outcomes among high-risk women not receiving magnesium supplements (n = 4,023). The results showed that women receiving either level of magnesium did not develop pregnancy-induced hypertension and preeclampsia; among those not receiving supplements, 97 cases (2 percent) occurred. Women with the higher intake of magnesium had a lower incidence of intrauterine growth retardation than did women with the lower intake.

Three prospective trials of magnesium supplementation during pregnancy have been conducted (Table 6-5). One study was a double-blind, randomized, controlled trial (Sibai et al., 1989), one was a quasi-randomized trial (group assignment determined by mother's date of birth) (Spatling and Spatling, 1988), and the randomization method of the other was not clear (Kuti et al., 1981). In the first two studies, women were supplemented with magnesium aspartate-hydrochloride containing 365 mg (15.2 mmol)/day of magnesium. In the third study, women were supplemented with magnesium citrate, which provided a daily magnesium average intake of 170 to 340 mg (7.1 to 14.2 mmol). Women were categorized into three levels of total magnesium consumed throughout the pregnancy. Daily magnesium intake from supplements was estimated to be 127 to 202 mg (5.3 to 8.4 mmol) for the category with the highest level of magnesium consumed (Table 6-5).

Baseline magnesium intake was not reported in any of the studies. The mean daily magnesium intake for women in Hungary at the time the study by Kuti and coworkers (1981) was conducted was 330 mg (13.8 mmol). Daily magnesium intakes by pregnant women in the United States, where the study by Sibai and coworkers was completed, ranged from 158 to 259 mg (6.6 to 10.8 mmol) (Franz, 1987). Based on these baseline estimates of dietary magnesium intake and the amounts provided in the above trials, total magnesium intakes in the supplemented groups would have ranged from 420 to 625 mg (17.5 to 26 mmol). The results of magnesium supplementation trials indicate that the incidence of preeclampsia and intrauterine growth retardation was not affected by magnesium supplementation in two studies, the incidence of preterm delivery decreased in only one of three studies, and preterm labor was less frequent in one of two studies (see Table 6-5).

Accretion Rate during Pregnancy. The increase in body weight caused by lean tissue accretion during pregnancy is expected to result in a greater requirement for magnesium if there are no pregnancy-induced increases in intestinal absorption and renal reabsorption. Data are not available on accretion of magnesium in lean tissue during pregnancy, but this accretion can be estimated (see following section). Given that fat-free body mass contains about 470 mg (19.6 mmol) of magnesium/kg (Widdowson and Dickerson, 1964), it is possible to determine the amount necessary for accretion for an appropriate weight gain.

EAR Summary for Pregnancy

Inconsistent findings on the effect of magnesium supplementation on pregnancy outcome make it difficult to determine whether magnesium intakes greater than those recommended for non-pregnant women are beneficial. In addition, there are no data indicating that magnesium is conserved during pregnancy or intestinal absorption is increased. The gain in weight associated with pregnancy alone may result in a greater requirement for magnesium.

The EAR for pregnancy is set at an additional 35 mg (1.5 mmol)/day. This additional requirement is based on the following assumptions:

- Appropriate added lean body mass (LBM) is 6 to 9 kg with a midpoint of 7.5 kg (IOM, 1991).
- The magnesium content of 1 kg of LBM is 470 mg (19.6 mmol) (Widdowson and Dickerson, 1964).
- The adjustment factor for a bioavailability of 40 percent (Abrams et al., 1997) is 2.5.

Calculation: (7.5 kg /270 days) × 470 mg/kg × 2.5 = 33 mg/day (rounded up to 35) This value is to be added to the EAR for the woman's age group.

EAR for Pregnancy All ages + 35 mg (1.5 mmol)/day

Based on the 1994 CSFII intake data for 33 pregnant women and adjusted for day-to-day variation (Nusser et al., 1996), the median magnesium intake of pregnant women is 292 mg (12.2 mmol)/day, and the seventy-fifth percentile of intake is 332 mg (13.8 mmol)/day (see Appendix D). The EAR of 290 mg (12.1 mmol)/day for pregnant women ages 19 through 30 years and the EAR of 300 mg (12.7 mmol)/day for pregnant women ages 31 through 50 would fall close to the median of magnesium intake. The seventy-fifth percentile of intake, 332 mg (15.3 mmol)/day, is near the magnesium EAR of 335 mg (15.2 mmol)/day for pregnant women ages 14 through 18 years.

Determination of the RDA: Pregnancy

The variance in requirements cannot be determined from the available data for pregnant women. Thus a CV of 10 percent is assumed. This results in an increase in the RDA for pregnancy for magnesium as follows:

EAR for Pregnancy	
14 through 18 years	**335 mg (14.0 mmol)/day**
19 through 30 years	**290 mg (12.7 mmol)/day**
31 through 50 years	**300 mg (12.7 mmol)/day**
RDA for Pregnancy	
14 through 18 years	**400 mg (16.7 mmol)/day**
19 through 30 years	**350 mg (15.0 mmol)/day**
31 through 50 years	**360 mg (15.0 mmol)/day**

Special Considerations

Diabetes Mellitus. Infants of mothers with Type I insulin-dependent diabetes mellitus are at risk of hypocalcemia and hypomagnesemia, possibly due to magnesium deficiency in the mother (Mimouni et al., 1986; Tsang et al., 1976). Lower intracellular magnesium concentrations have been recently reported in women with gestational diabetes (Bardicef et al., 1995). It is not known whether this is a sequellae of the condition or a factor in its causation.

Pregnant Adolescents, Multiparous Births. A prospective study of 53 nulliparous teenagers found no difference in serum or erythrocyte magnesium concentrations between those pregnant adolescents who developed pregnancy-induced hypertension and those who had normal term deliveries, with both groups having decreasing concentrations of magnesium over gestation (Boston et al., 1989). However, Caddell and coworkers (1975) found a greater renal retention of a parenteral load of magnesium in pregnant adolescents and women with twin pregnancies, suggesting that magnesium requirements during these periods may be increased.

Lactation

Indicators Used to Set the EAR

Human Milk Content. The concentration of magnesium in human milk averages between 25 to 35 mg (1.0 to 1.5 mmol)/liter and is not influenced by the mother's magnesium intake (Moser et al., 1983, 1988). Assuming a milk production of 780 ml/day, a lactating woman may secrete from 9 to 26 mg (0.4 to 1.1 mmol)/day of magnesium in her milk (Allen et al., 1991).

Despite the secretion of magnesium in milk during lactation, plasma and erthyrocyte magnesium concentrations do not differ between lactating and nonlactating women at daily magnesium intakes of approximately 250 mg (10.4 mmol) (Moser et al., 1983), and milk concentrations do not change throughout lactation (Dewey et al., 1984; Moser et al., 1983; Rajalakshmi and Srikantia, 1980).

Balance Studies. A magnesium balance study in six lactating women, six nonlactating postpartum women, and seven women who were never pregnant found lower urinary magnesium concentrations in lactating women compared with women who were never pregnant (Dengel et al., 1994). A positive magnesium balance of 20 mg (0.84 mmol)/day was reported in lactating women consuming a daily magnesium intake of 217 mg (9 mmol). However, there was only a 5-day adaptation period, and although the women appeared to conserve magnesium, the small number of subjects may have lead to an insufficient ability to detect a difference. Whether the increased bone resorption that occurs during lactation contributes to the magnesium pool available for milk production, or whether renal conservation is sufficient to meet the increased need, is unknown. Urinary magnesium concentrations in the lactating women were similar to those of nonlactating postpartum women; however, the 24-hour urinary magnesium losses in these lactating women were similar to urinary losses in women determined to be magnesium depleted based on the results of magnesium loading tests (Caddell et al., 1975). Although this study found lower urinary magnesium excretion in lactating women consuming an estimated daily average magnesium intake of 217 mg (9 mmol), another study found no difference in urinary magnesium concentrations between lactating and never-pregnant women who consumed higher average daily intakes of magnesium, around 270 mg (11.3 mmol) (Klein et al., 1995).

EAR and RDA Summary for Lactation

Currently, no consistent evidence exists to support an increased requirement for dietary magnesium during lactation. It appears that decreased urinary excretion of magnesium and increased bone resorption during lactation may provide the necessary magnesium for milk production. Therefore, the EAR and RDA are estimated to be the same as that obtained for nonlactating women of similar age and body weight.

EAR for Lactation	
14 through 18 years	**300 mg (12.5 mmol)/day**
19 through 30 years	**255 mg (11.3 mmol)/day**
31 through 50 years	**265 mg (11.3 mmol)/day**

RDA for Lactation	
14 through 18 years	**360 mg (15.0 mmol)/day**
19 through 30 years	**310 mg (13.3 mmol)/day**
31 through 50 years	**320 mg (13.3 mmol)/day**

Based on the 1994 CSFII intake data and adjusted for day-to-day variation (Nusser et al., 1996), the median intake of magnesium in 16 lactating women is 316 mg (13.2 mmol)/day; the fifth percentile of intake for the 16 women (of unspecified age) was 267 mg (11.1 mmol)/day (see Appendix D), which is slightly above the magnesium EAR for lactating women 19 through 30 years and close to the magnesium EAR of 265 mg (11.3 mmol)/day for lactating women ages 31 through 50 years. The twenty-fifth percentile intake is 296 mg (12.3 mmol)/day, which is slightly below the EAR of 300 mg (13.8 mmol)/day for lactating women ages 14 through 18 years.

Special Considerations

Mothers Nursing Multiple Infants. Increased intakes of magnesium during lactation, as with calcium, should be considered in mothers nursing multiple infants concurrently. Magnesium requirements may be higher due to the increased milk production of a mother while nursing multiple infants. It is not known whether decreased urinary magnesium and increased maternal bone resorption provide sufficient amounts of magnesium to meet these increased needs.

TOLERABLE UPPER INTAKE LEVELS

Hazard Identification

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 intakes from nonfood sources such as various magnesium salts used for pharmacologic purposes. Thus, a Tolerable Upper Intake Level (UL) cannot be based on magnesium obtained from foods. All reports of adverse effects of excess magnesium intake concern magnesium taken in addition to that consumed from food sources. Therefore, for the purposes of this review, magnesium intake that could result in adverse effects was from that obtained from its pharmacological use.

The primary initial manifestation of excessive magnesium intake from nonfood sources is diarrhea (Mordes and Wacker, 1978; Rude and Singer, 1980). Magnesium has a well-known cathartic effect and is used pharmacologically for that purpose (Fine et al., 1991b). The diarrheal effect produced by pharmacological use of various magnesium salts is an osmotic effect (Fine et al., 1991b) and may be accompanied by other mild gastrointestinal effects such as nausea and abdominal cramping (Bashir et al., 1993; Marken et al., 1989; Ricci et al., 1991). Osmotic diarrhea has not been reported with normal dietary intakes of magnesium. Magnesium ingested as a component of food or food fortificants has not been reported to cause this mild, osmotic diarrhea even when large amounts are ingested.

Magnesium is absorbed much more efficiently from the normal concentrations found in the diet than it is from the higher doses found in nonfood sources (Fine et al., 1991a). The presence of food likely counteracts the osmotic effect of the magnesium salts in the gut lumen (Fine et al., 1991a). In normal individuals, the kidney seems to maintain magnesium homeostasis over a rather wide range of magnesium intakes. Thus, hypermagnesemia has not been documented following the intake of high levels of dietary magnesium in the absence of either intestinal or renal disease (Mordes and Wacker, 1978).

Hypermagnesemia can occur in individuals with impaired renal function and is most commonly associated with the combination of impaired renal function and excessive intake of nonfood magnesium (for example, as antacids) (Mordes and Wacker, 1978; Randall et al., 1964). Hypermagnesemia resulting from impaired renal function and/or intravenous administration of magnesium can result in more serious neurological and cardiac symptoms, but elevated serum magnesium concentrations greater than 2 to 3.5 mmol/liter (4.8 to 8.4 mg/dl) must be attained before onset of these symptoms (Rude and Singer, 1980). Intakes of nonfood magnesium have rarely been reported to cause symptomatic hypermagnesemia in individuals with normal renal function.

Although magnesium supplements are used (see Table 2-2), comparatively few serious adverse reactions are reported until high doses are ingested (see data following). However, some individuals in the population may be at risk of a mild, reversible adverse effect (diarrhea) even at doses from nonfood sources that are easily tolerated by others. Thus, diarrhea was chosen as the most sensitive toxic manifestation of excess magnesium intake from nonfood sources.

It is not known if all magnesium salts behave similarly in the induction of osmotic diarrhea. In the absence of evidence to the contrary, it seems prudent to assume that all dissociable magnesium salts share this property. Reports of diarrhea associated with magnesium frequently involve preparations that include aluminum, and therefore a specific magnesium-associated effect cannot be ascertained.

Large pharmacological doses of magnesium can clearly result in more serious adverse reactions. An 8-week-old infant suffered metabolic alkalosis, diarrhea, and dehydration after receiving large amounts of magnesium oxide powder on each of two successive days (Bodanszky and Leleiko, 1985). Urakabe et al. (1975) reported that a female adult suffered from metabolic alkalosis and hypokalemia from the repeated daily ingestion of 30 g (1,250 mmol) of magnesium oxide. Several cases of paralytic ileus were encountered in adult patients who had taken large, cathartic doses of magnesium: in one case, two bottles of magnesium citrate and several doses of milk of magnesia, and in the other case, several doses of magnesium sulfate in a patient with mild renal impairment (Golzarian et al., 1994). Cardiorespiratory arrest was encountered in a suicidal patient given 465 g (19.1 mol) of magnesium sulfate as a cathartic to counteract an intentional drug overdose (Smilkstein et al., 1988). Deaths from very large exposures to magnesium in the form of magnesium sulfate or magnesium oxide have been reported following cardiac arrest, especially in individuals with renal insufficiency (Randall et al., 1964; Thatcher and Rock, 1928).

Dose-Response Assessment

Adolescents and Adults: Ages > 8 Years

Data Selection. A review of the scientific literature revealed relatively few reports that were useful in establishing a UL for magnesium. Because magnesium has not been shown to produce any toxic effects when ingested as a naturally occurring substance in foods, a UL cannot be established for dietary magnesium at this time. In addition, studies involving intravenous administration of comparatively large doses of magnesium used in the treatment of preterm labor, pregnancy-induced hypertension, or other clinical conditions were not considered applicable for the derivation of ULs. Based on limited data described below, a UL can be established for magnesium from nonfood sources.

Identification of a NOAEL (or LOAEL) and Critical Endpoint. As the primary initial manifestation of excessive magnesium intake, diarrhea was selected as the critical endpoint. The few studies that report mild diarrhea and other gastrointestinal symptoms from uses of magnesium salts were reviewed to identify a No-Observed-Adverse-Effect Level (NOAEL) (or Lowest-Observed-Adverse-Effect-Level [LOAEL]). Gastrointestinal symptoms, including diarrhea, developed in 6 of 21 patients (51- to 70-year-old males and females) receiving long-term magnesium chloride therapy at levels of 360 mg (15 mmol) of magnesium (Bashir et al., 1993). Gastrointestinal manifestations developed in 5 of 25 pregnant women being given 384 mg (16 mmol) of daily magnesium as magnesium chloride supplements for the prevention of preterm delivery, although one patient receiving the placebo treatment also developed diarrhea (Ricci et al., 1991). Diarrhea was also noted in 18 of 50 healthy white and black men and women (aged 31 through 50 years) who were ingesting 470 mg (19.6 mmol) of magnesium as magnesium oxide daily (Marken et al., 1989). Levels of fecal output of soluble magnesium and fecal magnesium concentration were elevated in individuals with diarrhea induced by 168 to 2,320 mg (7 to 97 mmol) of magnesium as magnesium hydroxide (Fine et al., 1991b).

However, other studies using similar or even higher levels of supplemental magnesium reported no diarrhea or other gastrointestinal complaints. Healthy 18- to 38-year-old males given diets enriched with magnesium oxide at levels up to 452 mg (18.9 mmol) daily for 6 days did not report the occurrence of any gastrointestinal symptoms (Altura et al., 1994). This study of the effect of magnesium-enriched diets on absorption involved the fortification of foods with magnesium, which may have different effects from the administration of magnesium supplements outside the normal diet. Furthermore, no diarrhea was reported in patients of varying ages receiving an average of 576 mg (24 mmol)/day of supplemental magnesium as magnesium oxide in a metabolic balance study for 28 days (Spencer et al., 1994). Diarrhea or other gastrointestinal complaints were not observed in patients receiving up to 1,200 mg (50 mmol) of magnesium in the form of an aluminum-magnesium-hydroxycarbonate antacid over a 6-week trial period (Nagy et al., 1988). In a longer-term study, a group of postmenopausal women received daily supplements of 226 to 678 mg (9.4 to 28.3 mmol) of magnesium as magnesium hydroxide for 6 months followed by 226 mg (9.4 mmol) of magnesium for 18 months without any observations of gastrointestinal complaints (Stendig-Lindberg et al., 1993). Diabetics were supplemented with 400 mg (16.7 mmol) of magnesium daily for 8 weeks in the form of magnesium oxide or magnesium chloride without any gastrointestinal complications (Nadler et al., 1992). Elderly subjects supplemented with 372 mg (15.5 mmol) of magnesium daily over a 4-week period did not report any diarrheal effects or other gastrointestinal complaints (Paolisso et al., 1992).

The LOAEL identified for magnesium-induced diarrhea in adults is 360 mg (15 mmol)/day of magnesium from nonfood sources based on the results of Bashir et al. (1993). Studies by Fine et al. (1991b), Marken et al. (1989), and Ricci et al. (1991) provide evidence to support the use of this dose as the LOAEL.

Uncertainty Assessment. Due to the very mild, reversible nature of osmotic diarrhea caused by ingestion of magnesium salts, an uncertainty factor (UF) of approximately 1.0 was selected. Unlike possible adverse effects of other nutrients, osmotic diarrhea is quite apparent to the individual and thus is not a symptom that is masked until serious consequences result.

Derivation of the UL. Because excessive magnesium intake from nonfood sources causes adverse effects, the UL will be established for magnesium from nonfood sources. The UL for magnesium for adolescents and adults is established at 350 mg (14.6 mmol)/day, based on a LOAEL of 360 mg (15 mmol)/day and a UF very close to 1.0. Although a few studies have noted mild diarrhea and other mild gastrointestinal complaints in a small percentage of patients at levels of 360 to 380 mg (15.0 to 15.8 mmol)/day, it is noteworthy that many other individuals have not encountered such effects even when receiving substantially more than this UL of supplementary magnesium, as indicated previously.

UL for Adolescents and Adults > 8 years	**350 mg (14.6 mmol) of supplementary magnesium**

Infants: Ages 0 through 12 Months

No specific toxicity data exist on which to establish a UL for infants, toddlers, and children. The lack of any available data regarding the effects of magnesium supplements in infants makes it impossible to establish a specific UL for infants. Thus, it is important to get magnesium via food sources only in this age group.

UL for Infants	**0 through 12 months**	**Not possible to establish for supplementary magnesium**

Children: Ages 1 through 8 Years

It is assumed that children are as susceptible to the osmotic effects of nonfood sources of magnesium as are adults. Thus, adjusting the value for adults on a body-weight basis established a UL for children at a magnesium intake of 5 mg/kg/day (0.2 mmol/kg/day) (see Table 1-3 for reference weights).

UL for Children	**1 through 3 years**	**65 mg (2.7 mmol) of supplementary magnesium**
	4 through 8 years	**110 mg (4.6 mmol) of supplementary magnesium**

Pregnancy and Lactation

No evidence suggests increased susceptibility to adverse effects of supplemental magnesium during pregnancy and lactation. Therefore, the UL for pregnant and lactating women is set at 350 mg (14.6 mmol)/day—the same value as used for other adults.

UL for Pregnancy	**14 through 50 years**	**350 mg (14.6 mmol) of supplementary magnesium**
UL for Lactation	**14 through 50 years**	**350 mg (14.6 mmol) of supplementary magnesium**

Special Considerations

Individuals with impaired renal function are at greater risk of magnesium toxicity. However, as noted above, magnesium levels obtained from food are insufficient to cause adverse reactions even in these individuals. Patients with certain clinical conditions (for example, neonatal tetany, hyperuricemia, hyperlipidemia, lithium toxicity, hyperthyroidism, pancreatitis, hepatitis, phlebitis, coronary artery disease, arrhythmia, and digitalis intoxication [Mordes and Wacker, 1978]) may benefit from the prescribed use of magnesium in quantities exceeding the UL in the clinical setting.

Exposure Assessment

In 1986, the most recent year that data were available to estimate nonfood nutrient supplement intakes, approximately 15 percent of adults in the United States reported taking a supplement containing magnesium (although it is unclear whether supplements were taken on a daily basis) (Moss et al., 1989). Of those, the ninetieth percentile of daily supplemental magnesium intake was 200 mg (9.1 mmol) for men and 240 mg (10 mmol) for women; the ninety-fifth percentile was 350 mg (14.4 mmol) for men and 400 mg (16.6 mmol) for women. Thus, approximately 5 percent of the men and over 5 percent of the women who used magnesium supplements exceeded the UL of 350 mg (14.6 mmol)/day in 1986.

Children's intakes from nonfood nutrient supplements were estimated to be much lower. The ninetieth percentile of intake for children 2 to 6 years of age who used magnesium supplements in 1986 was 70 mg (2.9 mmol)/day, which is approximately the UL for a 2-year-old child weighing 14 kg; the ninety-fifth percentile of intake from supplements was 117 mg (4.9 mmol)/day, or approximately the UL (115 mg [4.8 mmol]/day) for a 6-year-old child weighing 23 kg. Assuming older children were taking the higher doses, it appears that about 5 percent of the users in this study were exceeding the UL.

Risk Characterization

Using data from 1986, almost 1 percent of all adults in the United States took a nonfood magnesium supplement that exceeded the reference UL of 350 mg (14.6 mmol)/day in the 2-week period preceding the survey (Moss et al., 1989). It is important to note that many of the individuals whose intakes of supplemental magnesium exceeded the UL may be self-selected as not experiencing diarrhea, but this is uncertain. More recent data on estimates of supplement intakes of a national sample have not been published, but it is unlikely that usage has declined.

The data on supplement use in 1986 also indicate that at least 5 percent of young children who used magnesium supplements exceeded the UL for magnesium, 5 mg (0.2 mmol)/kg/day. However, because less than 10 percent of the children had taken a magnesium supplement in the past 2 weeks, less than 1 percent of all children would be at risk of adverse effects. These estimates assume that older children (with a higher UL) are taking the higher doses; the percentage at risk would be higher if dosage were not related to age (and, therefore, to body size). More information on supplement use by specific ages is needed.

RESEARCH RECOMMENDATIONS

The ability to determine reference dietary intakes for magnesium is, as indicated throughout this chapter, hampered by available data. Areas of investigation that are particularly needed include the following:

- Reliable data on population intakes of magnesium are required based on dietary surveys that include estimates of intakes from food, water, and supplements in healthy populations in all life stages.
- Biochemical indicators that provide an accurate and specific marker(s) of magnesium status must be investigated in order to assess their ability to predict functional outcomes that indicate adequate magnesium status over prolonged periods.

- Basic studies need to be initiated in healthy individuals, including experimental magnesium depletion studies that measure changes in various body magnesium pools.
- Magnesium balance studies may be one indicator utilized. If so, strict adherence to criteria suggested in the chapter would improve their application to dietary recommendations. Moreover, a determination of the most valid units to use in expressing estimates of requirements (body weight, fat-free mass, or total body unit) is needed.
- Investigations are needed to assess the inter-relationships between dietary magnesium intakes, indicators of magnesium status, and possible health outcomes that may be affected by inadequate magnesium intakes, such as hypertension, hyperlipidemia, atherosclerotic vascular disease, altered bone turnover, and osteoporosis.
- Based on the evidence of abnormal magnesium status and health outcomes (as noted above), intervention studies to improve magnesium status and to assess its impact on specific health outcomes would be appropriate.
- The toxicity of pharmacological doses of magnesium requires investigation.