OPINION OF THE SCIENTIFIC COMMITTEE ON FOOD ON THE TOLERABLE UPPER INTAKE LEVEL OF MAGNESIUM

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FOREWORD

This opinion is one in the series of opinions of the SCF on the upper levels of vitamins and minerals. The terms of reference given by the European Commission for this task, the related background and the guidelines used by the Committee to develop tolerable upper intake levels for vitamins and minerals used in this opinion, which were expressed by the SCF on 19 October 2000, are available on the Internet at the pages of the SCF, at the address: http://www.europa.eu.int/comm/food/fs/sc/scf/index_en.html.

1. INTRODUCTION

Magnesium (Mg) belongs to group II of the third period of the Periodic Table of Elements, a group that includes two other physiologically important elements: calcium and zinc. Mg has an atomic weight of 24.312; its atomic number is 12; its valency 2. The earth's crust contains approximately 2% Mg and seawater up to 55 mmol/L. The adult healthy body contains approximately 21-28 g (about 1 mole) of Mg; related to an average body weight of 70 kg, this corresponds to circa 14.3 mmol/kg, or to 0.034% of body weight. It is the fourth most abundant cation in the mammalian body and the second most abundant cation in intracellular fluid. Nevertheless Mg deficiency may occur in plants (chlorosis, low crop yields, forest damage), livestock (grass staggers, or grass tetany in ruminants) and man. Depending on the degree of the deficiency, symptoms are latent, moderate or even life threatening because Mg is a cofactor in hundreds of enzymatic reactions, many of which involve energy metabolism. It also plays an important role in protein and nucleic acid synthesis and has a stabilizing and protecting effect on membranes. Finally, Mg is also considered essential in maintaining Ca, K and Na homeostasis (Aikawa, 1981; Durlach, 1988; Seelig, 1989; Wacker, 1980). As early as in the 19th century magnesia was used as antacid and as an antidote against various poisons, e.g. acids and arsenic, and magnesium sulphate as laxative (Epsom salt).

In food derived from plant and animal sources, Mg is mostly bound or chelated, e.g. to phytic acid, phosphates, chlorophylls or it is included in biological apatites (skeleton). In aqueous solutions, Mg salts (e.g., sulphate, chloride, phosphate, citrate, and carbonate) are mostly dissociated depending on the concentration, pH and temperature. Most Mg salts are hygroscopic and have a bitter taste ("Bittersalz", "Bittererde" in German).

2. NUTRITIONAL BACKGROUND

2.1. Food levels and intake estimates

The Mg content of food varies substantially. It is generally accepted that fats, refined sugars and pure alcohol are more or less free of Mg. Foods containing less than 25 mg Mg/100 g wet weight are: meat and most kinds of fish, fruit, most vegetables and dairy products (Seelig, 1980). Chlorophylls contain maximally 0.2% Mg (Aikawa, 1981). Cacao and bitter chocolate, conches, shrimps, soybeans, butter beans, and beet greens contain over 100 mg Mg/100 g. The Mg content of grain and grain products largely depends on food technology processes: high concentrations (110-180 mg/100 g) are found in whole barley, whole rye or wheat flour or brown rice (Seelig, 1980) but high amounts of phytic acid as well as high levels of dietary fibre probably decrease bioavailability (Schümann *et al*, 1997). In Germany the Mg concentration in drinking water is limited to maximally 50 mg/L but geologically caused higher concentrations up to 120 mg/L are tolerated (Trinkwasser VO). Studies in Germany (Schimatschek *et al*, 2001) revealed median-, 5th and 95th percentile concentrations in tap water of 9.9 (2.2 to 28.4) mg/L, n = 14,330 samples and in mineral water of 33.5 (4 to 101) mg/L, n = 150 samples.

Estimates of intake are usually calculated by using data from food questionnaires together with nutrition tables. However, with respect to Mg, these data are probably by 20 to 30% too high because the concentrations measured in food duplicates were considerably lower than values derived from nutritional tables (Glei and Anke, 1995; Schimatschek *et al*, 1997; Stehle *et al*, 1991; Wörwag *et al*, 1999). With these reservations in mind, the following estimates of intake are presented (in mg Mg per day) in Table 1.

Table 1. Estimates of magnesium intake

Country	Mean	2.5th Percentile	97.5th Percentile
Austria[a]	319	116	628
Germany[b]	327	148	558
males	353	188	618
females	288	134	499
Italy[c]	208	117	350
Netherlands[d]	312	139	558
US[e]			
males	323	177 (5^{th} P)	516 (95^{th} P)
females	228	134 (5^{th} P)	342 (95^{th} P)

[a] Elmadfa *et al* (1999) [b] Heseker *et al* (1992) [c] Turrini *et al* (1996)
[d] Hulshof and Kruizinga (1999) [e] FNB (1997)

2.2. Nutritional requirements

Magnesium kinetics represent an open system consisting of several compartments: the intestinal tract (absorption compartment), blood (central compartment), cells, skeleton, central nervous system (deep compartments) and faeces, urine, sweat and milk during lactation (excretion). Mg balance is positive when the input is greater than the output in urine and faeces. This calculation seems simple at a first glance but becomes highly variable aiming to the following individual factors:

a) At low dietary Mg intakes enteral absorption considerably increases from the normal level of 30-40% up to 80% probably via an active transport system (although this has not yet been proven); this system can, however, be completely defective (so-called "primary Mg deficiency") or insufficient ("poor absorbers"). As in the latter cases Mg uptake depends mostly or exclusively on passive diffusion (10-30%) a Mg deficit will result at intake levels which are sufficient for normal individuals (Durlach, 1988; Schimatschek *et al*, 1997; Seelig, 1980; Wörwag *et al*, 1999).

b) Mg turnover also differs individually, depending for example on age, growth, physical activity, pregnancy-lactation, fluid consumption, stress exposure, drugs and diseases (Classen, 1990). Estimates of requirement have therefore been performed on healthy individuals under strictly standardized essentially steady state conditions (FNB, 1997).

c) Mg losses represent an important variable: Diarrhoea or bowel diseases adversely affect absorption. Under physiological conditions the healthy kidney can reduce daily Mg excretion from 5 mmol to less than 0.5 mmol within a few days of low Mg intake. However, this Mg-sparing mechanism may be disturbed genetically, or affected by diseases associated with polyuria such as diabetes mellitus or by drugs (e.g. most diuretics) or alcohol.

The Food and Nutrition Board of the Institute of Medicine (FNB, 1997) in the USA has established the following EAR (Estimated Average Requirement) and the RDA (Recommended Dietary Allowance) based on data obtained under strictly standardized conditions (metabolic unit; adaptation period of at least 12 days; at least two Mg levels) (Table 2).

Table 2. EAR and RDA for magnesium (FNB, 1997)

	EAR (mg)	RDA (mg)
Men, 19-30 years Women, 19-30 years	330 255	400 310
Men, 31-70 years Women, 31-70 years	350 265	420 320
Pregnancy	+ 35 mg	-

The SCF (31^{st} Series, 1993) determined an Acceptable Range of Intake for Adults of 150-500 mg/day.

2.3. Magnesium deficiency

Mg deficiency always includes secondary electrolyte disturbances (since rats respond in a unique to Mg deficiency these experimental data are not considered here). Extracellularly, hypomagnesaemia is frequently associated with hypocalcaemia (as a consequence of disturbed vitamin D metabolism and disturbed parathyroid hormone activity) and sometimes with hypokalaemia (renin-aldosterone-interactions). Intracellularly, K is decreased and the concentration of Na and Ca is increased (owing to decreased activity of Mg-ATP-dependent ionic pumps and "leaky" membranes). In the CNS, the activity of excitatory amino acids (especially glutamate) is enhanced because Mg is a specific blocker of the glutamate-NMDA receptor. Consequently central-nervous and spastic symptoms predominate in Mg deficiency. The clinical diagnosis should be ascertained by reliable biochemical tests. Although serum/plasma Mg represents only about 0.3% of total body Mg it is today generally accepted that hypomagnesaemia is evidence for a Mg deficit (if pseudohypomagnesaemia owing to hypoalbuminaemia is excluded). Under certain conditions, a Mg deficit may, however, exist despite actual normomagnesaemia; such a diagnosis requires special tests, e.g. retention tests using balance techniques (FNB, 1997; Schümann *et al*, 1997; Spätling *et al*, 2000; Wörwag *et al*, 1999).

Mg deficiency, respectively hypomagnesaemia, generally conditions the body for stress reactions (Classen, 1990; Solymoss *et al*, 1969). Epidemiological studies have revealed significant relations between hypomagnesaemia and increased health risks, for example:

- Low concentration of serum/plasma-Mg and increased cardiac disease (FNB, 1997; Ford, 1999; Gartside and Glueck, 1993; Gottlieb *et al*, 1990; Liao *et al*, 1998; Ma *et al*, 1995; Seelig, 1989; Tjuji *et al*, 1994).

- Low concentration of serum/plasma-Mg and hypertension (Joffres *et al*, 1987; Ma *et al*, 1995; Witteman and Grobbee, 1990) or increased risk of stroke (Ascherio *et al*, 1998).

- Low concentration of serum/plasma-Mg and gestational complications (Seelig, 1980; Spätling *et al*, 1989).

3. BIOLOGICAL CONSIDERATIONS

3.1. Interactions with other electrolytes and drugs

Because Mg has been apostrophized "the natural Ca antagonist", it is frequently claimed that calcium inhibits enteral Mg absorption and *vice versa*. This is not the case under physiological conditions as proven in volunteers Spencer *et al* (1994). On the contrary, as Mg is required for the renal hydroxylation of vitamin D and for the activity of parathyroid hormone, Ca-resistant hypocalcaemia can be compensated by Mg supplements (Schimatschek *et al*, 1997). Similarly, potassium does not inhibit Mg absorption in monogastric mammals, which is in contrast to ruminants and plants.

On the other hand, clinically significant interactions occur between iron and magnesium, Mg-hydroxide or Mg-trisilicate *in vitro* (Disch *et al*, 1994), under experimental (Chadwick *et al*, 1982; Corby *et al*, 1985/86; Hall and Davis, 1969) and also under clinical conditions (Thurnher and Kresbach, 1961; Wallace *et al*, 1998). In a randomized controlled crossover study on 13 healthy adult male subjects, serum-Fe concentrations were determined following the oral administration of 5 mg Fe/kg bw over 12 hours alone, or followed 1 hour later by the oral administration of 4.5 g of $Mg(OH)_2$ per g elemental iron ingested. Mean AUC ± SEM amounted to 144 ± 33 µmol (hr)/L in the controls *versus* 78 ± 23 µmol (hr)/L in the Mg group, $p = 0.03$ by signed rank test. In other words, Fe absorption was inhibited by 46%. Probably a Mg:Fe-precipitate was formed under these conditions, as a water soluble Mg salt did not interfere with Fe-gluconate, neither *in vitro* nor under *in vivo* conditions (Disch *et al*, 1994 and 1996). Interactions with zinc absorption owing to the inhibition of gastric acid by Mg may occur (Sturniolo *et al*, 1991) as well as interactions with certain drugs like tetracycline, penicillin and digoxin (Griffin and D'Arcy, 1981).

Both Mg (see later) and sulphate (Cocchetto and Levy, 1981) may exert an osmotic effect in the intestine resulting in laxation. Thus the osmotic effect of $MgSO_4$ is greater than that of other Mg salts due to the additional osmotic effect of sulphate. High intakes of sulphate ion are required to cause diarrhoea and sulphate, like Mg, is better tolerated when consumed in divided doses. For example, a single dose of 8.0 g sodium sulphate (56 mmol) caused severe diarrhoea in normal adults but when consumed as four equally divided hourly doses providing 2.0 g of sodium sulphate (16.8 mmol) per dose it caused only mild or no diarrhoea (Cocchetto and Levy, 1981). Furthermore, over 4 g sodium sulphate (>30 mmol) was well tolerated in normal adults when consumed in drinking water at a concentration of 1.8 g/l (12.5 mM) throughout the day (Heizer *et al*, 1997).

3.2. Acid-base alterations

The pH of the extracellular fluid is determined by the concentration and chemical properties of the acids and bases dissolved in it. In general, carbonic acid is regulated by pulmonary ventilation. Metabolizable acids -being absorbed from the diet or arising in intermediary metabolism- are regulated by intermediary metabolism. Non-metabolizable acids and bases are absorbed from the diet, they cannot be disposed of by intermediary metabolism or by pulmonary ventilation and hence must be disposed of by renal mechanisms (Shaw, 1989). The principal inorganic bases contributing to the balance are Na, K, Ca and Mg (Sack and Stephensen, 1985) and the principal non-metabolizable acids are hydrochloric acid, phosphoric acid and sulphuric acid. In plasma, [c], i.e. the concentration (mmol/L) of non-metabolizable bases, amounts to:

$[cNa^{+} + cK^{+} + 2 \times cCa^{2+} + 2 \times cMg^{2+}] - [cCl^{-} + 2 \times cSO_4^{2-} + 1.8 \times cP]$
$[140 + 4.5 + (2 \times 2.5) + (2 \times 0.75)] - [102 + (2 \times 0.9) + (1.8 \times 3.4)] = 41$ mmol/L

The anion gap is covered by proteins and organic metabolizable acids. From these data, it can be concluded that the supply of higher amounts of earth alkali and alkali metals tends to alkalinization whereas chloride and o-phosphate favour acidification.

A tendency towards Mg-induced extracellular compensated metabolic alkalosis may be advantageous [e.g., reduction of post-exercise acidosis (Ball and Maughan, 1997); renal Mg conservation (Durlach, 1988); inhibitory effects of Mg plus citrate on Ca oxalate formation (Durlach, 1988)] or it may be harmful [e.g. supporting the development of the tetany syndrome due to decreased concentrations of ionized Mg and Ca (Durlach, 1988; Wacker, 1980), inducing hypokalaemia owing to K-shift into the intracellular space (Urakabe *et al*, 1975); increasing cardiotoxicity of catecholamines (Schimatschek *et al*, 1987)]. Finally the development of the milk-alkali syndrome following ingestion with milk and ice cream has been reported (Yamada *et al*, 1991). It has also been discussed whether high doses of citrates might increase the intestinal absorption of toxic metals like aluminium (Sakhaee *et al*, 1996) or whether alkalinization of the urine favours urinary infections (Sökeland and Sulke, 1992). Alkalinization of the urine affects renal clearance of drugs that are weak acids or bases. Therapy with alkalinizing Mg compound increases e.g. the rate of elimination of salicylates and phenobarbital and decreases the elimination of amphetamine, ephedrine, mecamylamine, pseudoephedrine, and quinidine (Goodman and Gilman, 1990).

A tendency towards compensated extracellular acidoses, e.g. by $MgCl_2$, markedly increases the cardioprotective capacity of Mg salts (Seelig, 1989), as well as antitetany effects (Schimatschek *et al*, 1997), the urinary excretion of weak acids is facilitated and enteral Mg absorption is improved. However high chloride load evokes magnesiuric and calciuric responses and favours Ca-oxalate formation (Classen *et al*, 1995; Houillier *et al*, 1996).

In summary it becomes evident that acid-base metabolism must be evaluated considering the sum of acids and bases; it also becomes evident that with Mg salts one has to consider the respective anion in addition to the cation.

4. HAZARD IDENTIFICATION

Magnesium in foods derived from plant or animal sources has not been demonstrated to induce diarrhoea nor other adverse effects in healthy persons, probably as Mg is bound to matrices and hence is mostly not easily dissociable (see Introduction). On the other hand, easily dissociable magnesium salts (e.g. chloride or sulphate; included are compounds like MgO becoming readily dissociable after the reaction with gastric hydrochloric acid) which are present in water, many supplements and drugs, exert dose-dependent laxative effects. Fine *et al* (1991) analyzed stool samples of 19 normal subjects ranging in age from 23 to 36 years. Mean faecal Mg output amounted to 136 mg/day with a standard deviation (SD) of 73 mg. Using 3 x SD, the upper limit of normal faecal Mg excretion was calculated to amount to 345 mg Mg/day. The mean normal concentration of Mg amounted to 362 mg Mg/L, the standard deviation was 245 mg/L and the upper normal level (mean + 3 SD) was 1,097 mg Mg/L of formed stool. When the volunteers received daily doses of (rounded) 1,200 mg, 2,300 mg or 47,000 mg Mg (as hydroxide) diarrhoea was induced. Fine *et al* concluded that for each 24.3 mg increase in faecal Mg output faecal weight increased by approximately 7.3 g.

One of the first cases of accidental poisoning with Mg sulphate was published by Sang in 1891: a 35 years old woman died 75 minutes after drinking 4 ounces of ordinary Epsom salt (about 120 g) dissolved in a tumbler of hot water. Severe poisoning requiring artificial respiration also occasionally occurred

following the intraduodenal administration of magnesium sulphate during deworming (Thurnher and Kresbach, 1961). According to Stevens and Wolf (1950) seven cases of poisoning with Epsom salt with 5 fatalities were published between 1841 and 1909.

Animal experiments have proven a significant cubic relation between the logarithm of orally administered Mg and the Mg concentrations in plasma and bone (Classen *et al*, 1983). In other words, oral Mg supply has to be considerably increased to increase plasma Mg. Depending on plasma/serum Mg levels the following dose-response relations can be established (Spätling *et al*, 2000; Woods, 1991):

0.76 - 1.10 mmol/L	Reference value
0.80 - 1.10 mmol/L	Optimal concentration
1.10 - 2.50 mmol/L	Therapeutic range (infusion therapy)
2.50 - 3.50 mmol/L	Decreased neuromuscular transmission
3.50 - 7.00 mmol/L	Curare-like effect requiring artificial respiration
10.0 - 12.5 mmol/L	Cardiac arrest

In 6 healthy volunteers about 4% of a 56.5 mmol oral dose of $MgSO_4$ (ca. 1,400 mg of Mg) given in 4 hours was enterally absorbed (Morris *et al*, 1987) without inducing hypermagnesaemia. In the literature, only few cases of toxic hypermagnesaemia (>2.5 mmol/L) have been published, mostly owing to the (ab-)use of Mg as laxatives or antacids in single doses of >100 mmol Mg (ca. 2,500 mg). Woodard *et al* (1990) observed maximal blood levels of 2 mmol Mg/L in 102 patients receiving ca. 380 mmol Mg daily (ca. 9,200 mg of Mg; multiple doses, therapy of drug overdose) and Smilkstein *et al* (1988) observed levels up to 2.5 mmol/L after daily doses of up to 360 mmol $MgSO_4$ (ca. 8,800 mg of Mg). Symptoms were hypotension, nausea and vomiting. Hypoventilation and respiratory depression were reported by Jones *et al* (1986) and by Gren and Woolf (1989) in young women treated with Mg citrate (136 mmol, ca. 3,300 mg of Mg) for salicylate and tricyclic overdose; serum Mg levels were 5.7 and 4.0 mmol/L, respectively. Fung (1995) reported the case of a 69 years old multimorbid woman who took about 990 mmol Mg (ca. 24,000 mg of Mg) daily as an antacid; serum levels increased up to 6.7 mmol/L and caused hypoventilation. The patient recovered. Clark and Brown (1992) identified 12 elderly patients (70 ± 6 yr) among 19,761 hospital admissions with hypermagnesaemia (maximally 3.3 mmol/L); oral daily Mg doses (citrate, hydroxide) ranged between 84 and 256 mmol (2,000 to 6,300 mg of Mg). Hypotension was the most frequent clinical sequelae; 2 patients died due to refractory hypotension to which hypermagnesaemia may have contributed. As bowel disorders were present in most patients it is speculated that active ulcer disease, gastritis, colitis, etc. may enhance Mg absorption. Severely impaired renal function (inulin clearance <10 mL/min) is another risk factor (Aikawa, 1981; Randall *et al*, 1964). High age *per se* is however not a risk factor since Kinnunen and Salokannel (1987) did not observe hypermagnesaemia in 64 geriatric patients (mean age 81 years) receiving daily doses of 28 mmol Mg hydroxide (ca. 680 mg of Mg).

5. DOSE-RESPONSE ASSESSMENT

Easily dissociable magnesium salts, especially the sulphate ("Epsom salt", "Bittersalz") are used as "osmotic" and "saline" laxatives, respectively. Nevertheless mild diarrhoea can be taken as the most sensitive non-desirable effect if Mg supplements are taken for nutritional purposes. However it must be kept in mind that adaptation of the bowel to higher oral Mg intake is known (Nadler *et al*, 1992; Stendig-Lindberg *et al*, 1993; Widman *et al*, 1993), that a mild laxative effect may be desirable ("four patients reported mild diarrhoea in the Mg group, and a similar number felt that their bowel function improved with less constipation"; Gullestadt *et al*, 1991), that mild laxative effects have been frequently observed also in the placebo groups (perhaps caused by taste adjusters, vehicles a.o.) (Sibai *et al*, 1989), that a given daily dose of Mg is better tolerated when it is divided into several portions, and finally that the galenic form (aqueous solution, capsules, tablets, etc.) may play a role. Data from the literature are summarized in Table 3 (next page) including children, pregnant women, tetanic, hypertensive and cardiac patients as well as volunteers. Papers were only considered when the presence or absence of "mild diarrhoea" was stated. Table 3 does not include Mg contained in food derived from plant or animal sources this being considered to be poorly dissociable (e.g. phytates).

As discussed, mild diarrhoea is the most sensitive non-desirable effect of orally administered easily dissociable magnesium salts. From the data presented in Table 1 one can conclude that mild diarrhoea occurs in a small percentage of adult subjects at oral doses of about 360/365 mg Mg per day, hence presenting the LOAEL.

No laxative effects have been observed in adult men and women -also during pregnancy and lactation- at doses up to 250 mg Mg per day. Therefore, this dose is considered as being the no-observed-adverse-effect level (NOAEL).

6. DERIVATION OF A TOLERABLE UPPER INTAKE LEVEL (UL)

The NOAEL was derived from studies in which pharmaceutical type of dosage formulation was taken in addition to Mg present in normal foods and beverages. The amounts in food and beverages were not measured or taken into account in the calculation of the NOAEL and therefore the UL for Mg cannot be derived for the intake from all sources. Based on a NOAEL of 250 mg Mg per day and an uncertainty factor of 1.0 an UL of 250 mg Mg per day can be established for readily dissociable magnesium salts (e.g., chloride, sulphate, aspartate, lactate) and compounds like MgO in nutritional supplements, water, or added to food and beverages. This UL does not include Mg normally present in foods and beverages. An uncertainty factor of 1.0 is justified in view of the fact that data are available from many human studies involving a large number of subjects from a spectrum of lifestage groups, including adults, pregnant and lactating women, and children. In addition, the NOAEL is based on a mild, transient laxative effect, without pathological sequelae, which is readily reversible and for which considerable adaptation can develop within days. This UL holds for adults, including pregnant and lactating women, and children from 4 years on.. As no data were available for children from 1 to 3 years, and since it was considered that extrapolation of the UL for older children and adults on the basis of body weight was inappropriate, no UL could be established for this age group.

Table 3. Mild diarrhoea induced by daily oral magnesium supplements

Total Mg Dose* (mg/day)	Diarrhoea (n)	Doses per day	Form	Subjects		Salt	Weeks	Ref.
				Mean age (range) (yr)	Gender			
180	0/130	3	Tablets	5.3-17.4	M, F	Asp. HCL#	3	1
245	0/112	2	Granules	8.1 (4-12)	M, F	Asp.HCL	3	2
245	0/181	2	Granules	4-12	M, F	Asp.HCL	3	3
250	0/31	1	Tablets	58	F	Hydroxide	72	4
360	1/32	3	Granules	37 (18-65)	M, F	Pyrrolidone carboxylic acid salt	4	5
365	0/17	3	Tablets	52 (33-66)	M, F	Asp.HCL	4	6
365	0/39	3	Granules	40 (20-59)	M, F	Asp.HCL	8	7
365	1/278	3	Tablets	28 (20-38)	F	Asp.HCL	26	8
365	4/17	3	Tablets	71 (56-88)	nd	Lactate Citrate	6	9
365	4/22	nd	Tablets	62	M, F	Hydroxide	12	10
384	1/25	6	Ent.coated	21	F	Chloride	4	11
384	2/21	Divided	Ent.coated	63 (42-73)	M, F	Chloride	6	12
400	2/20	nd	Ent.coated	46 (26-65)	M, F	Chloride Oxide	8	13
476	18/50	2	Capsules	30 (21-50)	M, F	Oxide	8.5	14
480	2/12	nd	nd	16 (11-21)	M, F	Asp.HCL	12	15
480	2/37	2	Granules	28.5 ± 4.5	F	Asp.HCL	4	16
500	2/20	3	Capsules	57	M, F	Oxide	12	17
576	0/5	3	Tablets	54 (38-75)	M, F	Oxide	6	18
970	Adaptation to doses	1-3	Tablets	50	M, F	Hydroxide	3x3	19
1095	8/8	nd	Tablets Granules Capsules	nd	M, F	Asp.HCL	1	20

* Referred to elemental Mg; nd = no data; M = males; F = females; # Asp. = aspartate.

1 Classen *et al* (1986) 2 Schimatschek *et al* (1997) 3 Schimatschek *et al* (2001) 4 Stendig-Lindberg *et al* (1993)
5 Fehlinger *et al* (1988) 6 Cappuccio *et al* (1984) 7 Plum-Wirell *et al* (1994) 8 Spätling and Spätling (1988)
9 Gullestad *et al* (1991) 10 Rasmussen *et al* (1989) 11 Ricci *et al* (1991) 12 Bashir *et al* (1993)
13 Nadler *et al* (1992) 14 Marken *et al* (1989) 15 Rueddel *et al* (1990) 16 Spätling *et al* (1998)
17 Daly *et al* (1990) 18 Spencer *et al* (1994) 19 Widman *et al* (1993) 20 Muehlbauer *et al* (1991)

7. CHARACTERISATION OF RISK

Diarrhoea induced by easily dissociable Mg-salts or compounds like Mg-oxide is completely reversible within 1 to 2 days and does not represent a significant health risk in subjects with intact renal function. Poorly dissociable Mg salts (e.g. phytates) have a lower, if any, potential to induce diarrhoea.

While the UL is expressed as a daily intake it should be noted that most of the studies used in its derivation involved daily intake obtained from two or more doses. Therefore the UL should apply to daily intake of Mg consumed on two or more occasions. This is of greater importance for the sulphate salt than for other readily dissociable salts of Mg, given the additional osmotic effect of sulphate ion.

No UL could be established for 1-3 year old children. Although the incidence of diarrhoea is generally higher and its effects potentially more significant in this age group than in older children or adults, there is otherwise no basis for considering that they are more susceptible to the laxation effects of Mg.

Toxic hypermagnesaemia, presenting e.g. with hypotension or muscular weakness, is only seen at oral Mg doses greater than 2,500 mg, i.e. doses exceeding the UL by a factor of more than 10.

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