Brief profiles on systemic toxicological effects of common counter-ions in metal substances:

2. Magnesium

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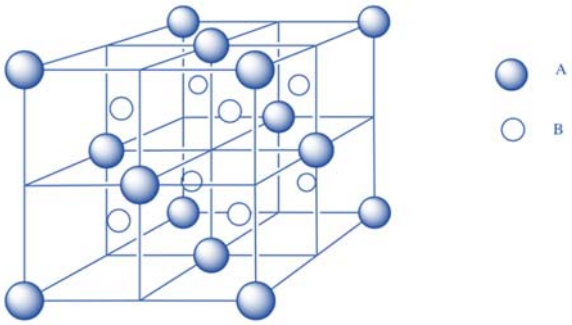

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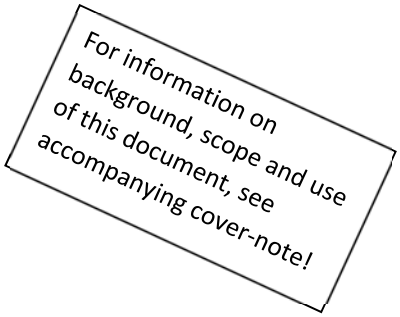
Magnesium: Brief profile on systemic toxicological effects



1. Identification

Name: magnesium (cation)
Chemical formula: Mg^{2+}
Molecular mass: 24.31 g/mol

2. Introductory remarks

Magnesium (Mg^{2+}) cations do not meet the criteria of a substance with registration obligations under REACH. Thus, toxicological hazard information is not required for magnesium ions. However, magnesium occurs as s cation in a wide range of various inorganic salts. The objective of the following summary is to contribute to the assessment of potential health hazards of magnesium containing substances regarding the toxicity of magnesium. This summary makes reference to the most recently published regulatory reviews, including the European Food Safety Authority, but does not aim to review all available primary studies in detail. Unless stated otherwise, the "Scientific opinion on dietary reference values for magnesium" by EFSA (2015) is the main source of information summarised in the following.

3. Natural occurrence, physiological function and dietary intake

Magnesium is an alkaline earth metal. It is the eighth most abundant element in the earth's crust and the eleventh most abundant element in the human body. An average adult human body contains approximately 25 g magnesium, 50-60 % of which are located in bones. Further 30-40 % of the magnesium is found in soft tissues functioning as a cofactor in hundreds of enzymatic reactions and particularly in energy metabolism. Magnesium is further involved in protein and nucleic acid synthesis, maintenance of the electrical potential of nervous tissues and cell membranes, hormone and neurotransmitter release, muscle contraction, cellular differentiation and many others. Intestinal absorption and excretion (mostly via urine), intra- and extracellular levels of dissolved Mg^{2+} are tightly regulated, maintaining homoeostasis, depending on the body's needs and dietary supply.
Similar to calcium, the oxidation state is +2 and magnesium does not occur naturally in the metallic form. Magnesium is a major constituent of many mineral groups, including silicates, carbonates, sulphates, phosphates and borates. Magnesium is likely to be present almost exclusively as Mg^{2+} cation under the pH, redox and conductivity conditions typically found in environmental solutions.
According to the WHO report on vitamin and mineral requirements in human nutrition (2ndedition, 2004) magnesium is widely distributed in plant and animal foods, and geochemical and other environmental variables rarely have a major influence on its content in foods. Most green vegetables, legume seeds, beans, and nuts are rich in magnesium, as are some shellfish, spices, and soya flour, all of which usually contain more than 500 mg/kg fresh weight. Although most unrefined cereal grains are reasonable sources, many highly refined flours, tubers, fruits, fungi, and most oils and fats contribute little dietary magnesium (<100 mg/kg fresh weight). The recommendation for daily intake of magnesium ranges from 300 to 350 mg/day for female and male adults, respectively, and depends further on age and health (EFSA, 2015).

4. Toxicokinetics – "ADME"

4.1. Absorption

Magnesium absorption takes place in the distal small intestine through a paracellular process via tight junctions and is driven by electrochemical gradients and solvent drag. Saturable transcellular absorption seems to be significant only at low dietary intakes. At usual intake, magnesium absorption is only loosely regulated; relative absorption is typically considered to be 40–50 % but can range from 10 to 70 %. The

fractional absorption of magnesium decreases with increasing magnesium intake, which makes the comparison between studies difficult (Sabatier et al., 2003). Magnesium absorption can be inhibited by phytic acid and phosphate and enhanced by the fermentation of soluble dietary fibre. However, the physiological relevance of these interactions for the intake remains to be established.

4.2. Distribution

Magnesium is an essential mineral nutrient. The adult human body contains approximately 25 g magnesium. Thirty to forty per cent of the body's magnesium stores are found in muscles and soft tissues, 1 % in extracellular fluid, and the remainder in the skeleton, making up approximately 1 % of bone ash. The small amount in the serum is mainly present as the free cation. In soft tissues, magnesium functions as a co-factor of many enzymes involved in energy metabolism, protein synthesis, RNA and DNA synthesis, and maintenance of the electrical potential of nervous tissues and cell membranes. Most cells are able to actively and rapidly buffer magnesium loss or accumulation through the involvement of specific magnesium transporters. Further, magnesium levels in the body are subject to homoeostasis, regulated via the rate of renal excretion.

4.3. Metabolism

Magnesium cations are used as cofactor for essential enzymatic processes. Magnesium is absorbed, stored and eliminated but no metabolism occurs.

4.4. Elimination

Absorbed magnesium is predominantly excreted via urine. The kidney plays an important role in homoeostatic regulation of the magnesium balance with active reabsorption of magnesium in Henle's loop. Renal excretion is the key mechanism for maintaining magnesium homoeostasis: the excretion rate varies according to magnesium supply and concentration in body fluids, thereby regulating systemic magnesium levels in the body.

5. Toxicological effects

Magnesium is ubiquitous, an essential nutrient involved in many physiological functions and is generally considered non-toxic. However, each formal REACH information requirement for toxicological effects is addressed further below.

A Tolerable Upper Intake Level (UF) was determined by SCF (2001) based on studies in which mild diarrhoea occurred after ingestion of magnesium supplements and in which magnesium intake from foods and beverages was not taken into account. A No Observed Adverse Effect Level (NOAEL) of 250 mg/day was derived and, using an uncertainty factor of 1, a UL of 250 mg/day was established for adults, including pregnant and lactating women, and children from 4 years of age and older. The UL was established for readily dissociable magnesium salts (such as chloride, sulphate, aspartate, lactate) and substances such as magnesium oxide in nutritional supplements or water, or added to foods and beverages, but does not include magnesium present in foods and beverages (SCF, 2001).

Thus, daily intake recommendations by EFSA (2015) are considerably higher (see below). For the assessment of potential health hazards, the UF of 250 mg Mg/day for an average body weight of 70 kg/person as established by SCF (2001), corresponding to a dose of about 3.6 mg/kg_{bw}/d is applied.

5.1. Acute oral toxicity

Humans must orally consume magnesium at regular intervals via diet or supplementation. The daily recommendation for magnesium is controversial, as the literature is conflicting and varies between countries, although values of > 300 mg/day are usually reported for healthy adults with adjustment for age, sex and nutritional status" (Kass et al., 2017). According to EFSA's scientific opinion on dietary reference values for magnesium (2015), the adequate daily intake for magnesium is between 300 and

350 mg/day for female and male adults, respectively, depending further on age and health. However, an excessive consumption can lead to mild laxative effects.
When unabsorbed magnesium reaches the intestine or colon it can attract water from nearby tissue through osmosis and can lead to diarrhoea. Side effects such as dose-dependent laxative effects or hypoventilation are known but mostly owing to the overconsumption of magnesium. Mild diarrhoea is the most sensitive non-desirable effect of orally administered easily dissociable magnesium salts. Mild diarrhoea was observed in a small percentage of adult subjects at oral doses of about 360 mg Mg per day, hence presenting the Low Observed Adverse Effect Level (LOAEL). Laxative effects were not observed in adult men and women - also during pregnancy and lactation- at doses up to 250 mg Mg per day. This level was therefore considered as NOAEL and applied as UL for adults including pregnant/lactating women and children from 4 years of age and older (SCF, 2001).

5.2. Acute dermal toxicity

Commercially available cosmetic products, such as body creams or lotion for daily use contain magnesium sulfate and magnesium stearate. Magnesium sulfate, a soluble salt, is safely used in leave-on and rinse-off cosmetic products at concentrations up to 11 % and 25 %, respectively (CIR, 2014). Furthermore, following the HERAG guidance for metals and metal salt, a dermal absorption rate in the range of maximally 0.1 - 1.0 % can be anticipated for inorganic magnesium substances. Dermal absorption in this order of magnitude is not considered to be significant. Thus, considering the low dermal adsorption potential and the low potential for acute toxicity, magnesium can safely be considered not acutely toxic via the dermal route.

5.3. Sensitisation

As mentioned in the previous chapter, magnesium salts are frequently used in cosmetic products. According to the Cosmetic Ingredient Review (CIR) Expert Panel (2014), the history of safe medical use of magnesium sulphate does not indicate any toxicity concerns relating to its systemic exposure. The skin sensitization potential of anhydrous magnesium sulphate (in propylene glycol) was evaluated using the mouse local lymph node assay, according to OECD TG 429. The stimulation index (SI) was calculated to $\leq$ 3 when tested up to a concentration of 50 %, concluding that anhydrous magnesium sulphate can be considered a non-sensitiser.

5.4. Repeated dose toxicity

Based on daily consumption of magnesium via drinking water, food and supplements, humans are daily exposed to magnesium for the entire life. Magnesium is an essential element for many cellular processes. Mild laxation is the most sensitive non-desirable effect of orally administered readily dissociable magnesium salt supplements. Diarrhoea induced by easily dissociable magnesium salts or substances such as magnesium oxide is completely reversible within 1 to 2 days and does not represent a significant health risk in subjects with intact renal function (SCF, 2001). Altogether, none of the plethora of human data sets available report adverse effects upon repeated chronic oral exposure.
The tolerable upper intake level (UL) of 250 mg/day for magnesium intake from nutritional supplement or added to foods and beverages, not including magnesium naturally present in foods and beverages, as proposed for adults including pregnant and lactating women, and children from 4 years of age and older (SCF, 2001) corresponds to a dose of about 3.6 mg/kg_{bw}/d taking an average body weight of 70 kg/person into account. This UL is considered protective against any repeated dose oral toxicity.

5.5. Mutagenicity/genotoxicity

Since magnesium is ubiquitous and an essential nutrient with a crucial role in cellular processes such as DNA-polymerase functioning and DNA repair processes, it is justified to assume that magnesium is not genotoxic. Furthermore, all cells are highly dependent on magnesium for maintaining cell functionality. Magnesium sulfate, a soluble magnesium substance, is not genotoxic in in vitro or in vivo assays (CIR,

2014). Thus, it is highly unlikely that magnesium as essential element exerts any genotoxic or mutagenic effects.

5.6. Reproductive and developmental toxicity

Magnesium is ubiquitous and an essential nutrient critical for human fertility, reproduction and development. Magnesium is a cofactor of more than 300 enzymatic reactions, acting either on the substrate (especially for reactions involving ATP, where its binding to the nucleotide induces an adequate conformation and helps to weaken the terminal O–P bond of ATP, thereby facilitating the transfer of phosphate or on the enzyme itself as a structural or catalytic component. As ATP utilisation is involved in many metabolic pathways, magnesium is essential in the intermediary metabolism for the synthesis of carbohydrates, lipids, nucleic acids and proteins, as well as for specific actions in various organs such as the neuromuscular or cardiovascular system (EFSA, 2015 and references therein). Thus, magnesium is critical for processes such as cell growth, DNA replication and bone development during pregnancy and lactation - examples to demonstrate its pivotal role for fertility in men and women, reproduction and lactation. Magnesium has a direct impact on bone health through its role in the structure of hydroxyapatite crystals in bone. The fetus accumulates daily 5 - 7.5 mg of magnesium during the third trimester. During lactation, considering a mean magnesium concentration of breast milk of 31 mg/L and a milk secretion of 0.75 L/day, 24 mg magnesium are transferred daily via breast milk.

The UL derived by SCF (2001, see section on repeated dose toxicity) is considered protective against any potential reproductive and developmental effects. Recommendation for an adequate daily magnesium intake for children below the age of 4 are provided below.

5.7. Carcinogenicity

In a study by Kurata et al. (1989), the administration of 2% $MgCl_2 * 6\ H_2O$ to male and female B6C3F1 mice for 96 weeks resulting in doses of 336 and 470 mg $Mg/kg_{bw}/d$ for males and females, respectively, did not generate any evidence for a carcinogenic potential. Furthermore, magnesium is ubiquitous and an essential nutrient crucial for cell growth, including receptor-mediated intracellular signalling and transphosphorylation reactions, gene transcription, protein synthesis, DNA duplication and cell division. According to EFSA (2015), meta-analyses point to a possible association between magnesium intake and reduces colorectal cancer risk but the database is insufficient for the derivation of a Dietary Reference Value (DRV). In sum, it is justified to conclude that magnesium does not have a carcinogenic potential.

6. Discussion and conclusion

Magnesium is ubiquitous, an essential nutrient critical for many physiological functions and considered non-toxic. Furthermore, magnesium is known for its U-shaped dose-response relationship. The U-shape dose-response describes a biphasic response to exposure to increasing amounts of a substance or condition. According to EFSA's scientific opinion on dietary reference values for magnesium (2015), the adequate daily intake for magnesium is between 300 and 350 mg/day for female and male adults, respectively, depending further on age and health (see Table 1 below). However, redistribution, reduced intake, reduced intestinal absorption, increased gastrointestinal loss or increased renal loss are causes of hypomagnesaemia. Magnesium deficiency entirely due to reduced dietary intake in otherwise healthy subjects is very uncommon. This kind of deficiency is mainly observed in patients with diseases.

Table 1: Adequate intake (AI) for magnesium recommended by EFSA (2015)

Age	Adequate Intake (mg/day)	
	Males	**Females**
7 - 11 months	80	80
1 - < 3 years	170	170
3 - < 10 years	230	230
10 - < 18 years	300	250
≥ 18 years [(a)]	350	300

[(a)] including pregnant and lactating women

The Scientific Committee on Food developed an opinion on the Tolerable Upper Intake Level (UL) of magnesium in 2001 by evaluating sources, properties and effects of magnesium in animals and in different human subgroups. The SCF (2001) based the derivation of the UL for magnesium on evidence from different interventional studies of long duration in adults, some of which were placebo-controlled and in which total daily magnesium intakes of 250 mg were tolerated without any adverse effects. Based on the findings, an UL of 250 mg magnesium per day for magnesium intake from dietary supplements, not including diet, is proposed for adults including pregnant and lactating women, and children from 4 years of age and older, corresponding to a dose of about 3.6 mg magnesium/kg_{bw}/day for a 70 kg-person. The UL is considered to also protect against any potential systemic effects.

Magnesium "in a nutshell":

Key / leading adverse systemic effect on human health:	None identified; see discussion and conclusion
Relevant (CLP) Hazard Classification(s) for systemic effects:	none
Numerical toxicological descriptor:	Upper tolerable limit of intake from dietary supplements, not including regular diet, for adults including pregnant and lactating women, and children from 4 years of age and older: 250 mg Mg/day (SCF, 2001) corresponding to ca. 3.6 mg Mg/kg_{bw}/day for a 70-kg adult

References

CIR (2014) Cosmetic Ingredient Review Expert Panel: Safety assessment of magnesium sulfate as used in cosmetics. Final report 2014.

EBRC (2007) HERAG fact sheet - assessment of occupational dermal exposure and dermal absorption for metals and inorganic metal compounds. EBRC Consulting GmbH, Hannover, Germany. August 2007.

EFSA (2015) Scientific opinion on dietary reference values for magnesium. EFSA Journal 13/7: 4186.

Kass L et al. (2017) Effect of transdermal magnesium cream on serum and urinary magnesium levels in humans: A pilot study. PLoS ONE 12(4): e0174817. https://doi.org/10.1371/journal.pone.0174817

Kurata Y et al. (1989). Lack of carcinogenicity of magnesium chloride in a long-term feeding study in B6C3F1 mice. Fd. Chem. Toxic. 27: 559-563.

Sabatier M et al. (2003) Comparison of stable-isotope-tracer methods for the determination of magnesium absorption in humans. Am. J. Clin. Nutr. 77, 1206-1212

SCF (2001) Opinion on the Scientific Committee on Food on the tolerable upper intake level of magnesium (expressed on 26 September 2001). SCF/CS/NUT/UPPLEV/54. Final 11 October 2001.

WHO (2004) Report on vitamin and mineral requirements in human nutrition (2nd edition).