Magnesium oxide (fume)

(CAS No: 1309-48-4)

Health-based Reassessment of Administrative Occupational Exposure Limits

Committee on Updating of Occupational Exposure Limits,
a committee of the Health Council of the Netherlands

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1 Introduction

The present document contains the assessment of the health hazard of magnesium oxide fume by the Committee on Updating of Occupational Exposure Limits, a committee of the Health Council of the Netherlands. The first draft of this document was prepared by AAE Wibowo, Ph.D. (Coronel Institute, Academic Medical Centre, Amsterdam, the Netherlands).

The evaluation of the toxicity of magnesium oxide fume has been based on the review by the American Conference of Governmental Occupational Hygienists (ACGIH) (ACG96). Where relevant, the original publications were reviewed and evaluated as will be indicated in the text. In addition, in January 1998, literature was searched in the databases Medline, Chemical Abstracts, Embase (starting from 1966, 1970, and 1988, respectively), and HSELINE, NIOSHTIC, CISDOC, and MHIDAS (backwards from 1997) and Poltox (Toxline, Cambr Sc Abstr, FSTA) (backwards from 1994), using the following key words: magnesium oxide and 1309-48-4.

In June 2000, the President of the Health Council released a draft of the document for public review. The committee received no comments.

An additional literature search in Toxline and Medline in October 2003 did not result in information changing the committee's conclusions.

2 Identity

name	:	magnesium oxide
synonyms	:	-
molecular formula	:	MgO
CAS number	:	1309-48-4

3 Physical and chemical properties

molecular weight	:	40.3
boiling point	:	3582°C
melting point	:	2800°C
flash point	:	not available
solubility in water	:	slightly soluble
log $P_{octanol/water}$	:	1.43 (estimated)
conversion factors	:	not applicable

Data from ACG96, http://esc.syrres.com.

Magnesium oxide is a white, very fine, odourless powder that occurs in nature as the mineral periclase. Magnesium oxide fumes (aerosols) are produced when magnesium undergoes high-temperature processes (burning, thermal cutting, welding). The fumes have no particular smell (ACG96, NLM02).

In the health risk assessment of exposure to the metal fumes, a difference should be made with that of metal dust particles.

4 Uses

Magnesium oxide as a powder finds its applications in ceramics, fire bricks, pharmaceuticals, as an enteric acid neutralising agent, in boiler scale control, and as a food additive (ACG96).

5 Biotransformation and kinetics

In 1931, Brown studied the retention of magnesium oxide fumes in the respiratory tract of human volunteers. The particle sizes were close to 1.5 μm, but the majority were less than 1 μm. The results showed that the percentage retained during normal breathing, while at rest, varied from about 60 to 45% when inhaling concentrations of magnesium oxide fumes of 10 and 50 mg/m^3, respectively. The retention of magnesium oxide after mouth breathing at rest was about 10% less than after normal (nose) breathing at rest (Bro31a). In a consecutive study in the same volunteers, Brown claimed that a few factors influenced the retention of magnesium oxide fumes. The retention was inversely proportional to the respiration rate for rates below 20/min and to the minute-volume of air breathed. On the other hand, the retention was directly proportional to particulate size and to density of dust suspended in air. The retention was not affected by volume per respiration, vital capacity, and relative humidity of inspired air (Bro31b).

Magnesium oxide is not soluble in water. Therefore, it is doubtful whether a significant amount of absorption takes place in the respiratory tract. For the same reason, less magnesium oxide is absorbed after ingestion compared with magnesium aspartate HCl (Muh91) or magnesium citrate (Lin90).

In Wistar rats, 41 and 20% of the deposited dust was eliminated 25 days after single (6 hours) or repeated (200 hours) exposure, respectively, to aerosols prepared from dust collected from electrostatic filters of a magnesite work, containing about 89% MgO. Moderately increased serum magnesium levels, returning to initial levels 25 days after ending exposure, and increased magnesium levels in urine and in liver (by 16%) and spleen (by 20%) indicated

that some absorption into the body occurred. No more data were presented (Rei92).

Magnesium is an essential element. Normal serum magnesium concentrations range from 0.5-1.3 mmol/L, averaging 0.87-0.93 mmol/L, in adults of either sex. An average of 34% of total serum magnesium is bound to protein. Normal urine contains 1-6 mmol/L of magnesium. In dogs, magnesium was quickly distributed throughout the body after administration, with the highest concentrations found in kidneys, liver, and heart. About 22% of a dose was eliminated in the urine within 3 hours, and 25% within 24 hours. Only about 1% was excreted in the faeces. Skeletal muscle and bone account for a large portion of body burden of magnesium (Bas90).

6 Effects and mechanism of action

Human data

Unspecified magnesium oxide fume concentrations were stated to have caused slight irritation of eyes and nose in an examination of 95 workers (Ple36). It has been reported that the fumes, like zinc oxide fume, may induce metal fume fever (Bel94). According to Hartmann et al., only the freshly formed metal fume particles with diameters between 0.01 and 1.0 μm induce the typical symptoms (Har83).

Drinker et al. exposed 4 volunteers to a concentration of freshly prepared magnesium oxide fumes of 5.8 mg/m^3. Three volunteers were exposed for 1, 2, or 3 minutes, respectively, while standing and breathing at their normal rates resulting in estimated uptakes of 5, 10, and 15 mg, respectively. The 4th subject was exposed for 4 minutes while sitting down and breathing at a slower rate and more deeply, resulting in an uptake of 16 mg of magnesium oxide. Only the 4th person, exposed for 4 minutes, showed a physiological reaction although the subject exposed for 2 minutes was said to have been conscious of a malaise (not further specified). In a second experiment, performed 3 days later, the same persons were exposed to concentrations of 4.1-4.3 mg/m^3, for 3, 5, 7, or 9 minutes, respectively, resulting in uptakes of 15, 17, 29, and 26 mg, respectively. Physiological responses were only observed in the persons exposed for 5 and 9 minutes, being those having the malaise and the physiological response, respectively, in the first experiment. In the second experiment, maximum increases in body temperature (from ca. 36.9°C to ca. 37.3°C) and in white blood cell count (from 7000 to ca. 15,500) were observed 5-6 hours after ending the 9-minute exposure. No data were given on the other person (Dri27).

Hartmann et al. reported 7 cases of foundry workers in Switzerland who developed pulmonary symptoms and (in the majority) recurrent occupational fever. The onset of these episodes coincided with the introduction of a new founding technique resulting in exposure to magnesium oxide fumes. There were no data on the magnitude and duration of exposure. The feverish episodes were interpreted as metal fume fever (Har83). The weekly cycle of symptoms usually begins again after the following exposure on Monday, and is, therefore, called the 'Monday fever' (Sum81).

D'Andrea et al. reported 4 cases of patients - workers of a magnesium production factory in Italy - with 'coin lesion' type opacities of the lungs. The surgical and histological findings suggested a pneumoconiotic aetiology. Chemical analysis of the nodules showed them to be rich in double phosphate, calcium, and magnesium. According to D'Andrea et al., this was caused by excessive exposure to dusts occurring in the production of magnesium oxide from dolomite, a magnesium-containing mineral ($MgCO_3$•$CaCO_3$) (DAn80).

Kuschner et al. exposed 6 human volunteers (n=1/concentration) without any history of occupational exposure to magnesium oxide or of acute or chronic lung disease to concentrations of 5.8, 110, 123, or 143 mg/m^3 for 45 minutes, to 210 mg/m^3 for 20 minutes, or to 230 mg/m^3 for 15 minutes, resulting in cumulative magnesium doses of 261 to 6435 mg/m^3 x minutes. None of the exposed reported symptoms consistent with metal fume fever. In addition, there were no significant differences in bronchoalveolar lavage (BAL) inflammatory cell concentrations and inflammatory-mediating factors (tumour necrosis factor, interleukine-1, -6, and -8), pulmonary function, and peripheral blood neutrophil concentrations when compared with control values obtained from the same volunteers without prior exposure to magnesium oxide (Kus97).

Heldaas et al. performed a retrospective cohort cancer incidence and mortality study on workers of a magnesium metal and its alloys production factory in Norway. The cohort comprised of 2391 male employees with more than one year of work experience in the study plant between 1951 and 1974. The cohort was observed from 1953 to 1984. The production of magnesium metal and alloys involved combined exposures to many agents, such as volatile coal tar pitch products, chlorinated hydrocarbons (mainly hexachlorobenzene), asbestos, magnesium oxide, and magnesium chloride. Due to the complexity of possible causes, the authors divided the population into 9 different exposure categories, membership of which was generally defined as that category with the longest duration of work. One of the categories was designated as 'magnesium oxide' and comprised of 393 workers exposed to magnesium oxide and coal dust having 9082 person-years experience. Using a constructed Norwegian population with

an identical age distribution as reference, observed/expected (O/E) ratios of 68/74.3 and of 35/25.2 were found for ‘all deaths’ and ‘all cancers’, respectively; the 95% confidence interval (CI) of the standardised incidence ratio (SIR) was 1.0-1.9. When selected for specific types of cancer, they found the following O/E ratios in the ‘magnesium oxide’ category: lung cancer: 6/3.5 (95% CI: 0.6-3.7); stomach cancer: 5/2.5 (95% CI: 0.6-4.5); and lip cancer: 1/0.4 (Hel89). From this study, the committee concluded that there is no clear evidence that exposure to magnesium oxide is carcinogenic, but feels that the number of subjects studied is too small to be conclusive.

Gwizdek and Kochanowski reported an increased incidence of gastric disorders in workers (n=76; age: <30-60 years) occupationally exposed to magnesium oxide vapour: 36.8% of the workers complained of gastric disorders, of which 23.7% were diagnosed with gastric or duodenal ulcer. Depending on the process activity, exposure levels varied between 50 and 116 mg/m^3 for magnesium oxide vapour. In the exposed workers, mean urinary magnesium concentrations 516 (n=6) and 496 mg/L (n=16) at the start and the end of the shift, respectively, vs. 240 mg/L (n=10) in the control group; serum magnesium concentrations were 2.93 and 3.33 mg/100 mL, at the start and end of the shift, respectively, vs. 2.37 mg/100 mL in controls (Gwi67).

Animal data

The committee did not find data from experimental animal studies on eye and skin irritation or sensitisation of magnesium oxide or its fumes.

Experiments showed that exposure of experimental animals to magnesium oxide fumes induced an adverse reaction that was different from the general picture of metal fume fever. A common trait was the increase of leukocytes, a few hours after exposure, accompanied by a decline in body temperature instead of an increase like in humans.

Drinker and Drinker exposed 6 cats to freshly generated magnesium oxide fumes plus approximately 10% carbon dioxide for 15 minutes to 3 hours. The total amount of magnesium inhaled was estimated to range from 21 to 156 mg for the 15-minute and 3-hour exposure, respectively. There was no evidence of discomfort for cats exposed for 2 hours (total magnesium inhaled: 126 mg) or less. Cats exposed for 3 hours showed breathing distress. At the end of exposure, there was a decline of rectal temperature from 39ºC to just above 35ºC. The authors reported also an increase of leukocyte numbers (Dri28).

Mori et al. studied the effects of exposure to freshly prepared magnesium oxide fumes on body temperature and leukocyte counts in rabbits. Body

temperature and leukocyte counts were measured every half hour and every hour, respectively, from the start of exposure (t=0) during the subsequent 8 hours. Small decreases in body temperature of 0.8 to 0.4ºC, when compared to pre-exposure values, were found in the 3 rabbits at the start and during the next 1.5 hours of a 30-minute exposure to a concentration of magnesium oxide fumes (generated at 500ºC) of 0.17 mg Mg/m^3. Thereafter, body temperature values were, generally, similar to pre-exposure values. Leukocyte counts were maximally increased, by 80%, at t=2 hours, showing rather inconsistent results with great individual variation thereafter. When 3 rabbits were exposed to fume concentrations of 0.31 mg Mg/m^3 (generated at 1000ºC), for 30 minutes, small decreases in body temperature of ca. 0.4ºC were found at t=0 and t=1.5 hours while temperatures were comparable to pre-exposure values at all other measurement points. Leukocyte counts were maximally increased, by about 100%, at t=2 hours, and showed a similar picture as that at exposure to 0.17 mg Mg/m^3 (Mor75). The committee considered this study to be invalid because of the absence of a control group, of statistical analysis, and of data on particle size (distribution) and because of the inconsistency and variability of the results.

Reichrtová et al. studied the effects of exposure to magnesite 'dusts' in rats, in laboratory as well as in field conditions in which animals housed in stations built on a distance from magnesite works were exposed to magnesite-work emissions ('dust fallout'). These studies were published in Slovak (see Rei82a) and only partly in more detailed reports or as a brief summary in English (see below). The committee will present the results of the laboratory experiments only.

In experimental exposure chambers, aerosols were prepared using particulates that were collected from electrostatic filters in a Slovak magnesite work, consisting of 88.5% MgO, 7.6% Fe_2O_3, 2.7% CaO, 0.5% Al_2O_3, SiO_2, and traces of other elements and having a mean dust particle diameter of 1.8 μm. Wistar rats and C57 BL mice were exposed to concentrations ranging from 10-1000 mg/m^3, 3-5 hours/day, 5 days/week, for 3-9 months. Generally, exposure induced increases in calcium levels in serum and spleen, decreases in liver, while no changes were seen in the lungs. Analysis of blood samples showed a moderate haemolytic effect that was similar to that of silica with an intermediate fibrogenic effect. Following histological examinations, dust particles were seen in the lungs in thickened interalveolar septa and macrophages, but there were no signs of fibrosis. Proliferated histiocytic elements with particles present were found in the subcapsular sinuses and medulla of hilus lymphatic nodes. The spleen had particles (sinusoid macrophages) present and haemorrhages (Rei92).

In rats exposed to dust aerosols of 50 mg/m^3, 4 hours/day, 5 days/week, for 70 days, statistically significant increases in the number of B lymphocytes in blood, in lactate dehydrogenase activity in lymphocytes, and in the acid phosphatase activity in alveolar macrophages were found at the end of the exposure period. Histological examination of the organs showed a marked stimulation of the reticuloendothelial cells in the lungs and spleen. The overall lung tissue structure retained its normal appearance, except for a slight hypertrophy of interalveolar septa. Some alveoli were packed with macrophages. The histological changes in the spleen were characterised by growth of malphigian corpuscles and migration of lymphocytes into the spleen red pulp. The reticulin stroma of the spleen was unaltered. No histological changes were observed in liver and kidneys. Reichrtová et al. concluded that subchronic exposure to these dusts might modulate the activity of cells participating in the induction and expression of immune response (Rei82b). Other experiments by these authors suggested possible modulating effects on the immune processes as well. In rats immunised using sheep erythrocyte suspensions 4 days after intravenous or intratracheal administration of single doses of the aforementioned dust of 25 mg/animal, there were statistically significant increases in antibody response as indicated by increased numbers of plaque-forming cells in spleen ($p<0.01$) and lungs (bordeline; $p<0.05$) when compared to controls. In rats exposed to 1000 mg/m^3 for 2 or 3 months, there was an increase in total serum complement but titers of lung autoantibodies were similar to those of controls (Rei77, Rei92). Contrary to a fibrogenic silica dust, which was investigated in parallel experiments, MgO-containing dust did not have an immunomodulatory/ suppressive effect on the survival of transplanted ear skin allograft in inbred Berlin Druckrey and Lewis rats (Rei92). Due to the lack of experimental details and/or use of only one, very high exposure level, the committee considers these studies and effects of borderline significance.

Carcinogenicity

Stenbäck et al. exposed 30 male Syrian golden hamsters to magnesium oxide ‘dusts’ by intratracheal instillation of doses of 2 mg per animal, once a week, for 30 weeks. The particle size distribution was: >25 μm: 98.2%, >5 μm: 91.6%, and >1 μm: 63.4%. The compound did not produce significant changes in the respiratory system (no tumours in the respiratory tract, nasal cavity, trachea, and lungs). However, 9 animals developed histiocytic-type lymphomas and 2 had adrenocortical adenomas. When intratracheal instillations of magnesium oxide were combined with subcutaneous injection of diethylnitrosamine (1 mg, once a

week, during 12 weeks), no lymphomas were induced. At present, no explanation can be given for the results (Ste73). The committee notes that no control group was used in the experiment, and moreover, that the exposure period was inadequate for an unequivocal evaluation of the (potential) carcinogenicity of magnesium oxide.

Mutagenicity and genotoxicity

In vitro, *m*agnesium oxide was negative when tested – probably without metabolic activation – at only one concentration (50 mM) in a gene mutation assay using *S. typhimurium* strain TA102 (Cro96).

In vivo, the Reichrtová research group (see above) reported that long-term exposure to MgO-containing dust did not induce statistically significant increases in the frequency of chromosomal aberrations or structural chromosomal changes in bone marrow of DBA/2 mice. No more data were presented (Kov90).

The committee did not find data from other studies on the mutagenicity or genotoxicity of magnesium oxide.

Reproduction toxicity

The Reichrtová group (see above) did not observe an increase in the frequency of abnormal sperm in Wistar rats (n=10) exposed to MgO-containing dust aerosols of 120 mg/m^3, 5 hours/day, 5 days/week, for 3 months, when compared to controls (1.2 and 0.9%, respectively; number of sperm analysed: 350/animal) (Kov90). The same group reported that there were no changes found in the reproduction properties of males exposed 3 months before mating and mated with unexposed females (see below) (Rei92).

Reichrtová et al. performed a reproduction toxicity study in which Wistar rats were exposed to MgO-containing dust levels, 3 months before mating, 3 months before mating and during pregnancy, or during pregnancy (day 2-19) only, and allowed to mate in a variety of combinations. Exposure resulted in a higher incidence of stillborn rats, lower pup weights, and a change in sex ratio (more males born), but not of congenital malformations. Changes were more pronounced in groups where females were exposed during pregnancy. Young F1 offspring of exposed females had higher calcium serum levels. Adult F1 animals were exposed for 4 months, but no further data were presented. For F2 females exposed for 2 months before mating and during the pre-nidation period of pregnancy, an increased fetal resorption was reported (Rei92). Because of lack of

data on experimental design and exposure level(s) and of detailed results, the committee cannot assess the significance of these findings.

7 Existing guidelines

The current administrative occupational exposure limit (MAC) for magnesium oxide fumes in the Netherlands is 10 mg/m^3 (as Mg), 8-hour TWA.

Existing occupational exposure limits for magnesium oxide fumes in various European countries and in the USA are summarised in the annex.

8 Assessment of health hazard

In the hazard assessment, a difference should be made between magnesium oxide fumes and magnesium oxide powder or dusts. Fumes consist of freshly generated particles of magnesium oxide, formed at high temperatures, with smaller dimensions than powder or dusts. Hartmann et al. (Har83) reported diameters between 0.01 and 1.0 μm for the fumes, which can be classified as respirable particles reaching the alveolar spaces of the lungs. Uptake takes place only by inhalation, with the respiratory system as the target organ.

Human case reports showed that exposure to magnesium oxide fumes, comparable to exposure to zinc oxide fumes, may induce symptoms consistent with metal fume fever, although no such symptoms were found in volunteers exposed to fume levels of ca. 145 and 230 mg Mg/m^3, for 45 and 15 minutes, respectively. However, the committee did not find valid data from studies on effects in man or experimental animals following repeated inhalation exposure or from studies on the potential carcinogenicity or reproduction toxicity.

Magnesium oxide was negative in an *in vitro* mutation assay in *S, typhimurium* strain TA102 and in a poorly reported *in vivo* chromosome aberration mouse bone marrow assay.

The committee considers the toxicological database on magnesium oxide fumes too poor to justify recommendation of a health-based occupational exposure limit.

The present MAC-value for magnesium oxide fumes is 10 mg/m^3, 8-hour TWA, which means that it is considered an inert dust. The available data, however, show that fumes of magnesium oxide are not inert, certainly not the freshly generated fumes. Therefore, the committee concludes that the present MAC-value may be too high.

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Annex

Occupational exposure limits for magnesium oxide fumes[a].

country - organisation	occupational exposure limit		time-weighted average	type of exposure limit	note[b]	reference[c]
	ppm	mg/m^3				
the Netherlands						
- Ministry of Social Affairs and Employment	-	10	8 h	administrative		SZW04
Germany						
- AGS	-	6[d]	8 h			TRG03
	-	24[d]	15 min			
- DFG MAK-Kommission	-	-[e]				DFG03
	-	1.5[f]	8 h			
	-	4[d]	8 h			
Great-Britain						
- HSE	-	10[f]	8 h	OES		HSE02
	-	4[g]	8 h	OES		
	-	10[g]	15 min			
Sweden	-	-				Swe00
Denmark	-	6	8 h			Arb02
USA						
- ACGIH	-	10[f]	8 h	TLV	A4[i]	ACG04
- OSHA	-	15[h]	8 h	PEL		ACG03
- NIOSH	-					ACG03
European Union						
- SCOEL	-	-				EC04

[a] As Mg.

[b] S = skin notation, which means that skin absorption may contribute considerably to body burden; sens = substance can cause sensitisation.

[c] Reference to the most recent official publication of occupational exposure limits.

[d] Respirable dust.

[e] Fume: Listed among substances for which studies of the effects in man or experimental animals have yielded insufficient information for the establishment of MAK values.

[f] Total inhalable dust.

[g] Fume and respirable dust.

[h] Total particulate matter.

[i] Classified in carcinogenicity category A4, i.e., not classifiable as a human carcinogen: agents which cause concern that they could be carcinogenic for humans but which cannot be assessed conclusively because of a lack of data. *In vitro* or animal studies do not provide indications of carcinogenicity which are sufficient to classify the agent into one of the other categories.