

## SUMMARY OF DATA FOR CHEMICAL SELECTION

### **Magnesium Oxide**

1309-48-4

#### BASIS OF NOMINATION TO THE CSWG

Magnesium oxide (MgO) is brought to the attention of the CSWG as a very high production inorganic chemical that has not received adequate testing to ensure its safety to humans, particularly to workers exposed to this substance by inhalation.

Worldwide, about 6 million tons of MgO are produced each year, with US consumption around 730 thousand tons. Refractory applications account for about two-thirds of MgO use, with the additional one-third having a variety of uses in environmental pollution abatement and in manufacturing, construction, agriculture, and pharmaceuticals. Data from a 1981-1983 survey indicated that 765,812 US workers were potentially exposed to MgO.

Magnesium is an essential mineral, and with the exception of very high and unusual exposures, ingestion of MgO does not appear to present a significant health problem to humans. Limited information in humans and animals, however, leaves many unanswered questions regarding the effects of inhaled MgO on the respiratory system. Whether the apparent inconsistencies in the available data are a reflection of differences in various grades of MgO created by their manufacturing process cannot be answered from the data available.

#### SELECTION STATUS

ACTION BY CSWG: 12/11/01

Studies requested:

- Distribution studies to determine whether compound is retained in lung
- Chronic toxicity via inhalation

Priority:

- Distribution studies - high
- Toxicity studies - medium

Rationale/Remarks:

- Request for testing is based on very high annual production volume and significant worker exposure, primarily via inhalation.
- MgO is an inorganic chemical not covered in the EPA HPV Challenge Program.
- The limited information on the toxicity of magnesium oxide via inhalation suggests that chronic toxicity may be a factor even though magnesium via ingestion is an essential element
- Existing human studies are limited in design and by the presence of other toxic chemicals present in the environment.
- The inhalation toxicity of magnesium oxide may be influenced by the manufacturing process, which produces grades of magnesium oxide that differ greatly in their physical characteristics.

## CHEMICAL IDENTIFICATION

<u>CAS Registry Number:</u>	1309-48-4
<u>CAS Name:</u>	Magnesium oxide
<u>Synonyms and Trade Names:</u>	Calcined brucite, calcined magnesium, calcined magnesite, heavy calcined magnesia, light magnesia, maglite, magnesia, magnesia nonoxide, magox, periclase, seawater magnesia
<u>Structural Class:</u>	Inorganic

## Structure, Molecular Formula, and Molecular Weight

MgO	MgO	Mol. wt.: 40.31
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## Chemical and Physical Properties:

<u>Description:</u>	White, very fine, odorless powder (Merck, 2000)
<u>Melting Point:</u>	2827 ± 30 EC (Martin Marietta Magnesia Specialties, 2001)
<u>Density:</u>	Available in very bulky form termed "Light" or in a dense form termed "Heavy" (Merck, 2000); 3.58 g/cm <sup>3</sup> (periclase) (Jackson <i>et al.</i> , 1995)
<u>Solubility:</u>	Dead-burned magnesia: 0.00062 g/100 mL @ 20EC; 0.0086 g/100 ml @ 30EC (Jackson <i>et al.</i> , 1995)  Light-burned magnesia: sol in dil acids (Jackson <i>et al.</i> , 1995)  Hard-burned magnesia: reacts slowly with strong acids (Jackson <i>et al.</i> , 1995)
<u>Reactivity:</u>	The most reactive grades of light-burned magnesia combine with moisture and carbon dioxide eventually to form basic magnesium carbonates (Jackson <i>et al.</i> , 1995)

Technical Products and Impurities: Magnesium oxide (MgO), also known as magnesia, occurs in nature infrequently as the mineral periclase. The properties of commercially prepared MgO depend on the manufacturing process, the nature of the magnesium-containing precursor, and

other chemicals in the process. Light-burned magnesia is characterized by small crystallite size (<0.5  $\mu\text{m}$ ) and moderate to high chemical reactivity. Hard-burned magnesia is characterized by moderate crystallite size (1-20  $\mu\text{m}$ ) and moderately low chemical reactivity. Dead-burned magnesia is characterized by large crystallite size (>40  $\mu\text{m}$ ) and very low chemical reactivity. Pure fused magnesia has extremely large crystal size. One crystal may weigh 200 g or more (Jackson *et al.*, 1995).

Reagent grade MgO >98% pure, based on calcined substance, is available from Sigma-Aldrich (Sigma-Aldrich, 2001a).

Other sources of MgO include the following:

Magnesium Oxide: Alfa Aesar-Johnson Matthey; American International Chemical Inc., Ashland Distribution Chemical Co., Industrial Chemicals & Solvents Div.; B & D Nutritional Ingredients Inc., BKM Resources, Inc. Global Chemicals; BPI, Inc., By-products Industries; Barrington Chemical Corp.; Bruchem, Inc.; C & P Sales Inc.; R.E. Carroll, Inc.; Chemco Industries; Enerchem Inc.; Flavine International Inc.; Generichem Corp.; J.F. Henry Chemical Co., Inc.; Jost Chemical Co., Inc.; Kraft Chemical Co.; Lobel Chemical Corp.; Los Angeles Chemical Co.; Martin Marietta Magnesia Specialties Inc.; Maypro Industries, Inc.; Mays Chemical Co., Inc.; Merrand International Corporation; Mitsui & Co. (U.S.A.) Inc.; Mutchler Chemical Co., Inc.; Noah Chemical, Div. Noah Technologies Corp.; Optipure/Chemco; Pharmline, Inc.; Prince Agri Products, Inc.; RIA International; Rohm & Haas Co., Inorganic Specialties; Ruger Chemical Co., Inc.; Sattva Chemical Div., Pechiney World Trade (USA), Inc.; Serra International Trading Inc.; Southeastern Minerals, Inc.; [www.spectrumchemical.com](http://www.spectrumchemical.com), Division of Spectrum Chemical Mfg. Corp.; Stauber Performance Ingredients, Inc.; Van Waters & Rogers Inc.; Westco Chemicals, Inc.; and Whittaker, Clark & Daniels, Inc.

Magnesium Oxide, ACS: ACS Chemical Inc.; American International Chemical Inc.; and [www.spectrumchemical.com](http://www.spectrumchemical.com), Division of Spectrum Chemical Mfg. Corp.

Magnesium Oxide DP, Microencapsulated: DCV Bionutritionals

Magnesium Oxide FCC: Aerchem, Inc.; American International Chemical Inc.; [www.spectrumchemical.com](http://www.spectrumchemical.com), Division of Spectrum Chemical Mfg. Corp.; and Westco Chemicals, Inc.

Magnesium Oxide, Fused: Sunapee Chemical, Inc.

Magnesium Oxide, Granular: American International Chemical Inc.; American Minerals, Inc.; Ashland Distribution Company, Fine Ingredients Division; Barrington Chemical Corp; Martin

Marietta Magnesia Specialties Inc.; Morse Chemical, Inc.; Particle Dynamics, Inc.; Stauber Performance Ingredients, Inc.; and Westco Chemicals, Inc.

Magnesium Oxide, Light, USP: Jost Chemical Co., Inc. and [www.spectrumchemical.com](http://www.spectrumchemical.com), Division of Spectrum Chemical Mfg. Corp.

Magnesium Oxide Powders: American International Chemical Inc.; Lobel Chemical Corp.; Martin Marietta Magnesia Specialties Inc.; Particle Dynamics, Inc., Pred Materials International, Inc.; Reade Advanced Materials; and Stauber Performance Ingredients, Inc.

Magnesium Oxide, USP: Aerchem, Inc.; American International Chemical Inc.; Barrington Chemical Corp.; DNP International Co., Inc.; GDL International, Inc.; Parchem Trading Ltd.; Premium Ingredients; [www.spectrumchemical.com](http://www.spectrumchemical.com), Division of Spectrum Chemical Mfg. Corp.; and Westco Chemicals, Inc. (Tilton, 2000).

## EXPOSURE INFORMATION

### Production and Producers:

*Production Volume.* MgO is the most commercially important of the magnesium chemicals. In 1999, approximately 5 million tons of MgO were produced worldwide from magnesite ores with 1 million tons produced from brines and seawater. China was the largest producer from natural magnesite, accounting for nearly one half the amount produced. Western Europe and the United States accounted for three-fourths of the seawater or brine production (Lacson *et al.*, 2000).

In 1999, the apparent<sup>1</sup> US consumption of refractory and fused magnesia was 541 thousand tons. An additional 300 thousand tons of caustic-calcined magnesia, USP, and technical grade MgO was consumed. The estimated 1999 US production of refractory and fused magnesia was 216 thousand tons, with an additional 180 thousand tons of caustic-calcined and other magnesia produced (Lacson *et al.*, 2000).

In 2000, the US produced approximately 400 thousand tons of magnesia. An additional 380 thousand tons was imported, primarily from China. About 50 thousand tons was exported, for an apparent consumption of 730 thousand tons. The annual capacity for MgO production was 876 thousand tons, indicating that <50% of US production capacity is actually used. Domestic production of caustic-calcined magnesia declined slightly from that in 1999. US production of dead-burned magnesia dropped about 9% because of the closure of a plant in California, but net imports increased by 36%. Caustic-calcined magnesia production declined by about 4%, and net imports remained about the same (Kramer, 2000).

*Production Processes.* MgO is produced by dead-burning or calcining magnesium hydroxide or magnesite. Magnesium ores that are used commercially include magnesite (MgCO<sub>3</sub>), dolomite (CaCO<sub>3</sub>•MgCO<sub>3</sub>), brucite (Mg[OH]<sub>2</sub>), and olivine (Mg<sub>2</sub>FeSiO<sub>4</sub>). Magnesium

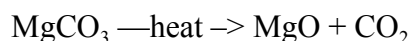
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<sup>1</sup>Apparent consumption equals MgO shipped and used by producers plus imports minus exports; caustic calcined MgO consumption does not include material used to produce refractory magnesia (Lacson *et al.*, 2000).

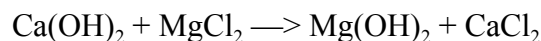
hydroxide is commonly recovered from brines, which are saturated salt solutions that contains magnesium chloride ( $\text{MgCl}_2$ ), calcium chloride ( $\text{CaCl}_2$ ), and water (Jackson *et al.*, 1995; Lacson *et al.*, 2000).

There are many processes for producing MgO (Jackson *et al.*, 1995).

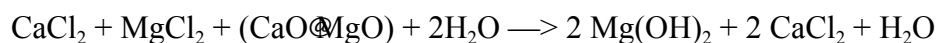
1. A process, used worldwide, involves mining, crushing, sizing, and calcination of natural magnesite. MgO is produced by driving off carbon dioxide:



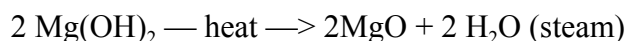
2. Seawater and underground deposits of brine are also important sources of MgO. The production of MgO from seawater follows the same process as that used for a typical brine source. The sea or brine water is treated with hydrated lime,  $\text{Ca}(\text{OH})_2$ , to precipitate magnesium hydroxide [ $\text{Mg}(\text{OH})_2$ ].



3. Another way to extract magnesium from brine is to mix brine with calcined dolime ( $\text{CaO} \cdot \text{MgO}$ ) obtained from dolomitic limestone to produce an aqueous suspension containing magnesium hydroxide [ $\text{Mg}(\text{OH})_2$ ].



The magnesium hydroxide precipitate is then filtered, dried, and calcined to produce magnesia (MgO).



The original magnesium hydroxide particle is usually large and loosely bonded. Exposure to thermal degradation alters the particle structure so that the surface pores are slowly filled and the particle edges become more rounded. Thermal alteration dramatically affects the reactivity of MgO because of this change in particle structure (Martin Marietta

Magnesia Specialties, 2001).

Different grades of MgO are created by manufacturing process variables. Dead-burned or refractory MgO, which is relatively unreactive, is produced when calcining temperatures range from 1500 °C to 2000 °C. Hard-burned magnesia is produced from calcining at temperatures ranging from 1000 °C to 1500 °C and light-burned (caustic-calcined) magnesia is produced by calcining at temperatures ranging from 700 °C to 1000 °C. Hard-burned magnesia has a narrow range of reactivity but light-burned magnesia is highly reactive. Fused magnesia is calcined MgO that has been melted in an electric arc furnace (>ca 2750 °C), cooled, and crushed. It is the most stable and strongest of all the types of magnesia (Ewsuk, 1993; Jackson *et al.*, 1995; Lacson *et al.*, 2000; Martin Marietta Magnesia Specialties, 2001).

In the US, about 63% of all magnesium compounds produced come from seawater and well and lake brines. The remainder is recovered from magnesite, dolomite, olivine, and brucite (USGS, 2001).

US companies that produce MgO from brines include Dow Chemical USA (captive consumption), Martin Marietta Magnesia Specialties, Inc. (various grades of refractory and caustic-calcined magnesia), RHI Refractories America (various grades of refractory magnesia), and Rohm and Haas Inorganic Specialties (specialty caustic-calcined magnesia). Premier Chemicals produces caustic calcined magnesia from magnesite ores and by processing seawater. Additional companies purchase magnesium compounds to produce high-purity grades of fused magnesia (Lacson *et al.*, 2000).

Use Pattern: MgO usage varies widely. Higher-purity products produced from seawater/brine tend to be used for refractory or industrial uses. Caustic-calcined products are generally used for agricultural, construction, or water-treatment markets (Lacson *et al.*, 2000). Several uses of MgO are outlined in Table 1.



**Table 1. Uses of MgO.**

Abrasives	Binder in grinding wheels
Animal feed supplement	Source of Mg ions for chickens, cattle, etc.
Boiler (oil-fired) additives	Raises melting point of ash generated to produce a friable material easily removed; reduces corrosion of steel pipes holding steam; reduces sulfur emissions
Boiler feedwater treatment	Reduces iron, silica, and solids
Chemicals	Starting material for production of other magnesium salts
Coatings	Pigment extender in paint and varnish
Construction	Basic ingredient of oxychloride cements
Electrical	Semiconductors; insulating filler between wire & outer sheath in heating elements
Fertilizers	Source of magnesium for plant nutrition
Foundries	Catalyst and water acceptor in shell molding
Glass manufacture	Ingredient for specialty, scientific, and decorative glassware and fiberglass
Insulation	Light, flexible mats for insulating pipes
Lubricating oils	Additive to neutralize acids
Pharmaceuticals	Special grades of magnesium hydroxide, oxide, and carbonate are used in antacids, cosmetics, toothpaste, and ointments
Plastics manufacture	Filler, acid acceptor, thickener catalyst, and pigment extender
Refractory and ceramics	Ingredient in product formulations for the steel industry
Rubber compounding	Filler, acid acceptor, anti-scorch ingredient, curing aid, pigment
Steel industry	Annealing process; coating for grain-oriented silicon steel used in electrical transformers
Sugar refining	Reduces scale buildup when used in juice clarification and precipitation
Sulfite wood pulping	Source of base for cooking liquors
Uranium, gallium, and boron processing	Precipitation initiator by acid neutralization
Wastewater treatment	Acid stream neutralizer

Source: Martin Marietta Magnesia Specialties, 2001

Approximately 65% of the total consumption of magnesium compounds is for refractory applications. The iron and steel industry is the largest consumer of refractory (dead-burned) MgO which is used in furnace linings to handle molten steel. The development of longer-life refractories and the use of furnaces requiring limited refractory maintenance have contributed to a decline in MgO demand for this application (Kramer, 2000; Lacson

*et al.*, 2000; USGS, 2001).

A special grade of refractory magnesia, electrical grade fused magnesia is used in water-heating elements, kilns, welding machines, and general heating systems. This grade of magnesia is also used as an electrical insulator in sheathed heating elements for domestic appliances (Lacson *et al.*, 2000).

The remaining 35% of MgO consumed, mostly as caustic-calcined magnesia, has a variety of uses. In 2000, environmental applications (water treatment and stack gas scrubbing) accounted for 41% of all shipments of caustic-calcined magnesia. Other uses were chemical, 34%; animal feeds and fertilizers, 18%; construction, 18%; manufacturing (rubber, fuel additives, and electrical), 3%; and pharmaceuticals and nutrition (sugar, medicine, cosmetics), <1%. Hard-burned MgO is used mostly when slow degradation or chemical reactivity is required, such as with animal feeds and fertilizers (Jackson *et al.*, 1995; Kramer, 2000; Lacson *et al.*, 2000; Martin Marietta Magnesia Specialties, 2001; USGS, 2001).

MgO has the following indirect food additive functions: processing aid, pH control agent, nutrient supplement, anticaking agent or free-flow agent, drying agent, humectant, formulation aid, flavor enhancer, and flavoring agent or adjuvant (Clydesdale, 1997).

Human Exposure: Humans are potentially exposed to MgO primarily through inhalation of contaminated air. Although dermal contact is possible, and ingestion also occurs through its use as an indirect food additive, these exposures to MgO are unlikely to pose a hazard to humans under normal circumstances.

*Occupational Exposure*. The National Occupational Exposure Survey (NOES), which was conducted by the National Institute for Occupational Safety and Health (NIOSH) between 1981-1983, estimated that 765,812 workers, including 149,523 females, were potentially exposed to MgO in the workplace (Sigma-Aldrich, 2001b).

Occupational exposure to MgO appears to occur primarily through inhalation of dusts and fumes generated from high-temperature processes, e.g, calcining of magnesite ores.

Several NIOSH Health Hazard Evaluations (HHE) have reported worker exposure to MgO as follows:

- Ship building and repair (SIC 3731), grit blasting - workers potentially overexposed to various metal fumes, with magnesium levels of 1.0-5.5 mg/m<sup>3</sup> (NIOSH, 1983)
- Aluminum magnesium castings foundry (SIC 3321), furnace tenders - magnesium consistently present at levels <0.4 mg/m<sup>3</sup> (NIOSH, 1987)
- Steel mill (SIC 3312), basic oxygen furnace (BOF) area - workers potentially exposed to fumes from Syn Slag containing 3-7% MgO (NIOSH, 1995a)
- Aluminum recycling facility (SIC 3341), workers exposed during pouring and skimming and during cleanup - magnesium detected in 8 of 8 samples (NIOSH, 1995b).

In magnesite mining and processing, MgO is the major component of dusts generated from hot operations. Samples collected on electrostatic filters at various sites around a Slovak factory processing magnesite ores showed total particulate concentrations of 0.1-0.5 mg/m<sup>3</sup>. The composition of the dust particles, determined by X-ray analysis, was 88.5% MgO, 7.6% Fe<sub>2</sub>O<sub>3</sub>, 2.7% CaO, <1% Al<sub>2</sub>O<sub>3</sub> and SiO<sub>2</sub>, and trace amounts of other metals. The mean geometric diameter of the airborne particles was 1 µm (3-4 µm in dust sediment) with a respirable portion of 12-30%. The particles had an uneven surface and were highly absorptive (Reichrtová & Taká., 1992a, 1992b).

*General Population Exposure.* The local population may be exposed to MgO through inhalation of contaminated air released into the atmosphere from magnesium producing facilities. The possibility that such exposures may cause adverse effects in residents of cities located near magnesite-processing facilities was examined, with studies showing pregnancy complications, increased morbidity from respiratory and digestive tract diseases in children, and magnesium excretion and alkaline urine in children cited as evidence to support an association (Reichrtová & Taká., 1992b). Any role contributed

by other air pollutants was not discussed.

*Environmental Exposure.* MgO deposited on soil would be converted into magnesium hydroxide [Mg(OH)<sub>2</sub>] upon exposure to water. Magnesium hydroxide gradually forms a non-permeable film on the surface of soil and trees, thus resulting in elevated magnesium levels and alkaline soil values of up to pH 9.5, causing phytocenological changes in vegetation and deleterious effects to livestock feeding on this vegetation (Reichrtová & Taká.,.1992b).

Environmental Occurrence: Magnesium is the eighth most abundant element in the Earth's crust and the third most plentiful element dissolved in seawater. Although magnesium is found in over 60 minerals, only dolomite, magnesite, brucite, carnallite, and alovine are of commercial importance (USGS, 1998).

Resources from which magnesium compounds can be recovered are virtually unlimited. Identified world resources of magnesite total 12 billion tons, and of brucite, several million tons. Resources of dolomite were described as enormous, with magnesia-bearing brines estimated to constitute a resource in billions of tons (USGS, 2001).

Regulatory Status: The OSHA permissible exposure limit (PEL) for magnesium oxide fume (total particulate) is 15 mg/m<sup>3</sup> averaged over an eight-hour work shift. A short-term exposure limit (STEL) has not been determined (OSHA, 1995).

OSHA's January 19, 1989 *Final Rule on Air Contaminants* contained an 8-hour time-weighted average (TWA) PEL of 10 mg/m<sup>3</sup> (total particulate) and 5 mg/m<sup>3</sup> (respirable particulate) for magnesium oxide fume. NIOSH did not concur with OSHA's limit for magnesium oxide fume, noting that exposure to magnesium oxide may cause chronic respiratory disease in addition to metal fume fever. The 1989 rule was remanded by the US Circuit Court of Appeals and the limits are not currently in force (NIOSH, 2001).

The ACGIH recommended threshold limit value (TLV) for magnesium oxide fume is a

TWA of 10 mg/m<sup>3</sup> based on irritation and metal fume fever (ACGIH, 2000).

FDA views magnesium oxide as an indirect food additive and GRAS compound (Clydesdale, 1997).

## EVIDENCE FOR POSSIBLE CARCINOGENIC ACTIVITY

### Human Data:

*Epidemiological Studies and Case Reports.* A study of the cancer incidence in male workers at a Norwegian plant producing magnesium metal from dolomite and sea water was conducted. The study was restricted to employees with more than one year of work experience between 1951 and 1974 for a total of 52,733 person-years of exposure. The cohort was observed from 1953 to 1984. Altogether 152 new cases of cancer were observed versus 132.6 expected. Among the 393 workers whose longest duration of work had involved exposure to MgO and coal dust or coke (9082 person-years), there were more cases of death by cancer (35) than expected (25.2), however, this observation was not statistically significant (CI 1.0-1.9). In this group, the incidence of lung (6/3.5; CI 0.6-3.7) and stomach (5/2.5; CI 0.6-4.5) cancer was higher than expected (Heldaas *et al.*, 1989).

A review by Reichrtová and Taká. (1992a) provides some information on epidemiological studies and clinical investigations of European workers exposed to dusts containing MgO. These studies reported the following:

- Chronic bronchitis in workers exposed to MgCO<sub>3</sub> dust in mines and MgO dust in surface operations.
- Duodenal and gastric ulcers among workers in the magnesite industry that increased as a function of exposure duration.
- A lymphotropic effect of MgO found in sections of lungs and hilus lymphatic nodes.
- A three-fold increase in serum magnesium and the incidence of pulmonary emphysema and chronic bronchitis in a 1-year study of workers producing MgO from magnesite. Increased serum calcium, reticulocyte count, and lymphocytosis were also observed.
- Impairment of upper airways and hearing in magnesite industry workers.
- No X-ray evidence of fibrosis in magnesite industry workers in a Slovakian study
- Pneumoconiotic lesions in the lungs of Italian workers with a long-term exposure to

dust during magnesite processing.

*Controlled Studies to Examine Metal Fume Fever.* Six healthy individuals were exposed to freshly purified MgO fume in a controlled experiment. By weight, 28% of the fume particles were  $<0.1 \mu\text{m}$  and over 98% were  $<2.5 \mu\text{m}$  in diameter. Exposure time (15-45 minutes), concentration (5.8-230  $\text{mg}/\text{m}^3$ ), and cumulative exposure (261-6435  $\text{min} \times \text{mg}/\text{m}^3$ ) differed for each subject. Post-exposure pulmonary response was compared with control studies from the same six subjects. At 18-20 hours after exposure, no significant differences were found in bronchoalveolar lavage (BAL) inflammatory cell concentrations, BAL interleukin (IL)-1, IL-6, IL-8, tumor necrosis factor, pulmonary function, or peripheral blood neutrophil concentrations in any of the subjects, suggesting that the exposure to respirable MgO had not produced measurable pulmonary inflammation (Kuschner *et al.*, 1997).

In contrast, the ACGIH cites a 1928 study by Drinker and associates who studied four volunteers exposed for 1-9 minutes to freshly generated MgO fume at 410-580  $\text{mg}/\text{m}^3$ . Inhalation of MgO produced a febrile reaction and a leukocytosis in the exposed subjects analogous to that caused by inhalation of ZnO. Although the reactions observed were slight, the authors believed that increased exposures would lead to more severe reactions (ACGIH, 1991).

#### Animal Data:

*Acute/Subacute Studies.* The  $\text{LD}_{50}$  for oral administration of MgO in mice was reported to be 810  $\text{mg}/\text{kg}$  (Sigma-Aldrich, 2001b). The  $\text{LD}_{50}$  for oral administration in rats was reported to be 3870  $\text{mg}/\text{kg}$  in males and 3990  $\text{mg}/\text{kg}$  in females (Clydesdale, 1997).

In humans, acute hypermagnesemia leads to hypotension, ECG changes, and impairment of neuromuscular transmission. The normal range for serum magnesium concentrations is 1.5-2.5  $\text{mEq}/\text{L}$ . Hypotension, nausea, and vomiting occur at 3-8  $\text{meq}/\text{l}$ , ECG changes and hyporeflexia occur at 2-10  $\text{mEq}/\text{L}$ , respiratory depression and coma occur at 10-14  $\text{mEq}/\text{L}$ , and cardiac arrest occurs at concentrations  $>15 \text{mEq}/\text{L}$  (HSDB, 2001).

*Subchronic/Chronic Studies.* Syrian golden hamsters, 48 animals per group, were administered MgO by intratracheal instillation at 3 mg per week for life. Particle size was 90% <25 µm, 46% <10 µm, 18% <5 µm, and 1% <1 µm. Necropsy of each lobe of the lung, larynx, trachea, and stem bronchi showed slight metaplasia in the tracheobronchial zone and moderate hyperplasia of the alveolar zone. Benzo[a]pyrene (1 mg/week) administered in combination with MgO (2 mg/week) produced similar premalignant lesions as well as squamous tumors in the upper respiratory tract. In contrast, benzo[a]pyrene administered in combination with talc (64-66% SiO<sub>2</sub>; 34-36% MgO) produced adenocarcinomas in the lower respiratory tract (Stenbäck *et al.*, 1986).

In an earlier study using a similar protocol, Stenbäck and coworkers (1975) observed that MgO strongly facilitated the tumor-inducing effects of benzo[a]pyrene. In this study 48 Syrian hamsters received 1 mg of MgO in combination with 2 mg of benzo[a]pyrene for 20 weeks by intratracheal instillation. The particle size for MgO was 100% <50µm, 90% <25µm, 46% <10µm, 18% <5µm, and 0%<1µm. MgO and benzo[a]pyrene produced squamous cell carcinomas and papillomas in the larynx with a latent period as short as 9 weeks. Benign and malignant tumors were also produced in the trachea and bronchi but tumors of any type were rarely seen at distant sites.

Brakhnova and Borodyuk (1974) administered what was described only as “magnesium powder” to rats by intratracheal administration. After 1 month, the animals had evidence of fibrosis in the bronchi; at 3 and 6 months edema and desquamation of the alveolar epithelium were also observed.

A carcinogenicity bioassay of MgO conducted by subcutaneous administration to rats was described as negative by the authors (Maltoni *et al.*, 1991). No experimental details were provided, making an independent analysis of the authors’ conclusions impossible.

Short-Term Tests: MgO was not mutagenic in *Salmonella typhimurium* strains TA102 with or without S-9, and it reduced, but did not eliminate the mutagenicity of methylglyoxal in the same strain. MgO was also not mutagenic in the TA97 and TA100 strains with or without



S-9 (CCRIS, 2001; Fujita *et al.*, 1988; Sawai *et al.*, 1998).

Metabolism: The retention of MgO particles in the lungs of laboratory rats has been described as far higher than that of MgCO<sub>3</sub> particles due to their different solubility. Part of the magnesium was transported from the lung by blood to a variety of internal organs and a considerable amount was excreted in the urine [Maass, cited in Reichrtová & Taká., 1992a]. No experimental details or information on the physical characteristics of the MgO were available for review.

Wistar rats were exposed by inhalation to a dust containing a high percentage of MgO. 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 (Reichrtová & Taká.,1992a).

A significant increase in the magnesium content in the lungs, muscles, brain, and spleen of female Wistar rats was observed following a 3-month exposure to atmospheric magnesium dust at a field station in the vicinity of a Slovak magnesite processing plant. After 6 months of exposure, magnesium levels were elevated in muscle, lung, liver, spleen, brain, and kidney (Reichrtová & Taká.,1992b).

Other Biological Effects:

*Reproductive Effects*. MgO was used as a positive control to examine the effects of an

industrial magnesite dust on avian embryos. The dust, collected from the electrostatic filters in a Slovak magnesite factory, contained 88.5% MgO. Peking duck eggs, 50 per group were injected with 0.2, 0.4, or 0.8 mg of magnesite dust or MgO, on days 6 and 7, and the eggs were incubated until day 19. Negative control eggs were injected with water. Treatment on days 6-7 was chosen as a critical period for axial anomalies in duck embryos. In groups injected with magnesite dust suspensions on day 7, lethality ranged from 94-98%, much higher than observed in groups treated on day 6, 24-50%. MgO application on day 7 induced dose-related embryoletality, ranging from 32-80%. Morphological screening of the skeleton on day 19 showed a dose-related incidence (5.2-14%) of skeletal anomalies in embryos treated with magnesium dust on day 6. Delayed ossification was also observed. Because of poor survival, this test could not be conducted on the day-7 embryos. Anomalies observed after magnesium dioxide application consisted of growth retardation and shortening of the limbs. The frequency was 5.8-20%. No anomalies were observed in control embryos (Reichrtová *et al.*, 1981).

MgO appears to interfere with the chick embryonic morphogenetic systems in a significant manner. Subgerminal and intraamniotical MgO injections to fertilized White Leghorns chicken eggs showed interference at doses of 30 and 100 µg. MgO also induced the “strait-jacket” syndrome after administration on day 3. This syndrome comprises hypoplasia of the central face, exencephaly, body-wall defects, and Kettler transposition, defects associated with amniotic smooth-muscle contraction (Panáková *et al.*, 1985). Inhalation of dust from the Slovak magnesite factory also adversely affected reproduction in Wistar rats. Animals inhaled the dust for 3 months before mating, 3 months before mating and during pregnancy, or during pregnancy only. This produced a higher incidence of stillborn pups, lower weight of living young, and a change in the sex index with more males being born. The changes were more pronounced when exposure to dust occurred during pregnancy. No significant increase in the incidence of congenital malformations was found. F<sub>2</sub> females exposed to dust for 2 months before mating into the preimplantation phase of pregnancy had a higher incidence of fetal resorption (Reichrtová & Taká., 1992a).

Female Wistar rats exposed to emissions from the magnesite factory for 6 months and mated with non-exposed males had a decreased fertility index. Average litter size was also smaller and the progeny weighed significantly less than control pups on the 21<sup>st</sup> postnatal day. The F<sub>1</sub> rats had significantly increased concentrations of magnesium in the lungs and muscles (Reichrtová and Taká.,.1992b).

*Effects on the Respiratory System from Exposure to Magnesium-Containing Air Pollutants.*

A total of 15 male Wistar rats, housed at a biomonitoring station, were exposed to the emissions from a magnesite facility for 6 months. Matched controls were housed in an area free from magnesium pollution. At the end of the experiment, the animals were killed and their lungs were lavaged to assess pulmonary damage. The findings - an increased number of alveolar macrophages; an increase in the activities of acid phosphatase, alkaline phosphatase, and lactate dehydrogenase in the bronchoalveolar lavage fluid; and of alkaline phosphatase in lung tissue homogenate - suggested an adverse effect on the lungs of the animals (Ková. iková, 1986).

In what appears to be the same study, Reichrtová and Taká..(1992b) summarized the histological findings in the lungs and liver of the rats. The lungs showed thicker intraalveolar septa, atelectatic sites and large numbers of pulmonary macrophages. There were instances of increased proliferation of Malpighi's bodies, lymphocytes, macrophages and plasma cells. The red pulp showed considerable haemorrhagia and accumulation of an iron-containing pigment. The liver showed vacuole formation in hepatocyte cytoplasm and Kupffer cell proliferation.

Similar studies conducted in rats and rabbits exposed for 6 months to atmospheric pollutants from magnesite plants reported adverse changes in the trachea (Reichrtová and Taká.,.1992b).

*Effects on the Heart from Exposure to Magnesium-Containing Air Pollutants.* F<sub>1</sub> generation rabbits were used for biological monitoring of emissions from the same Slovak magnesite factory. After 12 months of exposure to atmospheric pollutants from the factory, these

rabbits had elevated levels of magnesium and calcium in the heart. Changes in the myocardial structure as well as diminished adenosine triphosphatase activity in the heart muscle were observed. Other metals present in the magnesite emissions, e.g., Ni, Cu, Mn, and Fe, also showed accumulation in various tissues (Reichrtová & Taká.,(1992b).

*Effects of Magnesite Factory Dusts on Magnesium-Calcium Balance.* Serum calcium levels increased significantly after 4-month exposure of Wistar rats to dusts collected at the Slovak magnesite factory (Reichrtová & Taká.,1992a).

*Effects of Magnesite Factory Dusts on Proteosynthesis and Cyclic Adenosine Monophosphate (cAMP).* <sup>14</sup>C leucine incorporation into total proteins showed a transient increase as a function of the amount of magnesite factory dust inhaled by rats for 18 weeks. Plasma levels of cAMP also showed transient elevations after intratracheal administration of dust suspensions (Reichrtová & Taká.,1992a).

*Effects on of Magnesite Factory Dusts on Biological Membranes.* Erythrocyte membranes from blood samples collected during a long-term exposure to magnesite factory dust were reported to have lowered *in vivo* chemical resistance. *In vitro* studies of erythrocyte suspensions confirmed the hemolytic activity of the magnesite dust (Reichrtová and Taká.,1992a).

*Effects of Magnesite Factory Dusts on Acid Base Balance.* C57BL mice simultaneously exposed to magnesite factory dust and administered sodium salicylate had higher urine pH values resulting in impaired formation and excretion of salicylic acid. Free salicylic acid accumulated in the liver and spleen (Reichrtová & Taká.,1992a).

*Immunological Effects of Magnesite Factory Dusts.* The effects of dust from a magnesite factory on the immune response were examined in a review article by Reichrtová and Taká.,(1992a). These effects included:

- Increased number of plaque-forming cells in the lung and spleen after 4 days of immunizing Wistar rats with a sheep erythrocyte suspension;

- Moderately increased titres of pulmonary autoantibodies in Wistar rats following inhalation of the dust for 3 months; (Antigen was prepared from the lungs of young intact Wistar rats.)
- Increased levels of total serum complement ( $CH_{50}$ ) in Wistar rats 25 days after inhalation of the dust for 2 months;
- Partial inhibition of the immune binding to the membrane  $F_c$  receptor of rabbit pulmonary alveolar macrophages of sheep erythrocytes sensitized with rabbit antibody, an effect similar to that seen for MgO but substantially smaller than that seen for silica dust;
- Decreased nonspecific antitumor immunity of C57 BL mice to inoculated syngeneic lymphoma, resulting in more pronounced growth of the tumor than in control animals.

Structure Activity Relationships: Magnesium is an essential mineral that helps maintain normal muscle and nerve function, keeps the heart rhythm steady, and helps keep the bones strong. It is also involved in energy metabolism and protein synthesis. Magnesium deficiency may cause metabolic changes that contribute to heart attacks and strokes and may be a risk factor for postmenopausal osteoporosis. About half the body's magnesium stores are found inside the cells of body tissues and organs, and half are combined with calcium and phosphorus in the bone. Only 1% is found in the blood. The Recommended Dietary Allowance for magnesium for adults ranges from 310 to 420 mg depending on life-stage and sex (NIH, 2001).

Given the essential nature of magnesium, oral administration of soluble magnesium compounds would not be expected to pose a cancer risk. Supporting this statement is a 2-year study in B6C3F<sub>1</sub> mice. Magnesium chloride administered at 0, 0.5 or 2% in the diet for 96 weeks followed by 8 weeks of observation was reported to be negative (CCRIS, 2001).

Negative studies in the Ames assay for *S. typhimurium* strains TA98, TA100, TA1535, TA1537 with and without metabolic activation and in the *Escherichia coli* wp2 UVRA assay with and without S-9 for magnesium sulfate are consistent with the negative results

reported elsewhere in this summary sheet for magnesium oxide (CCRIS, 2001).

As the substantial information on several other metals, e.g., nickel, chromium, indicates, however, the results of oral administration may be a poor reflection of the toxicity of relatively insoluble inhaled particulates.

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