GreenScreen® Chemical Assessment

Magnesium Carbonate (546-93-0)

Method Version: GreenScreen® for Safer Chemicals v1.4

Assessment Details:

Assessment Type:	Certified
Assessment Prepared By:	WAP Sustainability Consulting, LLC (Eric Rosenblum Ph.D. DABT Donald K. Ward, NSF International)
Assessment Prepared For:	Tile Council of North America (TCNA)
Date Assessment Completed:	January 31st, 2021
Assessment Expiration Date:	January 31st, 2026
Assessor Type:	Licensed GreenScreen® Profiler

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GREENSCREEN BENCHMARK™ SUMMARY:

This chemical assessment report includes a GreenScreen Benchmark™ score and results for Magnesium carbonate (546-93-0) only. No marketing claims can be made without licensing through Clean Production Action.

GreenScreen Benchmark Score: BM-3DG

Magnesium carbonate (546-93-0) was assigned a GreenScreen® Benchmark Score of 3DG ("Use but Still Opportunity for Improvement") as it has Moderate Human Group II (single dose neurotoxicity). Data gaps (DG) exist for endocrine activity, respiratory sensitization. As outlined in CPA (2018) Annex 5 (Conduct a Data Gap Analysis to assign a final Benchmark score), Magnesium carbonate does not meet the requirements for a GreenScreen® Benchmark Score of 4 due to the data gaps and therefore is assigned a 3DG. In a worst-case scenario, if Magnesium carbonate were assigned a High score for data gap endocrine activity it would be categorized as a Benchmark 1 Chemical.

HAZARD CLASSIFICATION SUMMARY

Table 1. GreenScreen Hazard Summary Table

GreenScreen Hazard Summary Table for Magnesium Carbonate – BM-3$_{DG}$																			
Group I Human					Group II and II* Human									Ecotox		Fate		Physical	
Carcinogenicity	Genotoxicity/Mutagenicity	Reproductive Toxicity	Developmental Toxicity	Endocrine Activity	Acute Toxicity	Systemic Toxicity		Neurotoxicity		Skin Sensitization*	Respiratory Sensitization*	Skin Irritation	Eye Irritation	Acute Aquatic Toxicity	Chronic Aquatic Toxicity	Persistence	Bioaccumulation	Reactivity	Flammability
						single	repeat*	single	repeat*	*	*								
L	*L*	L	L	DG	L	L	L	*M*	L	*L*	DG	*L*	L	L	*L*	vH	*vL*	L	L

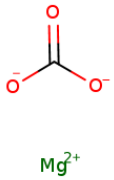
Note: Hazard levels (Very High (vH), High (H), Moderate (M), Low (L), Very Low (vL)) in italics reflect lower confidence in the hazard classification while hazard levels in BOLD font reflect higher confidence in the hazard classification. Group II Human Health endpoints differ from Group II* Human Health endpoints in that Group II Human Health endpoints have four hazard scores (i.e., vH, H, M and L) instead of three (i.e., H, M and L), and are based on single exposures instead of repeated exposures. Group II* Human Health endpoints are indicated by an * after the name of the hazard endpoint or after "repeat" for repeated exposure sub-endpoints

SCOPE OF ASSESSMENT

Magnesium carbonate (546-93-0):

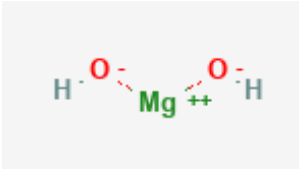
Also Called: anhydrous magnesium carbonate ; C.I. 77713 ; carbonic acid, magnesium salt (1:1), hydrate; CI 77713; E-504; magnesite; magnesite (Mg(CO3)); magnesium carbonate; magnesium carbonate (1:1) hydrate; magnesium carbonate anhydrous (PubChem 2020)

Chemical Structure:

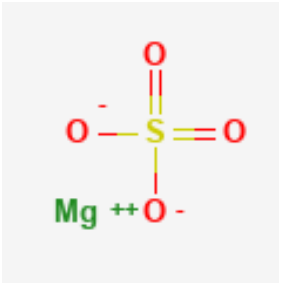


Suitable analogs or moieties of chemicals used in this assessment (CASRN(s)):

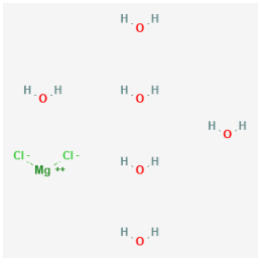
Chemical Structure(s) of suitable analog(s) and/or moieties:



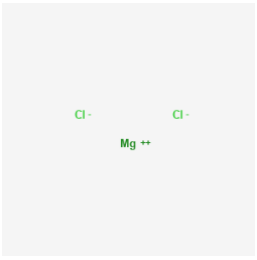
Magnesium hydroxide
(CAS# 1309-42-8)



Magnesium Sulphate
(CAS# 7487-88-9)



Magnesium chloride hexahydrate
(CAS# 7791-18-6)



Magnesium chloride
(CAS# 7786-30-3)

For Inorganic Chemicals and relevant particulate organics (if not relevant, list NA)

Define Properties:

1. Particle size (e.g., silica of respirable size): N/A
2. Structure (e.g., amorphous vs. crystalline): N/A
3. Mobility (e.g., water solubility, volatility) – Solubility 110 mg/L @ 20°C (ECHA 2020a): N/A
4. Bioavailability: N/A

Identify potential applications/functional uses of the chemical:

1. Fillers
2. Laboratory chemicals
3. Lubricants and lubricant additives
4. Paint additives and coating additives not described by other categories
5. Process regulators
6. Processing aids, not otherwise listed
7. Building/construction materials not covered elsewhere
8. Electrical and electronic products
9. Fabric, textile, and leather products not covered elsewhere
10. Intercompany shipments
11. Lubricants and greases
12. Metal products not covered elsewhere
13. Non-TSCA use
14. Paints and coatings
15. Personal care products
16. Plastic and rubber products not covered elsewhere

(PubChem 2020)

Table 2. Environmental Transformation Products Summary

Life Cycle Stage	Transformation Pathway	Environmental Transformation Product	CAS #	Feasible (Yes or No)	Relevant (Yes or No)	GreenScreen List Translator Score or GreenScreen Benchmark Score
		None				

HAZARD CLASSIFICATION SUMMARY

GROUP I HUMAN HEALTH EFFECTS (GROUP I HUMAN)

Carcinogenicity (C): L

Magnesium carbonate was assigned a hazard classification level of Low for carcinogenicity based on no evidence of carcinogenicity following oral exposures to magnesium chloride and inhalation exposures to magnesium sulphate. The hazard classification is based on a well reported study using a high-quality analog and therefore is reported as high confidence.

Lists

- Authoritative: not included on any authoritative lists
- Screening: not included on any screening lists

Measured Data

NRC 2000

The incidence of all cancers among 2,391 Norwegian males who worked between 1951 and 1974 in a factory producing magnesium metal was not significantly increased when compared with cancer incidence for the Norwegian national population of the same age (Heldaas et al. 1989). The number of cases of lip, as well as stomach, and lung cancers were significantly increased. Workers in this study were also exposed to magnesium oxide dust, coal dust, chlorine gas, hydrochlorine aerosols, chlorinated aromatics, and sulphur dioxide. Therefore, it is not possible to determine whether exposure to magnesium dust alone is responsible for the observed elevations in cancer incidence.

Mice fed 0.5% or 2% of aqueous MgCl2 in their diet for 96 wk (68, or 336 mg/kg-d for males; 87 or 470 mg/ kg-d for females) showed no significant change in the incidence of malignant lymphoma and leukemia (Kurata et al. 1989). Dose-related increases in incidence of malignant lymphoma and leukemia occurred in male mice (controls, five of 50; low dose, seven of 50; high dose, eleven of 50), but not in females (controls, nine of 49; low dose, 17 of 50; high dose, 11 of 50). The incidence of hepatocellular carcinomas in male mice was decreased in a dose-related manner (controls, 13 of 50; low dose, six of 50; high dose, four of 50) and the incidence in high-dose males was significantly different from that in controls. Toxicity in female mice (i.e., decreased body weight) suggests that the study was conducted at or near the maximum tolerated dose (MTD) for females.

ECHA 2020a

There are no lifetime animal studies available on magnesium carbonate in order to directly investigate its possible carcinogenic activity. Genotoxicity and repeat-dose toxicity studies on magnesium chloride are available and have been read across to magnesium carbonate. No evidence of mutagenic potential was seen in the genotoxicity studies with magnesium chloride and repeat dose studies showed no evidence of hyperplasia or pre-neoplastic lesions. Furthermore, the long term human data do not provide any indications of carcinogenicity.

Moreover, magnesium is essential for life and is ubiquitous in the natural environment. Humans are widely exposed to naturally occurring magnesium carbonate and chloride, e.g. via drinking water and food on a day to day basis. Ingested magnesium, carbonate and chloride ions are actively

regulated by the body and are therefore not considered to be systemically toxic in standard test systems.

No carcinogenicity classification is warranted for magnesium carbonate according to either the DSD or CLP based on evidence from genotoxicity, repeat dose studies and long Authoritative: not included on any authoritative liststerm human studies.

EHCA 2019c

Male Wistar rats were exposed to two types of magnesium sulphate whiskers by inhalation for six hours a day, five days a week, for four weeks (sub-chronic study), or for one year (chronic study) to clarify the biological effects of the whiskers. There were few whiskers detected in the rat lungs even at one day after the exposure, suggesting that they are dissolved and eliminated rapidly from the lungs. To measure the clearance rate of the whiskers from the lungs, an intratracheal instillation was performed in golden hamsters. The half life of the whiskers in the lung was determined as 17-6 minutes by temporally measuring the magnesium concentration up to 80 minutes after the instillation. A histopathological examination indicated a frequent occurrence of adenoma and carcinoma in the year after chronic exposure, but it was not significantly different between exposed and control rats.

The modulating effects of magnesium hydroxide and calcium lactate on the cholic acid-induced hyperproliferation of cells in rat colon epithelium were investigated. Rats were divided into six groups (10 rats/group) and fed the following diet for 8 weeks: 0.25% cholic acid alone (group 1), cholic acid plus 0.2% magnesium hydroxide (group 2), cholic acid puls 1.18% calcium in the form of calcium lactate (group 3), calcium lactate alone (group 4), magnesium hydroxide alone (group 5) and the basal diet alone (group 6). Rats were killed at the end of the experiment for immunocytochemicals examination of 5-bromo-2'-deoxyuridine (BrdU) incorporation in the cell nuclei of colonic epithelium. Magnesium hydroxide reduced the cholic acid-induced BrdU incorporation by 33% at the distal part and 40% at the proximal part. Calcium lactate also reduced the BrdU incorporation by 48% and 51% respectively. Exposure of magnesium hydroxide or calcium lactate alone had no influence on BrdU incorporation. The results suggest that magnesium hydroxide might exert anti-carcinogenic effects as does calcium by reducing increased cell proliferation of colonic epithelium induced by toxic effects of the bile acids, which are regarded as colon tumor promotors or co-carcinogens.

Estimated Data – None

Mutagenicity/Genotoxicity (M): L

Magnesium carbonate was assigned a hazard classification level of Low for mutagenicity based on negative results reported in numerous in vitro assays for high quality analogs of the substance. The hazard score is based on in vitro studies only, no in vivo studies were located. Therefore, the hazard score is reported as low confidence.

Lists

- Authoritative: not included on any authoritative lists
- Screening: not included on any screening lists

Measured Data

EHCA 2020a

The key studies for in vitro genotoxicity were performed on the analogue substances magnesium chloride and magnesium chloride hexahydrate. The results of an in vitro gene mutation study in bacteria (Ishidate et al, 1984), two in vitro chromosome aberration studies in mammalian cells (Ishidate et al, 1984 and BSL, 2010) and an in vitro gene mutation study in mammalian cells (Oberly et al, 1982) were all negative. As detailed in the read across justification, these studies are directly applicable to magnesium carbonate. Hence magnesium carbonate is not considered to be genotoxic based on the results from in vitro studies.

No in vivo genotoxicity studies are available on either magnesium carbonate or analogue substances. However, testing is not justified based on the negative results obtained in the in vitro studies.

EHCA 2020b

Bacterial reverse mutation assay Magnesium sulfate induced no increase in the number of colonies with reverse mutation in any of the strains irrespective of the absence of presence of metabolic activation in the dose-range-finding study or in the main study

Mutagenicity studies of magnesium sulfate--reverse mutation test with bacteria and chromosomal aberration test with mammalian cells in culture It was concluded that magnesium sulfate does not have mutagenic potential under the given experimental conditions.

Taking into consideration the biochemical role of magnesium in the human body, an in vivo genotoxic effect is considered highly unlikely at test concentrations usually applied in genotoxicity testing, and in consideration of normal dietary requirements (i.e. 800 mg/d).

Although no data is available on the genotoxic potential of metallic magnesium, one may safely assume that metallic magnesium as such cannot cross cellular membranes, but instead only the magnesium cation. Therefore, read across with reference to information on the mutagenicity of other magnesium substances is clearly warranted. For soluble magnesium compounds, there is no data gap for in vitro genotoxicity, since at least one study for the three relevant endpoints (bacterial reverse mutation, in vitro chromosome aberration, in vitro gene mutation) of reliability grade 2 exist.

EHCA 2020c

Magnesium hydroxide was tested in the Salmonella typhimurium reverse mutation assay with four histidine-requiring strains of Salmonella typhimurium (TA1535, TA1537, TA98 and TA100) and in the Escherichia coli reverse mutation assay with a tryptophan-requiring strain of Escherichia

coli (WP_2uvrA). The test was performed in two independent experiments in the presence and absence of S9-mix (rat liver S9-mix induced by a combination of Phenobarbital and β-naphthoflavone). The study procedures described in the report were based on the most recent OECD and EC guidelines. In the dose range finding test, Magnesium hydroxide was tested up to concentrations of 5000 µg/plate in the absence and presence of S9-mix in the strains TA100 and WP_2uvrA. Magnesium hydroxide did not precipitate on the plates at this dose level. The bacterial background lawn was not reduced at any of the concentrations tested and no biologically relevant decrease in the number of revertants was observed. Results of this dose range finding test were reported as part of the first experiment of the mutation assay. Based on the results of the dose range finding test, Magnesium hydroxide was tested in the first mutation assay at a concentration range of 100 to 5000 µg/plate in the absence and presence of 5% (v/v) S9-mix in tester strains TA1535, TA1537 and TA98. In an independent repeat of the assay with additional parameters, Magnesium hydroxide was tested at the same concentration range as the first assay in the absence and presence of 10% (v/v) S9-mix in tester strains TA1535, TA1537, TA98, TA100 and WP_2uvrA. The bacterial background lawn was not reduced at any of the concentrations tested and no biologically relevant decrease in the number of revertants was observed. Magnesium hydroxide did not induce a significant dose-related increase in the number of relevant (His^+) colonies in tester strain WP_2uvrA both in the absence and presence of S9-metabolic activation. The results were confirmed in an independently repeated experiment. In this study, the negative and strain-specific positive control values were within the laboratory historical control data ranges indicating that the test conditions were adequate and that the metabolic activation system functioned properly. Based on the results of this study it is concluded that Magnesium hydroxide is not mutagenic in Salmonella typhimurium reverse mutation assay and in the Escherichia coli reverse mutation assay.

The objective of this study was to evaluate the ability of magnesium hydroxide to induce chromosome aberrations in cultured peripheral human lymphocytes, in both the presence and absence of metabolic activation (S9 -mix). A preliminary test was performed to determine the cytotoxicity of the test substance and to determine the dose range to use for the cytogenetic assays. It was found that magnesium hydroxide precipitated at concentrations of 33 µg/ml and above. In the first cytogenetic assay, magnesium hydroxide was tested at up to 33 µg/ml for a 3 hour exposure time with a 24 hour fixation time in the presence and absence of S9 -mix. In a second cytogenetic assay, magnesium hydroxide was tested at up to 33 µg/ml for a 24 and 48 hour continuous exposure time with a 24 and 48 hour fixation time in the absence of S9 -mix. In the presence of S9 -mix, magnesium hydroxide was also tested at up to 33 µg/ml for a 3 hour exposure time with a 48 hour fixation time. Magnesium hydroxide had little or no effect on the mitotic index of lymphocyte cultures, a measure of cytotoxicity. In addition, magnesium hydroxide did not induce a statistically significant or biologically relevant increase in the number of cells with chromosome aberrations in the presence or absence of S9 -mix, in either of the two independently repeated experiments. Magnesium hydroxide had no effect on the number of polypoid cells and cells with endoreduplicated chromosomes observed in the presence or absence of S9 -mix. As such, it is concluded that magnesium hydroxide is not clastogenic under the conditions described in this report.

In the first experiment, Magnesium hydroxide was tested up to concentrations of 100 micrograms/ml in the absence and presence of 8 % (v/v) S9-mix. The incubation time was 3 hours. In the second experiment, Magnesium hydroxide was again tested up to the concentrations of 100 microgram/ml, but in the absence or presence of 12 % (v/v) S9-mix. The incubation times were 24 hours and 3 hours for incubations in the absence and presence of S9-mix. However Magnesium hydroxide

precipitated already in the culture medium at the dose level of 33 micrograms/ml. In the absence of S9-mix, Magnesium hydroxide did not induce a significant increase in the mutation frequency in the first experiment. This result was confirmed in an independent repeat experiment with modifications in the duration of the treatment time. In the presence of S9-mix, Magnesium hydroxide did not induce a significant increase in the mutation frequency in the first experiment. This result was confirmed in an independent repeat experiment with modifications in the concentration of the S9 for metabolic action. It is concluded that Magnesium hydroxide is not mutagenic in the mouse lymphoma L5178Y test system under the experimental conditions described in the report.

NRC 2000

MgCl2 was judged to be a nonmutagen in the Ames assay when tested with and without metabolic activation and it did not induce chromosomal aberrations in Chinese hamster fibroblast cells in vitro (Ishidate et al. 1984, as cited in Tanaka et al. 1994). Chromatid gaps, breaks, and exchanges were observed in Chinese hamster lung fibroblasts treated with MgCl2 at concentrations of 8.0 and 12.0 mg/ml but not at or below concentrations of 4 mg/mL (Ashby and Ishidate 1986). Since positive results occurred at only high concentrations, the authors suggest that the clastogenic effects observed may be an artifact induced by hypertonic solutions. MgCl2 did not induce mutations in mouse lymphoma L5178/TK+/− cells at concentrations of 5.7–18.1 mg Mg2+/ml (Amacher and Paillet 1980). MgSO4 was not mutagenic in Salmonella typhimurium (strains TA100, TA1535) and Escherichia coli WP2 uvrA at concentrations of 313–5,000 mg/plate (Oguma et al. 1998).

Estimated Data - None

Reproductive Toxicity (R): L

Magnesium carbonate was assigned a hazard classification level of Low for reproductive toxicity based on no reproductive effects observed using high quality analogs in numerous OECD reproductive toxicity studies. In addition, magnesium and carbonate are physiologically essential elements and nutrients for all mammals. The hazard score is based on study data using high quality analogs and therefore is reported as high confidence.

Lists

- Authoritative: not included on any authoritative lists
- Screening: not included on any screening lists

Measured Data

ECHA 2020a

Magnesium carbonate occurs in the natural environment and humans are widely exposed to naturally occurring magnesium carbonate and chloride, e.g. via drinking water and food on a day to day basis. Ingested magnesium, carbonate and chloride ions are actively regulated by the body. Any systemic toxicity is likely to be caused by absorption of the magnesium ion rather than either the carbonate or chloride counterions and hence studies on magnesium salts can be read across from one to the other.

ECHA 2020b

Magnesium is essential mineral nutrient for mammals including humans. Based on evaluation of a wealth of human medical and nutritional data Anonymous, 2001 [SCF opinion]), it is concluded that

magnesium, does not pose any hazard for reproduction and/or developmental toxicity. Classification for toxicity to reproduction and/or developmental toxicity is not required according to Regulation (EC) 1272/2008 and subsequent adaptations.

ECHA 2020c

In a combined repeated dose reproductive toxicity screening tests according to OECD No. 422 and GLP no effects on male and female fertility were observed up to the highest dose tested of 1000 mg/kg bw/day of magnesium hydroxide. No toxicologically relevant changes were noted in any of the parental parameters investigated (i. e. clinical appearance, functional observations, body weight, food consumption, clinical laboratory investigations, macroscopic examination, organ weights, and microscopic examination).

In addition the absence of effects of magnesium ions on the reproductive organs of males and females was also reported in an OECD 408 90-day dietary studies in rats and mice with magnesium chloride hexahydrate up to the highest dose levels tested (11400 mg/kg bw for males and 13830 mg/kg bw for females in mice; corresponding dose of magnesium hydroxide to 1856 mg/kg b day and 2251 mg/kg bw/day; 1600 mg/kg bw of test substance for male rats and 1531 mg/kg test substance for female rats corresponding to a $Mg(OH)_2$dose of 261 mg/kg bw/d and 249 mg/kg bw/day for males and females respectively)

The absence of effects of magnesium ions on the reproductive organs of males and females was also reported in a 92-week dietary carcinogenicity study with magnesium chloride hexahydrate up to the highest dose of2810 mg/kg bw per day in males and 3930 mg/kg bw in females corresponding to 457 and 640 mg magnesium hydroxide/kg bw/day. It can be concluded that the weight of evidence of existing studies indicates that magnesium hydroxide is unlikely to exert effects on male or female fertility at dose levels not causing other systemic effects.

The testes is a target organ for some toxic metal cations. In this study the relative cytotoxicity of six metal cations, Cd, Pb, Zn, Ca, Cu and Mg was compared in two primary cell culture systems prepared from rat testes. Cytotoxicity was assayed in Sertoli cell cultures from 21 day old rats after 24 hr incubation with a metal cation. Magnesium was without any effect in any assay. Although all four of the assays indicated cadmium as very toxic at low concentrations, and calcium and magnesium to be without effect, the results of the assays were not consistent with respect to lead, copper and zinc.

Estimated Data - None

Developmental Toxicity incl. Developmental Neurotoxicity (D): L

Magnesium carbonate was assigned a hazard classification level of Low for Developmental Toxicity incl. Developmental Neurotoxicity based on no developmental effects observed in studies using high quality analogs in developmental toxicity studies. In addition, magnesium oxide is a physiologically essential element and nutrient for all mammals. Furthermore, experience with therapeutic use of magnesium sulphate infusions as tocolytic agent in pregnant women showed no negative effect on newborn infants and their development at dose levels that do not lead to maternal effects. The hazard score is based on study data and therefore is reported as high confidence.

Lists

- Authoritative: not included on any authoritative lists
- Screening: not included on any screening lists

Measured Data

ECHA 2020a

Teratogenicity of magnesium chloride hexahydrate (MgCl2.6H2O) was examined in rats in an OECD Guideline 414 (Prenatal Developmental Toxicity Study). Magnesium chloride hexahydrate dissolved in distilled water was given to pregnant Wistar rats by gavage once a day from day 6 through 15 of pregnancy at doses of 0, 200, 400 and 800 mg/kg/day. The pregnant rats were sacrificed on day 20 of pregnancy and their fetuses examined for malformation. It was concluded that magnesium chloride hexahydrate has no teratogenicity in rats when given by gavage The NOAEL was estimated to be >800 mg/kg bw/day for both pregnant rats and rat fetuses.

ECHA 2020c

Teratogenicity of magnesium chloride hexahydrate was examined in rats. The pregnant rats were sacrificed on day 20 of pregnancy and their fetuses were examined for malformation. It was found that magnesium chloride hexahydrate caused no increased incidences of fetal malformation, and no toxic signs in the pregnant rats and the fetuses. Even a dose of 800 mg/kg/day, considered the maximum non-fatal dose of magnesium chloride hexahydrate in pregnant rats, did not increase the incidence of teratogenicity. The no observed adverse effect level was estimated to be over 800 mg/kg/day for both pregnant rats and rat fetuses. This is because, although no effects from magnesium chloride hexahydrate are observed in maternal rats at a dose of 800 mg/kg/day, sedation, decreased body temperature, salivation, watery stool and mortality were observed at a dose of 800 mg/kg/day.

In an additional supporting study, the effects of Magnesium sulphate on fetal rats after repeated intravenous administrations was investigated. The findings from these studies showed that Magnesium sulphate did not have an adverse effect on fetal body weight, size and brain development.

Experience with therapeutic use of magnesium sulphate infusions as tocolytic agent in pregnant women showed no negative effect on newborn infants and their development at dose levels that do not lead to maternal effects and do not lead to a clinically significant imbalance of the Ca^{2+}/Mg^{2+}ratio.

NRC 2000

There are no studies in humans that evaluated reproductive or developmental effects associated with the ingestion of Mg(OH)2.

Estimated Data - None

Endocrine Activity (E): DG

Magnesium carbonate was assigned a hazard classification level of Data Gap for endocrine activity based on based on the lack of available studies that directly address endocrine activity following exposures to the compound. No analog data was available to fill the data gap.

Lists

- Authoritative: not included on any authoritative lists
- Screening: not included on any screening lists

Measured Data- None

Estimated Data - None

GROUP II AND II* HUMAN HEALTH EFFECTS (GROUP II AND II* HUMAN)

Note: Group II and Group II* endpoints are distinguished in the v1.4 Benchmark system (the asterisk indicates repeated exposure). For Systemic Toxicity and Neurotoxicity, Group II and II* are considered sub-endpoints. See GreenScreen Guidance v1.4, Annex 2 for more details.

Acute Mammalian Toxicity (AT): L

Magnesium carbonate was assigned a hazard classification level of Low for acute mammalian toxicity based on LD50 values for oral exposures >2000 mg/kg. The low hazard score is supported by inhalation LC50s > 2.1 mg/L (the highest feasible concentration that could be tested) using high quality analogs. In addition, the ubiquitous use of magnesium hydroxide under therapeutic conditions that involve direct skin and oral exposure, further contributes to the evidence that magnesium is a substance of low toxicological concern. The hazard score is based on test data and therefore reported as high confidence.

Lists

- Authoritative: not included on any authoritative lists
- Screening: not included on any screening lists

Measured Data

EHCA 2020a

Acute toxicity, oral: The acute oral median lethal dose (LD50) of magnesium carbonate in the female Wistar strain rat was estimated to be greater than 2000 mg/kg bodyweight.

EHCA 2020b

Acute toxicity, oral: There is one valid study available on acute oral toxicity, which was conducted with magnesium chloride hexahydrate. The LD_{50} is > 2000 mg/kg bw. None of the 6 animals died, thus according to the OECD 423 the LD_{50} could be set to 5000 mg/kg bw. Two additional published data are found during the literature search which results in LD_{50} and LD_{100} values, respectively wide above the threshold value for acute toxicity (up to 8100 mg/kg bw). However, these values should only be used as supportive information.

Acute toxicity testing via the dermal route is considered not to be scientifically justified. However, following the HERAG guidance for metals and metal salts (see section 7.1.2 of the technical dossier, dermal absorption), a dermal absorption rate in the range of maximally 0.1-1.0 % can be anticipated. Dermal absorption in this order of magnitude is not considered to be “significant”.

Under the conditions of the present study, a single oral application of the test item magnesium chloride hexahydrate to rats at a dose of 2000 mg/kg body weight was associated with no signs of toxicity. A careful clinical examination was made several times on the day of dosing (at least once during the first 30 minutes and with special attention given during the first 4 hours post-dose). Thereafter, the animals were observed for clinical signs once daily until the end of the observation period. All abnormalities were recorded.

Cage side observations included changes in the skin and fur, eyes and mucous membranes. Also, respiratory, circulatory, autonomic and central nervous systems and somatomotor activity and

behaviour pattern were examined. Particular attention was directed to observations of tremor, convulsions, salivation, diarrhoea, lethargy, sleep and coma.

Necropsy of survivors performed: Yes

EHCA 2020c

According to the key study, the oral LD50 value of Magnesium hydroxide in Wister rats was established to exceed 2000 mg/kg body weight. According to OECD 423 test guideline, the LD50 cut-off value was considered to exceed 5000 mg/kg body weight.

Magnesium hydroxide is used extensively as a medical drug in humans as an antacid to neutralise stomach acid and assist in the treatment of indigestion and heartburn. It is also used as a laxative and as an antiperspirant deodorant and can be useful as a topical treatment for canker sores. In its form as an indigestion and heartburn treatment, it is sold over the counter in most supermarkets, chemists and convenience stores and does not require a prescription from a physician to be purchased. It is administered orally, usually as a chewable tablet, capsule or a suspension in water known as milk of magnesia. The ubiquitous use of magnesium hydroxide under these therapeutic conditions, with direct skin and oral exposure, further contributes to the evidence that magnesium hydroxide is a substance of low toxicological concern.

Groups of 5 male and female Wistar rats were treated with Magnesium hydroxide as aerosol during 4 hours. No mortality or other relevant adverse effects were observed. An inhalatory LC50 (4h) value for magnesium hydroxide exceeding 2.1 mg/L was determined, being this value the maximum feasible concentration that could be tested.

Estimated Data- None

Systemic Toxicity/Organ Effects incl. Immunotoxicity (ST-single) L

Magnesium carbonate was assigned a hazard classification level of Low for single dose systemic toxicity/organ effects based on no clinical signs of significant systemic toxicity following oral exposures to doses up to 2,000 mg/kg. In addition, the common use of magnesium as laxatives or antacids, with very infrequent incidence of inducing hypermagnesaemia, further contributes to the evidence that magnesium is a substance of low single dose toxicological concern. The hazard score is based on study data and human exposure and therefore reported as high confidence.

Lists

- Authoritative: not included on any authoritative lists
- Screening: not included on any screening lists

Measured Data

ECHA 2020a

In a OECD Guideline 420 (Acute Oral Toxicity - Fixed Dose Method) At the 300 mg/kg dose level, there were no mortalities and ataxia and/or hunched posture were noted in all animals. However, animals appeared normal two or five days after dosing. All animals showed expected gains in bodyweight over the observation period and no abnormalities were noted at necropsy.

ECHA 2020b

"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 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 >2,500 mg Mg. One published study reported maximal blood levels of 2 mmol Mg/L in 102 patients receiving ca. 9,200 mg of Mg daily (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 (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 ca. 24,000 mg 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 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)."

Kuschner (1997) reports that inhalation of fine and ultrafine MgO particles to humans at concentrations up to 230 mg/m³ over 15 minutes or 143 mg/m³ over 45 minutes did not result in any adverse effects (inflammation markers, or subjective symptoms). This result suggests that inhalation of MgO dust does not produce adverse effects up to these concentrations. In consequence, local effects are not anticipated for this substance.An acute inhalation study in human volunteers is available, in which the potential of MgO to cause symptoms similar to that of metal fume fever is investigated. Due to the fact that magnesium metal is passivated on its surface by the formation of an oxide layer, and since in the case of fine powders this oxide layer will form a substantial part of the particle mass, and also because magnesium oxide and magnesium metal are of similarly low solubility (interpreted as a measure of similar bioavailability), read across from data on magnesium oxide to magnesium metal is considered justified without restriction. However, the study conducted by Kuschner et al. was conducted with very fine MgO particles (98% < 2.5 µm), whereas the most representative magnesium powder placed on the market is characterized by a D90 of 86.1 µm (D50 53.1µm). Thus, commercial grades of magnesium powder are of much coarser nature than the MgO powder employed in the study by Kuschner et al. Thus, the alveolar deposition of MgO particles from the "Kuschner" study was obviously much higher than that of the much coarser commercial grades of magnesium powder. Therefore, any read across from MgO to Mg is intrinsically very conservative justified.

ECHA 2020c

The oral LD50 value of magnesium hydroxide in Wistar rats tested under OECD 423 test guideline established to exceed 2000 mg/kg body weight. No mortality occurred No abnormalities were found at macroscopic postmortem examination of the animals. Hunched posture and/or piloerection was

noted among all animals on Day 1. The mean body weight gain shown by the animals over the study period was similar to that expected of normal untreated animals of the same age and strain. No abnormalities were found at macroscopic postmortem examination of the animals.

Groups of 5 male and female Wistar rats were treated with Magnesium hydroxide as aerosol during 4 hours. No mortality or other relevant adverse effects were observed. An inhalatory LC50 (4h) value for magnesium hydroxide exceeding 2.1 mg/L was determined, being this value the maximum feasible concentration that could be tested. No clinical signs were noted during exposure. After exposure, ptosis and/or piloerection were noted in two males and one female on Day 1 only.

MAK 1984

In one study four volunteers inhaled fresh MgO fumes at a concentration of 15–29 mg/m3 for 5–9 minutes. In two persons a slight increase of body temperature and, after 5–6 hours, an increase in the white blood cell count from 7000 to 15600 were observed. The parameters had returned to normal by the next morning

NRC 2000

Most available toxicity data on Mg(OH)2 describe effects of acute exposure to Mg(OH)2 or of prolonged exposure to antacid or laxative products containing Mg(OH)2. Magnesium intoxication has been reported in infants (2–42 d old) that received Mg2+-containing oral laxatives at Mg2+ doses of 224–917 mg/kg-d for 2–11 d (Alison and Bulugahapitiya 1990, Brand and Greer 1990, Humphrey et al. 1981, Mofenson and Caraccio 1991). Whereas normal serum magnesium ranges from 1.4 to 2.4 mEq/L, these infants had concentrations of 3.5–11.7 mEq/L. In one case, Mg2+ body burden was high enough to cause perforation of the bowel (Mofenson and Caraccio 1991).

In adults, serious toxic effects associated with excess magnesium intake occur at very high intake levels equating to serum concentrations of 4 mEq/L (Mordes and Wacker 1978; Rude and Singer 1981). Toxicity has been limited to persons with intestinal or renal disease (Poisindex 1998).

The Hazardous Substance Data Bank (HSDB) entry for Mg(OH)2 states that the probable oral lethal dose of Mg(OH)2 in humans is 5–15 g/kg in a 70- kg person (HSDB 1998).

Cardiac arrest has been reported at serum Mg2+ concentrations of 15–16 mEq/L (Dreisbach 1977). Respiratory depression, depression of the central nervous system, and coma occur in adult patients with plasma Mg2+ concentrations of 10–14 mEq/L (Ferdinandus et al. 1981). Hypotension, nausea, and vomiting occur at plasma concentrations of 3–8 mEq/L. In its review of clinical studies, the Institute of Medicine (IOM 1997) concluded that Mg2+ in the diet is never high enough to cause adverse effects. The IOM set a “tolerable upper intake level” (TUL)2 for the ingestion of magnesium (Mg2+) supplements of 5 mg/d for anyone over 1 yr old. The TUL was based on the approximate no-observed-adverse-effects level (NOAEL) for osmotic diarrhea in humans reported by Marken et al. (1989), Fine et al. (1991), Ricci et al. (1991), and Bashir et al. (1993).

Gastrointestinal discomfort occurred in six of 21 patients with stable congestive heart failure who received 15.8 mmol MgCl2/d (5.5 mg/kg-d) for 6 wk (Bashir et al. 1993). Five of the six patients reported epigastric burning or distension and two reported diarrhea. Five of 50 pregnant women developed adverse gastrointestinal effects (nausea, soft stool, or diarrhea) given intravenous and oral doses of Mg2+ to suppress preterm delivery (Ricci et al. 1991). The women were initially given a 4-g bolus dose of MgSO4 by intravenous injection followed by intravenous infusion of MgSO4 at a dose of 2 g/hr for 12 hr. This approximates to a minimum dose of 353 mg/kg (assuming a female

body weight of 55 kg). Increases in the incidence of adverse neonatal outcomes were observed in women that ingested MgCl2 tablets (7 mg/kg-d over an average of 29 d) as compared with controls given no MgCl2 tablets (Ricci et al. 1991). Eleven of 25 neonates in treated mothers were diagnosed with jaundice as compared with 6 out of 25 infants born to control mothers. One fatal case of respiratory distress syndrome, one case of intraventricular hemorrhage, and 2 cases of necrotizing enterocolitis occurred in women taking MgCl2 tablets as compared with no cases among infants born to control mothers. These increases were judged not to be statistically significant by the study investigators. Diarrhea occurred in 18 of 50 (36%) healthy adult volunteers who received magnesium (as MgO) doses of 476 mg/d for 60 d (Marken et al. 1989). Diarrhea was also observed in 14 healthy male subjects who ingested Mg (OH)2 at a dose rate of 16.7, 33.3, or 67 mg/kg-d for 4 d (Fine et al.1991).

Estimated Data- None

Systemic Toxicity/Organ Effects incl. Immunotoxicity (ST-repeat) (Group II*) L

Magnesium carbonate was assigned a hazard classification level of Low for repeated dose systemic toxicity/organ effects based on oral exposure studies using high quality analogs which report NOAELs > 100 mg/kg/day. In addition, available inhalation studies using high quality analogs are available which report no effects on growth curves and organ weights at the highest concentrations tested. These results are reported in high-quality guideline studies using a high-quality analog. Therefore, the hazard score is reported as high confidence.

Lists

- Authoritative: not included on any authoritative lists
- Screening: not included on any screening lists

Measured Data

EHCA 2020b

Two published animal studies (Hori 1994) for sub-chronic and chronic inhalation provide tentative information on the health effects of magnesium. Inhalation exposure of rats to 2.3 – 4.0 mg/m^3 magnesium sulfate 6 hours per day, 5 days per week for 1 month or 1 year did not show any noticeable effects on growth curves and organ weights in the treatment group. The number of adenomas in the exposure groups was not significantly greater than that of the control group.

Reichrtová & Taká (1992) conducted a study where Wistar rats were exposed by inhalation to a dust (particles smaller than 5µm) containing a high percentage of MgO (up to 1000 mg/m3). This dust was collected from environmental sample collection devices around Slovak magnesite factory. Several results were reported. Animals receiving repeated exposures totaling 200 hours showed a diminished ability to eliminate magnesium as compared to animals that received a single exposure. Repeated exposures caused increased levels of magnesium in the serum and urine, indicating that the inhaled dust was gradually dissolved in the body. The inhaled dust was eliminated by the lymphatic system as well, as evidenced by histological examination of the spleen, where particles were present in sinusoid macrophages. Even though significant amounts of magnesium were excreted, increased magnesium levels were observed in the liver, spleen, and lung 25 days after the last exposure. In the lung, dust particles were found in thickened interalveolar septa and

macrophages, but no signs of pulmonary fibrosis were observed. The findings showed that MgO dust was eliminated by blood and lymph."

EHCA 2020c

A combined repeated dose reproductive toxicity screening study (OECD 422) study was performed with Magnesium hydroxide to assess sub-acute oral toxicity in rats. No test substance related effects were observed at the highest dose tested which was equal to the limit dose for the repeated dose toxicity test of 1000 mg/kg bw. Specifically, Parental Results: A number of clinical biochemistry and urinary changes were noted at 330 and 1000 mg/kg in males which included lower total protein, albumin and calcium levels in blood, and lower sodium and potassium excretion and higher calcium concentration in urine. Means of these changes only just exceeded or remained within the range considered normal for rats of this age and strain. Moreover, there were no histopathological correlates in eg. liver or kidneys that would support these changes. Therefore, these changes were considered not to be of toxicological relevance. Overall, no toxicologically relevant changes were noted in any of the parental parameters investigated in this study.

In an OECD Guideline 408 (Repeated Dose 90-Day Oral Toxicity in Rodents) in mice No treatment related effects were noted at any dose levels for survival, clinical observation, hematology or blood biochemistry. The average body weights of both sexes fed the diet containing 5 % magnesium chloride were lower than those fed the control diet. Significant increases in the relative weights of some organs were observed in both sexes of the 2.5 and 5 % groups. However, no blood biochemical or histopathological changes were found. A significant decrease in the relative spleen weight was noted in the male 2.5 and 5 % groups. Organ weight changes were considered to be simply related to the lower body weight, since no hematological or histopathological alterations were seen. Renal cell vacuolation was found in high dose males (but not in females). This change might reflect reabsorption of magnesium, but as this alteration was not linked with change in any blood biochemical parameters indicating renal failure, its toxicological significance was considered to be minimal. In conclusion, only high levels of magnesium chloride (2.5 and 5 %) exert any toxic effects and these are limited to minimal renal tubular changes in male mice. Therefore the toxic hazard of magnesium chloride is negligible.

In an OECD Guideline 408 (Repeated Dose 90-Day Oral Toxicity in Rodents) in rats No treatment-related death was observed during the study. Transient soft stool and increase in water consumption in males and females, and slight reduction in body weight gain in males, were noted at the higher dose level of 2.5 %. There were no toxic changes in food consumption, organ weights, hematology and biochemistry, and histopathological examinations in any treated-groups. It can be inferred from the observation of soft stool in the 2.5% group and the observation of inhibited gain in males in the 2.5% group when feeding rats solid food mixed with magnesium chloride for 90 days that the no observed adverse effect level of magnesium chloride is 0.5% (308 mg/kg in males and 299 mg/kg in females). However, that soft stool in the 2.5% group disappeared even after continued treatment suggested that 2.5% is the appropriate maximum dose for a 2 -year carcinogenic study.

Within the reproduction and developmental toxicity study a parental No Observed Adverse Effect Level (NOAEL) of at least 1000 mg/kg/day was determined. In addition 90 day oral studies in rats and mice are available with the structural analogue magnesium chloride that showed no significant toxic effects up to dose levels of 1600 mg/kg bw of test substance for males and 1531 mg/kg test substance for females and 5410 mg/kg bw/d for males and 6810 mg/kg bw/day for females respectively. This corresponds to NOAEL values calculated as magnesium hydroxide of 261 mg/kg

bw/d and 249 mg/kg bw/day for male and female rats respectively (highest dose tested) and 881 mg/kg bw/d and 1109 mg/kg bw for male and female mice respectively.

Estimated Data- None

Neurotoxicity (N-single) M

Magnesium carbonate was assigned a hazard classification level of Moderate for single dose neurotoxicity based on transient ataxia and/or hunched posture were noted in rats orally dosed. Additional studies in high quality analogs report no observed changes in autonomic and central nervous systems, somatomotor activity, and behavior pattern rales following oral exposures up to 2000 mg/kg/day. Results were reported from high quality studies and included high quality analogs; however, the studies were not specific to neurotoxicity. Therefore, the hazard score is reported as low confidence.

Lists

- Authoritative: not included on any authoritative lists
- Screening: not included on any screening lists

Measured Data

ECHA 2020a

In a OECD Guideline 420 (Acute Oral Toxicity - Fixed Dose Method) At the 300 mg/kg dose level, there were no mortalities and ataxia and/or hunched posture were noted in all animals. However, animals appeared normal two or five days after dosing. All animals showed expected gains in bodyweight over the observation period and no abnormalities were noted at necropsy.

ECHA 2020b

Under the conditions of the present study, a single oral application of the test item magnesium chloride hexahydrate to rats at a dose of 2000 mg/kg body weight was associated with no signs of toxicity. A careful clinical examination was made several times on the day of dosing (at least once during the first 30 minutes and with special attention given during the first 4 hours post-dose). Thereafter, the animals were observed for clinical signs once daily until the end of the observation period. All abnormalities were recorded. Cage side observations included changes in the skin and fur, eyes and mucous membranes. Also, respiratory, circulatory, autonomic and central nervous systems and somatomotor activity and behavior pattern were examined. Particular attention was directed to observations of tremor, convulsions, salivation, diarrhoea, lethargy, sleep and coma.

ECHA 2020c

The oral LD50 value of magnesium hydroxide in Wistar rats was established to exceed 2000 mg/kg body weight. Hunched posture and/or piloerection was noted among all animals on Day 1. The mean body weight gain shown by the animals over the study period was considered to be similar to that expected of normal untreated animals of the same age and strain. No abnormalities were found at macroscopic post mortem examination of the animals.

Estimated Data- None

Neurotoxicity (N-repeated) (Group II*) L

Magnesium carbonate was assigned a hazard classification level of Low for repeated dose neurotoxicity based on oral NOAELs >100 mg/kg/day body weight for neurological endpoints following oral exposures in rats. The hazard score is based on high quality studies which used exposures to magnesium chloride hexahydrate (a high-quality analog) and are therefore reported as high confidence.

Lists

- Authoritative: not included on any authoritative lists
- Screening: not included on any screening lists

Measured Data

ECHA 2020a

The repeated dose of magnesium chloride hexahydrate in deionised water to the male and female Wistar rats at dosages of 250, 500 and 1000 mg/kg bw/day following a OECD Guideline 422 (Combined Repeated Dose Toxicity Study with the Reproduction / Developmental Toxicity Screening Test) was conducted. The study revealed no major toxicological findings. The study included neurobehavioural examination which included time schedule for examinations of 5 randomly selected males and 5 lactating females from each group. The battery of functions tested: sensory activity to different modalities, grip strength, motor activity and other behaviour observations. No effects were observed.

Estimated Data- None

Skin Sensitization (SnS) (Group II*) L

Magnesium carbonate was assigned a hazard classification level of Low for skin sensitization based on weight of evidence which indicates no sensitization in most animal exposure studies. One animal study indicated a positive sensitization response to magnesium hydroxide. However, this finding is not supported by the extensive exposure of the general population to the magnesium hydroxide with no cases of contact allergy reported in world literature. The hazard score is based on weight of evidence and discounts a single study reporting sensitization associated with magnesium hydroxide. Therefore, the hazard score is reported as low confidence.

Lists

- Authoritative: not included on any authoritative lists
- Screening: not included on any screening lists

Measured Data

ECHA 2020a

Magnesium carbonate is an inorganic ionic solid and is expected to partition strongly to water rather than organic media. Given the physico-chemical properties of magnesium carbonate, it is expected that the substance would not penetrate the skin in any significant quantity and hence skin sensitisation following exposure is considered to be unlikely. Furthermore, magnesium carbonate is an approved ingredient of cosmetics for topical application to skin.

ECHA 2020b

The reference Witte (2007) is considered as the key study on skin sensitization and will be used for classification. With some magnesium alloys with a minimum Mg concentration of 89% (w/w) a sensitization study according to OECD 406 (GPMT) Magnusson and Kligman was performed which indicated that magnesium does not produce any signs of sensitizing potential. Therefore, no classification and labelling according to regulation (EC) 1272/2008 and subsequent regulations is required.

ECHA 2020c

Based on a weight of evidence approach using both animal testing and human information Magnesium hydroxide is not regarded and not classified as a skin sensitizer.

An expert opinion has been provided from the Informationsverbund Dermatologischer Kliniken (IVDK; Schnuch, A. 2010) which states that they have yet to observe a case of contact allergy with Magnesium hydroxide. Also, despite extensive exposure of the general population to the substance no case of contact allergy to Magnesium hydroxide has been reported in world literature.

Furthermore evidence that Magnesium portion of the compound is not a skin sensitizer was obtained from the results of a guinea pig maximisation test (GPMT) that was performed on behalf of the Magnesium chloride consortium, and shows a negative result. Regarding the hydroxide portion of the compound, there is ample evidence in the literature that hydroxides of other metals are not skin sensitizers (NICNAS, 2003; Banerjee et. al., 2003; DFE (EPA), 2008).

In a mouse local lymph node assay (LLNA) The SI values calculated for the magnesium hydroxide concentrations 10, 25 and 50% were 2.0, 3.6 and 5.9 respectively. These results indicate that the test substance could elicit an SI >= 3. The data showed a dose-response and an EC3 value (the estimated test substance concentration that will give a SI=3) of 19.4% was calculated. False positives in LLNA assays are not uncommon, and the LLNA was judged to be no more than 90 % accurate during its validation (Basketter et. al., 2010).

Given the combination of the epidemiological data, the Magnesium chloride test and the history of false positives using the LLNA test, there is a basis supporting a claim that the positive results obtained in the LLNA test are inaccurate and, thus, a sensitizing effect of Magnesium hydroxide is highly unlikely. Therefore Magnesium hydroxide should not be classified as a skin sensitizer.

CIR 2014

The skin sensitization potential of anhydrous magnesium sulfate (in propylene glycol) was evaluated using the mouse local lymph node assay, according OECD Guideline 429.19 Three groups of 5 mice were used, and the dorsal surface of both ears was epidermally treated with the test substance (10%, 25%, and 50%) at a dose volume of 25 µL/ear. A vehicle control group was also included in the study. The animals were then injected i.v. with 3 H-methyl thymidine, killed, and the draining auricular lymph node of each ear was excised. Lymph nodes were pooled for each animal, and cell suspensions prepared. The stimulation index (SI) was calculated for each group. The SI is defined as the ratio of the DPM/group compared to the DPM/vehicle control group. Because there was no indication that the test substance elicited an SI of ≥ 3 when tested up to a concentration of 50%, anhydrous magnesium sulfate was considered a non-sensitizer.

Estimated Data - None

Respiratory Sensitization (SnR) (Group II*) DG

Magnesium carbonate was assigned a hazard classification level of Data Gap for respiratory sensitization based on the lack of available studies that directly address respiratory sensitization following inhalation exposures to the compound. No analog data was available to fill the data gap.

Lists

- Authoritative: not included on any authoritative lists
- Screening: not included on any screening lists

Measured Data- None

Estimated Data- None

Skin Irritation/Corrosivity (IrS) L

Magnesium carbonate was assigned a hazard classification level of Low for skin irritation/corrosivity based on no irritation effects reported in an in vitro skin epidermal study and a poorly reported non-OECD study in mice using high quality analogs of the substance. The available data does not support the screening list which has therefore been discounted. The hazard score is based on in vitro skin irritation studies and therefore is reported with low confidence.

Lists

- Authoritative: not included on any authoritative lists
- Screening:
  - EU - Manufacturer REACH hazard submissions H315 - Causes skin irritation (unverified)

Measured Data

ECHA 2020a

In a reliable GLP in vitro study performed in accordance with EU Method B46, magnesium carbonate was applied to EPISKIN™ reconstituted human epidermis for a treatment period of 15 minutes followed by a post-exposure incubation period of 42 hours (Harlan Laboratories Ltd, 2010). A measurement of cytotoxicity in reconstituted human epidermal cultures was made by means of the colourimetric MTT reduction assay. The relative mean viability of the test material treated tissues was 98.3%. Hence, magnesium carbonate is considered to be non-irritating to skin.

In a reliable GLP in vitro skin corrosion study performed in accordance with OECD 431, magnesium carbonate was applied to EPISKIN™ reconstituted human epidermis for a treatment period of 3, 60 or 240 minutes (Harlan Laboratories Ltd, 2010). The relative mean viability of the test material treated tissues was 106.4% after an exposure period of 240 minutes. Magnesium carbonate is therefore not corrosive to the skin.

ECHA 2020c

The potential of magnesium hydroxide to induce skin corrosion was tested using a human three-dimensional epidermal model. The possible corrosive potential of magnesium hydroxide was tested using topical application for either 3 minutes or 1 hour. Twenty five mg of magnesium hydroxide was added directly on top of the skin tissue which was moistened with water. Water and potassium hydroxide were used as the negative and positive control substances, respectively. The positive

control had a mean relative tissue viability of 9 % after 3 minutes exposure, and the absolute mean optical density of the negative control tissues was within the historical control range, indicating the acceptability of the assay. The mean relative tissue viabilities for magnesium hydroxide after 3 minute and 1 hour treatments were 88 % and 95 %, respectively. Because the mean relative tissue viability for magnesium hydroxide was not below 50 % after the 3 minute treatment or 15 % after the 1 hour treatment, it was concluded that magnesium hydroxide is not corrosive under the conditions of this test.

The potential of magnesium hydroxide to induce skin irritation was tested using a human three-dimensional epidermal model. The possible skin irritation potential of magnesium hydroxide was tested using topical application for 15 minutes, followed by a 42 hour incubation period. Ten mg of magnesium hydroxide was added directly on top of the skin tissue which was moistened with water. Water and SDS were used as the negative and positive control substances, respectively. The positive control had a mean relative tissue viability of 4 % after 15 minutes exposure, and the absolute mean optical density of the negative control tissues was within the historical control range, indicating the acceptability of the assay. The mean relative tissue viabilities for magnesium hydroxide after 15 minutes of treatment was 91 %. Because the mean relative tissue viability for magnesium hydroxide was not below 50 % after the 3 minute treatment or 15 % after the 15 minute treatment, it was concluded that magnesium hydroxide is not a skin irritant under the conditions of this test.

CIR 2014

A preliminary skin irritation study (mice) on magnesium sulfate (in propylene glycol) was performed prior to the skin sensitization study described above. The test system, procedures, and techniques used in the skin irritation study were identical to those used during days 1 to 3 in the skin sensitization study, unless otherwise specified. Two young adult mice were used, and the ears were treated with 50% magnesium sulfate on 3 consecutive days. The test sites were evaluated for irritation at approximately 3 h to 4 h after the last application. Skin irritation of the ears was not observed in any of the animals tested with 50% anhydrous magnesium sulfate. Additionally, there was no evidence of macroscopic abnormalities of the surrounding area.

Estimated Data- None

Eye Irritation/Corrosivity (IrE): L

Magnesium carbonate was assigned a hazard classification level of Low for eye irritation/corrosivity based on studies which reported no corneal or iridial effects noted during a study conducted in accordance with OECD 405. Studies using high quality analogs report mild positive eye irritation responses that do not meet the criteria outlined within the GHS methodology for classification as an eye irritant. Specifically, the conjunctival scores for analogs were <2 and therefore not classifiable under GHS criteria. The available data does not support the screening list which has therefore been discounted. The hazard score of low is based on well-reported studies in both magnesium carbonate and high-quality analogs and is therefore reported with high confidence.

Lists

- Authoritative: not included on any authoritative lists
- Screening:

- EU - Manufacturer REACH hazard submissions H319 - Causes serious eye irritation (unverified)

Measured Data

ECHA 2020a

In a reliable GLP in vivo eye irritation study performed in accordance with OECD 405, magnesium carbonate was applied as a single application to the non-irrigated eye of two white rabbits (Harlan Laboratories Ltd, 2010). Assessment of ocular damage/irritation was made approximately 1 hour and 24, 48 and 72 hours following treatment. There were no corneal or iridial effects noted during the study; hence, the mean scores for 24, 48 and 72 hours for each animal were 0. The mean scores for 24, 48 and 72 hours for each animal for conjunctival chemosis and redness, although above 0, were below the limits for classification as irritating to eyes and the effects were fully reversible within an observation period of 72 hours. Magnesium carbonate is therefore non-irritating to eyes.

ECHA 2020b

In an OECD Guideline 405 (Acute Eye Irritation / Corrosion) study a single ocular instillation of the test item Magnesium chloride hexahydrate to rabbits at a dose of 0.1 g produced irritant effects, which were fully reversible. The test item produced irritant but reversible ocular effects after instillation into the eyes of 3 female rabbits. Upon fluorescein examinations at the end of the observation period of 72 h and further at the end or prolonged observation period no corneal lesions were found in any animal. Conjunctival discharge was observed in all animals, 1 hr post-instillation. No conjunctival discharge was observed 2 days post-instillation in all the animals. Conjunctival redness and chemosis were also observed in all animals. All conjunctival scores were <2 and therefore not classifiable under GHS criteria.

ECHA 2020c

Screening for the eye irritancy potential of Magnesium hydroxide using the BCOP test. The study procedures were based on OECD guidelines. Magnesium hydroxide did not induce ocular irritation through both endpoints, resulting in a mean in vitro irritancy score of 5.1 after 240 minutes of treatment. Since this score is below 55.1 after 240 minutes treatment, Magnesium hydroxide is not classified as an irritant in the BCOP test.

OECD Guideline 405 (Acute Eye Irritation / Corrosion) Instillation of approximately 57mg of Magnesium hydroxide into one eye of each of three rabbits resulted in effects on the cornea, iris and conjunctivae. The corneal injury consisted of a slight dulling of the normal lusture and/or epithelial damage (maximum 10% of the corneal area) in two animals. The corneal injury had resolved within 24 or 48 hours. Iridial irritation grade 1 was observed in all animals and had resolved within 24 hours. The irritation of the conjunctivae consisted of redness, chemosis and discharge and completely resolved within 72 hours in all animals. All conjunctival scores were <2 and therefore not classifiable under GHS criteria.

Estimated Data- None

ECOTOXICITY (ECOTOX)

Acute Aquatic Toxicity (AA): L

Magnesium carbonate was assigned a hazard classification level of Low for acute aquatic toxicity based on LC50 and EC50 values in all three trophic levels reported for high quality analogs at >100 mg/L. One study in algae reports that no effect was observed at the highest concentration of MgCl2 tested (12 mg/L), however, additional testing of magnesium hydroxide in Pseudokirchneriella subcapitata indicates an EC50 value of >100 mg/L. The hazard score is based on well reported guideline studies using high quality analogs and therefore is reported as high confidence.

Lists

- Authoritative: not included on any authoritative lists
- Screening: not included on any screening lists

Measured Data

ECHA 2020a

The concentration of magnesium carbonate that might cause acute toxicity would be greater than the maximum solubility of magnesium carbonate in water (110 mg/L at 20 °C).

Magnesium is naturally abundant in the environment meaning that aquatic organisms are constantly exposed to magnesium without suffering from any adverse or detrimental effects. Indeed, each of the Mg2+, Cl- and CO3^2- ions are ubiquitous and are not considered to pose a risk of ecotoxicity. Magnesium is present in all natural waters and is a major contributor to water hardness. Water from areas rich in magnesium-containing rocks may contain magnesium in the concentration range 10 to 50 mg/L. The sulfates and chlorides of magnesium are very soluble, and water in contact with such deposits may contain several hundred milligrams of magnesium per litre.

The abundance of magnesium in the aquatic environment and the lack of toxicity in the presented study demonstrate that any further testing is scientifically unjustified.

ECHA 2020b

Well documented study conducted according modified US EPA (1991) guidelines. The lowest LC50 was observed for MgCl2 toxicity to Fathead minnow in freshwater: 96h-LC50 is 541 mg Mg/L. This value was selected as the as the key value for acute toxicity to freshwater fish in the chemical safety assessment.

No guideline study but well described. A 48h-LC50 value for magnesium toxicity to silverside minnows in salt water of 2800 mg Mg/L was obtained. This value was selected as the key value for acute toxicity to marine water fish in the chemical safety assessment

Not a guideline study but meets generally accepted scientific standards and is well documented. A 48h-LC50 value for magnesium toxicity to Daphnids of 140 mg Mg/L is obtained. This value was selected as the key-value for acute toxicity of Mg to freshwater invertebrates.

No guideline study but well performed and well documented. A 48h-LC50 value for magnesium toxicity to salt water shrimp of 2650 mg Mg/L is obtained. This value was selected as the key value for acute toxicity to marine invertebrates in the chemical safety assessment.

Reliable GLP study performed according to OECD 201 guideline. A 72 hours NOEC and EC50 value for biomass, cell number and growth rate greater than 12 mg Mg/L was reported. This value is used as key value for toxicity to freshwater aquatic algae in the chemical safety assessment.

ECHA 2020c

A 96 hour acute static definitive toxicity test was conducted on Pimephales promelas. The effect criterion was survival. In the control exposure, survival was 100%. After exposure to six different concentrations of the test substance (61% magnesium hydroxide), survival ranged from 35-100%. The LC50 value for P. promelas was 511.31 mg of test substance. The LC50 (96h) of P. Promelas was recalculated to bring the concentration of Magnesium hydroxide up to 100% as the concentration of Magnesium hydroxide was only 60% when determining the original LC50 for P.Promelas and so to get a more accurate result the concentration was recalculated giving an LC50 of 306.79 mg/L for freshwater fish.

The 96-hour LC50 for Onchorinchus mykiss is 1293 mg/L test item (containing 61% magnesium hydroxide). The 96 -hour LC50 for Onchorinchus mykiss (rainbow trout) was recalculated to bring the concentration of Magnesium hydroxide up to 100% as the concentration of Magnesium hydroxide was only 60% when determining the original LC50 for Onchorinchus mykiss. The recalculated LC50 (96h) for Onchorinchus mykiss was determined to be 775.8mg/L.

In a 48 hour acute static definitive toxicity test with Daphnia magna, the LC50 value was determined to be 284.76 mg of test substance (61% Mg(OH)2 aqueous suspension). The recalculated LC50(96h) with pure magnesium hydroxide for D.Magna was determined as 170.86 mg/L.

Under the conditions of the present study with Pseudokirchneriella subcapitata, Magnesium hydroxide slightly reduced growth rate and inhibited the yield of this fresh water algae species at 100mg/l, being the highest test concentration. However, a 50% effect level could not be reached. In conclusion: both the EC50 for growth rate reduction (ErC50: 0-72h) and the EC50 for yield inhibition (EyC50:0-72h) exceeded an analytically confirmed concentration of 100 mg/l

Estimated Data- None

Chronic Aquatic Toxicity (CA): L

Magnesium carbonate was assigned a hazard classification level of LOW for chronic aquatic toxicity based on estimated chronic values (ChV) for magnesium hydroxide all of which are >10 mg/L and exceed the anticipated water solubility, suggesting NES. In addition, Magnesium is present in all natural waters and is a major contributor to water hardness. Water from areas rich in magnesium-containing rocks may contain magnesium in the concentration range 10 to 50 mg/L. The sulfates and chlorides of magnesium are very soluble, and water in contact with such deposits may contain several hundred milligrams of magnesium per litre. This natural abundance of magnesium ions in the environment means that aquatic organisms including fish are constantly exposed to magnesium without suffering from any adverse or detrimental effects. The hazard score is based on estimated and modeled values and professional judgement and therefore is reported as low confidence.

Lists

- Authoritative: not included on any authoritative lists
- Screening: not included on any screening lists

Measured Data

ECHA 2020a

Magnesium is present in all natural waters and is a major contributor to water hardness. Water from areas rich in magnesium-containing rocks may contain magnesium in the concentration range 10 to 50 mg/L. The sulfates and chlorides of magnesium are very soluble, and water in contact with such deposits may contain several hundred milligrams of magnesium per litre. This natural abundance of magnesium ions in the environment means that aquatic organisms including fish are constantly exposed to magnesium without suffering from any adverse or detrimental effects. Long-term toxicity testing of magnesium carbonate on fish is therefore scientifically unjustified.

ECHA 2020b

Magnesium hydroxide is of low acute toxicity to aquatic organisms and does not meet the criteria to be classified as dangerous under the CLP Regulation (EC) No 1272/2008 nor does it meet the criteria to be classified as persistent, bioaccumulative or toxic under the REACH Regulation.

Reported results on the physico-chemical properties of Magnesium hydroxide show that the substance is only slightly soluble in water (1.78 mg total solids/L at 8.3 pH and 20ºC) and has a low potential to adsorb to sediment (derived sediment-water partition coefficient (Kd) 1.65). Furthermore, Magnesium hydroxide is expected to break down in the environment to water and magnesium over time. Magnesium is ubiquitous in the environment and is an essential plant and animal nutrient.

Furthermore, Magnesium hydroxide is only slightly soluble in water (1.78 x 10mg total solids/L at 8.3 pH and 20.3ºC) and therefore aquatic plants are unlikely to be exposed to the substance.

Magnesium hydroxide is of low acute toxicity to aquatic organisms and does not meet the criteria to be classified as dangerous under the CLP Regulation (EC) No 1272/2008 nor does it meet the criteria to be classified as persistent, bioaccumulative or toxic under the REACH Regulation. Reported results on the physico-chemical properties of Magnesium hydroxide show that the substance is only slightly soluble in water (1.78 mg total solids/L at 8.3 pH and 20ºC) and has a low potential to adsorb to sediment (derived sediment-water partition coefficient (Kd) 1.65).

Furthermore, Magnesium hydroxide is expected to break down in the environment to water and magnesium over time. Magnesium is ubiquitous in the environment and is an essential plant and animal nutrient.

US EPA 2015

LOW: Estimated chronic values (ChV) for magnesium hydroxide are all >10 mg/L and exceed the anticipated water solubility, suggesting NES.

Fish ChV: 50-80 mg/L (Experimental) An acute to chronic ratio of 10 was applied to experimental acute data for Pimephalis promelas and Onchorinchus mykiss. Reported in a secondary source. Test material diluted to 61% in aqueous suspension.

Freshwater fish ChV = 403 mg/L. Estimated using an acute to chronic NES because this amount of test substance is not anticipated to dissolve in water at a concentration at which adverse effects may be expressed.

Daphnia ChV = 82 mg/L (Estimated) Estimated based on analogy to the measured ChV for Mg2+ ion; based on tests that were not standard but were judged to be of good quality; expected to display NES because this amount of test substance is not anticipated to dissolve in water at a concentration at which adverse effects may be expressed.

Green algae NOEC: 980 mg/L LOEC: 1,230 mg/L (Estimated) Estimated based on analogy to MgSO4; expected to display NES because this amount of test substance is not anticipated to dissolve in water at a concentration at which adverse effects may be expressed.

Estimated Data- None

ENVIRONMENTAL FATE (FATE)

Persistence (P): vH

Magnesium carbonate was assigned a hazard classification level of Very High for persistence based on being an inorganic material and is not expected to be biodegradable. GreenScreen® criteria classify chemicals as a Very High hazard for persistence when substances are recalcitrant (CPA 2012a). The hazard score is based on physical/chemical properties of the substance and is therefore reported as high confidence.

Lists

- Authoritative: not included on any authoritative lists
- Screening:
  - EC - CEPA DSL Persistent

Measured Data

ECHA 2020a

Magnesium carbonate is a simple inorganic substance. Therefore, a ready biodegradability study does not need to be conducted.

ECHA 2020c

Magnesium hydroxide is an inorganic hydroxide and has as such not subject to biodegradation. According to annex VII of Regulation (EC) 1907/2006, 9.2.1.1 the study does not need to be conducted if the substance inorganic. Furthermore, as an inorganic substance, Magnesium hydroxide has a very low propensity for adsorption to sediment.

Estimated Data- None

Bioaccumulation (B): vL

Magnesium carbonate was assigned a hazard classification level of Very Low for bioaccumulation based on professional judgement and estimated BCF and BAF values <100 for magnesium hydroxide. The hazard score is based on professional judgement and therefore reported as low confidence.

Lists

- Authoritative: not included on any authoritative lists
- Screening: not included on any screening lists

Measured Data

ECHA 2020a

Magnesium carbonate is an inorganic ionic solid for which an octanol/water partition coefficient cannot be reliably determined. Magnesium carbonate dissociates into the magnesium Mg2+ and carbonate CO32- ions at environmental pH. These are essential to all living organisms (flora and fauna) and their intracellular and extra-cellular concentrations are actively regulated. Bioaccumulation is therefore not expected.

US EPA 2015

LOW: Magnesium hydroxide is not expected to bioaccumulate based on professional judgment. This inorganic compound is not amenable to available estimation methods. BCF <100 estimated, BAF <100 estimated.

Estimated Data- None

PHYSICAL HAZARDS (PHYSICAL)

Reactivity (Rx): L

Magnesium carbonate was assigned a hazard classification level of Low for reactivity based on the absence of oxidizing properties or explosive properties and a NFPA instability rating of 0. The hazard score is based on the physical properties of the compound and therefore reported as high confidence.

Lists

- Authoritative: not included on any authoritative lists
- Screening: not included on any screening lists

Measured Data

ECHA 2020

Magnesium carbonate has been predicted not to possess explosive properties based on its chemical structure and also on experience of handling and use. Therefore, magnesium carbonate is not classified as explosive according to either the DSD or CLP.

Magnesium carbonate has been predicted not to possess oxidising properties based on its chemical structure and also on experience of handling and use. Therefore, magnesium carbonate is not classified as oxidising according to either the DSD or CLP.

PubChem 2020

No rapid reaction with air No rapid reaction with water

MAGNESITE has generally low chemical reactivity. Non-flammable and non-combustible. Reacts with acids and acidic salts to generate gaseous carbon dioxide with effervescence (bubbling). The reaction may be rapid and exothermic with concentrated solutions of acids.

Fisher Scientific 2007

NFPA Rating: (estimated) Health: 1; Flammability: 0; Instability: 0

Estimated Data- None

Flammability (F): L

Magnesium carbonate was assigned a hazard classification level of Low for flammability based on the results of a preliminary screening test performed according to Method N.1 specified in the UN Recommendations on the Transport of Dangerous Goods. The hazard score is based on test results and therefore reported as high confidence.

Lists

- Authoritative: not included on any authoritative lists
- Screening: not included on any screening lists

Measured Data

ECHA 2020

Method N.1 specified in the UN Recommendations on the Transport of Dangerous Goods, Manual of Tests and Criteria, 4th revised edition, 2003 Magnesium carbonate is not classified as a readily combustible solid under Division 4.1 as it failed to ignite in the preliminary screening test.

PubChem 2020

Not combustible.

Noncombustible Solid

Estimated Data- None

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APPENDIX A: HAZARD CLASSIFICATION ACRONYMS

(AA) Acute Aquatic Toxicity

(AT) Acute Mammalian Toxicity

(B) Bioaccumulation

(C) Carcinogenicity

(CA) Chronic Aquatic Toxicity

(D) Developmental Toxicity

(E) Endocrine Activity

(F) Flammability

(IrE) Eye Irritation/Corrosivity

(IrS) Skin Irritation/Corrosivity

(M) Mutagenicity and Genotoxicity

(N) Neurotoxicity

(P) Persistence

(R) Reproductive Toxicity

(Rx) Reactivity

(SnS) Sensitization- Skin

(SnR) Sensitization- Respiratory

(ST) Systemic/Organ Toxicity

APPENDIX B – PHAROS OUTPUT FOR MAGNESIUM CARBONATE (546-93-0)

Hazard Lists

Download Lists

ENDPOINT	HAZARD LEVEL	GS SCORE	LIST NAME	HAZARD DESCRIPTION	OTHER LISTS
Skin Irritation/Corrosivity	pC	NoGS	EU - Manufacturer REACH hazard submissions	H315 - Causes skin irritation (unverified)	
Eye Irritation/Corrosivity	pC	NoGS	EU - Manufacturer REACH hazard submissions	H319 - Causes serious eye irritation (unverified)	
Persistence	vH-H	LT-UNK	EC - CEPA DSL	Persistent	