
Calcium carbonate

(CAS No: 471-34-1)

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 calcium carbonate 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 C de Heer, Ph.D. and H Stouten, M.Sc. (TNO Nutrition and Food Research, Zeist, the Netherlands).

The evaluation of the toxicity of calcium carbonate has been based on the review by the American Conference of Governmental Industrial Hygienists (ACG91). Where relevant, the original publications were reviewed and evaluated as will be indicated in the text. In addition, literature was retrieved from the on-line databases Medline, Toxline, and Chemical Abstracts covering the periods 1966 to June 1998, 1965 to February 1998, and 1967 to June 1998, respectively, and using the following key words: calcium carbonate, calcinosis, 471-34-1, 1317-65-3, and 3983-19-5. HSDB and RTECS, databases available from CD-ROM, were consulted as well (NIO98, NLM98). The final literature search was carried out in June 1998.

In December 1998, 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 May 2002 did not result in information changing the committee's conclusions.

2 Identity

name	:	calcium carbonate
synonyms	:	carbon acid calcium salt (1:1); atomite; aragomite; calcite; chalk; limestone; marble
molecular formula	:	CCaO ₃
structural formula	:	CaCO ₃
CAS number	:	471-34-1 (calcium carbonate); 1317-65-3 (limestone)

Data from ACG91, NLM98.

3 Physical and chemical properties

molecular weight	:	100.1
boiling point	:	-
melting point	:	decomposes at 825°C (aragonite)
flash point	:	-
vapour pressure	:	-
solubility in water	:	practically insoluble
Log P _{octanol/water}	:	-
conversion factors (20°C, 101.3 kPa)	:	-

Data from ACG91, NLM98.

Calcium carbonate is an odourless, tasteless powder or crystal. It exist in nature as mineral aragonite and calcite (as in limestone, chalk, and marble). Aragonite changes to calcite when heated in dry air to about 400°C (ACG91).

4 Uses

Calcium carbonate is used in the manufacture of quicklime and Portland cement. In addition, it is used in the manufacture of paints, rubber, plastics, paper, inks, ceramics, putty, polishes, insecticides, and shoe dressings, and as a filler in the production of adhesives, matches, pencils, crayons, linoleum, insulating compounds, and welding rods. United States Pharmacopoeia (USP) grades are used in dentifrices, cosmetics, foods, antibiotics, and pharmaceuticals, e.g., antacids. It is also used for removal of acidity from wines. Finally, it is the major constituent of limestone (ACG91).

5 Biotransformation and kinetics

Calcium carbonate is converted into calcium chloride, carbon dioxide, and water by gastric acid. Some calcium (as calcium salts) is absorbed, but 80% is further converted into insoluble salts and excreted via faeces (NLM98, Ric93). Single doses of 1 to 12 g of calcium carbonate given to normal fasting human subjects caused a dose-dependent transient rise of blood calcium concentration.

Absorption of ^{45}Ca -labelled calcium carbonate after a single oral dose of 2 g amounted to $16.6 \pm 8.5\%$ in fasted subjects. This absorption was only slightly less than the percentage absorption of a comparable dose of the soluble calcium salt calcium gluconate. Patients who were found not to secrete free acid in their gastric juices failed to absorb calcium (Iva67).

6 Effects and mechanism of action

Human data

Pure calcium carbonate dust is considered harmless (ACG91, Ric93), probably because it is eliminated from the lungs by solution.

There may be a silicosis risk in using impure limestone containing 3-20% quartz for stone dusting in coal mines (ACG91, Ric93). Three Japanese schoolteachers had developed interstitial pneumonia with bullae. They had probably used blackboard chalk that most likely contained small amounts of silica and other minerals for many years. At autopsy of 2 of the schoolteachers, significant higher deposited amounts of total dust, inorganic dust, non- SiO_2 inorganic dust, calcium, free silica (in one case), and alpha-quartz (in the other case) were found in their lungs when compared with controls with chronic interstitial pneumonia (Oht95).

Occupational exposure of 107 workers to lime dust (>90% calcium carbonate; exposure levels and duration not indicated) during the making of lime at Pong Village (Chiang Mai Province, China) did not result in an increased prevalence of respiratory symptoms, pulmonary abnormalities, or chest radiograph abnormalities when compared to 58 matched controls (Jie87).

An association between lime dust exposure (calcium carbonate, 90-94%, and silica; concentrations not indicated) and the development of bronchitis was suggested in an epidemiological study of 161 limestone quarrymen in India (Das83).

In humans, hypercalcaemia and alkalosis can occur following regular use of calcium carbonate (Ric93). The milk-alkali syndrome (characterised as the triad of hypercalcaemia, alkalosis, and renal dysfunction) has occurred in individuals taking large doses of 4-60 g/day (Bea95, Jen87, Gor89, Kle91, Mul96, Pip71, Ric93). Clinically, these patients suffer from generalised weakness, myalgia, headache, vertigo, nausea, vomiting, and alterations in the sensorium. Especially patients with renal insufficiency are at risk for developing milk-alkali syndrome after ingestion of calcium carbonate.

In several countries, an inverse relationship between cardiovascular death rates and water hardness has been established. In England and Wales, the highest correlation coefficients were found with water calcium and the carbonate fraction (Cra72). However, in other studies, conclusions on a possible causal relationship between hardness of water and mortality from any cause were considered premature due to the existence of numerous confounding factors (Mey75).

Hypersensitivity may result from an interaction between calcium carbonate with vitamin D and thiazide diuretics (Ric93). Severe hypercalcaemia has also been reported after consuming large amounts of proprietary medicine containing calcium carbonate besides hydrochlorothiazide for the treatment of epigastric distress (Ric93).

Calcium carbonate has also been used clinically to reduce phosphate in dialysis patients. Long-term treatment (3 years) of haemodialysis patients with 4.5-9 g/day resulted in microcalcification in vessels and soft-tissue areas of the hand (Spe93). Others did not observe soft-tissue microcalcifications after long-term calcium carbonate treatment (Fou94).

Animal data

In rabbits, dermal contact with 500 mg calcium carbonate (24 hours) caused moderate irritation (NLM98, Ric93). Instillation of 750 µg into the eyes of rabbits caused severe irritation (NLM98, Ric93).

After introduction of 125-1500 µg calcium carbonate into the posterior chamber of the eyes of New Zealand White rabbits, no vitreal inflammatory response was observed (Par97). Injection of 8 mg of calcium carbonate powder into the anterior chamber of the eyes of rabbits caused a moderate rise of intraocular pressure lasting less than 24 hours (NLM98).

The oral LD₅₀ in rats is 6450 mg/kg (NLM98, Ric93).

A single intraperitoneal instillation of 50 mg calcium carbonate particles (mean and maximum size 0.8 and 5 µm, respectively) into male Sprague-Dawley rats resulted in adhesions and focal lesions scattered over the visceral and parietal peritoneal surfaces. Calcium carbonate appeared as a finely divided dispersion of white granules in irregular clusters clearly visible through a thin overlying film of tissue. The macroscopic appearance of these lesions did not change appreciably with time, although they were seen less frequently towards the end of the study at 52 weeks. Histologically, foci of calcium salt were surrounded

by a granulomatous reaction at 2 weeks after treatment. At later stages, occasional multinucleate giant cells and some fibrosis were seen, whereas with time there was some absorption of the mineral. This change was accompanied by such a reduction in the granulomatous reaction that, by week 13, the granulomas were generally small and formed mainly of a central basophilic or pale-staining core and a thin fibrous capsule with few inflammatory cells. The extent of the inflammatory reaction was further reduced by week 26 and 52 (Pel86).

Carcinogenicity

No urinary bladder tumour-promoting activity, pelvic hyperplasia, or forestomach hyperplasia were seen in male F344 rats when CaCO₃ was given in the diet (1.15%) for 72 weeks following tumour initiation by a 6-week treatment with 0.2% *N*-[4-(5-nitro-2-furyl)-2-thiazolyl]formamide (calculated CaCO₃ intake 845 mg/kg bw/day at week 6, 438 mg/kg bw/day at week 78). In this exposure regimen, CaCO₃ treatment did not result in effects on body weight gain and food and water consumption. Relative liver and spleen weights were not affected, and no gross abnormalities were observed. During the first 26 weeks of dietary exposure to CaCO₃, the urinary pH was significantly increased (Coh91).

Mutagenicity and genotoxicity

The committee did not find data from mutagenicity or genotoxicity studies of calcium carbonate.

Reproduction toxicology

In female Charles-River CD/VAF Plus rats, dietary exposure to calcium (up to 1.25% calcium as calcium carbonate, corresponding to an average daily intake of 2400-2600 mg/kg bw calcium carbonate) for 6 weeks before mating, during mating, and for 20 days after gestation, did not affect reproductive performance or parameters for fetotoxicity or teratogenicity. Both the non-pregnant and pregnant rats in the exposed groups ate slightly more than did the control group during most of the time intervals measured, but not all the increases were statistically significant. There was no consistent pattern of increase or decrease

in body weight gain and there were no dose-related changes in maternal clinical findings (Sha93).

In a study in female Sprague-Dawley rats, animals were fed diets containing 0.1 (low), 0.5 (normal), and 2.5% (w/w) (high) calcium as calcium carbonate for 1 week prior to mating, throughout gestation, and during 1 week of lactation. The supplementary intake (2% calcium in the diet as calcium carbonate) was calculated to be 3300-4100 mg/kg bw/day calcium carbonate*. The dose groups displayed no differences in body weight gain, water consumption, dam systolic blood pressure, litter size, and sex distribution. Femur calcium concentrations were lower in dams fed 0.1% calcium, but not affected in 1-day-old or 1-week-old pups. Treatment with the high calcium diet resulted in reduced liver, kidney, and femur iron concentrations of the dams and pups, and reduced brain iron concentrations in pups. Haematocrit and haemoglobin were reduced in dams and pups of the 2.5% calcium diet. Body weights and body lengths were reduced at 2.5% dietary calcium in the 1-day-old and 1-week-old pups (Bog95).

To study the effect of dietary calcium and cadmium levels of pregnant Sprague-Dawley rats on reproduction and on dam and progeny tissue mineral concentrations, animals were treated with diets differing in calcium and cadmium concentrations from the day following mating to parturition. Feed consumption, body weight gain, litter size, and pup birth weight were not affected by increasing the dietary calcium concentration from low (0.07%) to high (0.96%) at a given constant (0 or 200 ppm) cadmium concentration. High dietary calcium protected against accumulation of cadmium in the pups, but did not affect zinc, copper, iron, calcium, or magnesium levels in the pups (Pon75).

In a study in CD1 mice, female animals received a calcium-supplemented diet for at least 10 days prior to mating and throughout gestation until sacrifice on day 18 of gestation. The experimental group received an additional 3% calcium by weight as calcium carbonate added to the commercial chow and 4% calcium lactate added to the distilled water, whereas controls only received calcium through the commercial diet (1.2% calcium by weight). The treatment resulted in significantly higher calcium serum levels in exposed mothers, but did not affect body weight gain, mating frequencies, or the number of resorptions or fetal deaths. No gross fetal abnormalities were observed. High calcium dietary intake during pregnancy did however result in decreased fetal weights and delayed skeletal and dental calcification. It was hypothesised by the

* Body weights ranged from 270 g at the start of the experiment to 460 g at delivery. Additional calcium carbonate intake was calculated with $0.049 \cdot BW^{0.6087}$, resulting in calculated food intakes of 22.0-30.5 g/day. This food consumption corresponded to an intake of 3.3-4.1 g/kg bw/day calcium carbonate.

authors that fetal hypercalcaemia results in decreased fetal PTH (parathyroid hormone) levels and vitamin D metabolites necessary for bone mineralisation (Lie89).

7 Existing guidelines

The current administrative occupational exposure limit (MAC) for calcium carbonate in the Netherlands is 10 mg/m³, 8-hour TWA, as inhalable dust, and is based on the occupational exposure limit for nuisance dusts.

Existing occupational exposure limits for calcium carbonate in some European countries and in the USA are summarised in the annex.

8 Assessment of health hazard

Acute effects may include irritation of skin, eyes, and mucous membranes. Based on an oral LD₅₀ in rats of 6450 mg/kg bw, the committee considers calcium carbonate to be of low oral acute toxicity.

Human or animal data to estimate an concentration-effect relationship after inhalation exposure are lacking.

There is no adequate evidence for a tumour-promoting or genotoxic action of calcium carbonate. Effects on reproduction have not been shown. High dietary levels inducing maternal toxicity resulted in decreased fetal weights and delayed skeletal and dental calcification in rats and/or mice.

There may be a silicosis risk in using impure limestone or chalk containing (3-20%) quartz. No adverse health effects have been reported in the literature among workers using calcium carbonate. High oral doses did not produce systemic toxicity in laboratory animals, but the occurrence of local effects can not be excluded. Therefore, the committee considers a repeated-dose inhalation study a prerequisite for establishing a health-based occupational exposure limit for calcium carbonate.

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

The committee concludes that there is insufficient information to comment on the level of the present MAC-value.

References

- ACG91 American Conference of Governmental Industrial Hygienists (ACGIH). Calcium carbonate. In: Documentation of the threshold limit values and biological exposure indices. 6th ed. Cincinnati OH, USA; ACGIH, 1991: 195-6.
- ACG02a American Conference of Governmental Industrial Hygienists (ACGIH). Guide to occupational exposure values -2002. Cincinnati OH, USA: ACGIH®, Inc, 2002: 19.
- ACG02b American Conference of Governmental Industrial Hygienists (ACGIH). 2002 TLVs® and BEIs®. Threshold Limit Values for chemical substances and physical agents. Biological Exposure Indices. Cincinnati OH, USA: ACGIH®, Inc, 2002: 19.
- Arb02 Arbejdstilsynet. Grænseværdier for stoffer og materialer. Copenhagen, Denmark: Arbejdstilsynet, 2002; At-vejledning C.0.1.
- Bea95 Beall DP, Scofield RH. Milk-alkali syndrome associated with calcium carbonate consumption. Report of 7 patients with parathyroid hormone levels and an estimate of prevalence among patients hospitalized with hypercalcemia. *Medicine* 1995; 74: 89-96.
- Bog95 Bogden JD, Kemp FW, Han S, *et al.* Dietary calcium and lead interact to modify maternal blood pressure, erythropoiesis, and fetal and neonatal growth in rats during pregnancy and lactation. *J Nutr* 1995; 125: 990-1002.
- Coh91 Cohen SM, Ellwein LB, Okamura T, *et al.* Comparative bladder tumor promoting activity of sodium saccharin, sodium ascorbate, related acids, and calcium salts in rats. *Cancer Res* 1991; 51: 1766-77.
- Cra72 Crawford MD. Hardness of drinking-water and cardiovascular disease. *Proc Nutr Soc* 1972; 31: 347-53.
- Das83 Dasgupta AK. Prevalence of respiratory symptoms among radiologically diagnosed chronic bronchitic and non-bronchitic quarrymen. *J Indian Med Assoc* 1983; 80: 52-6.
- DFG02 Deutsche Forschungsgemeinschaft (DFG): Senatskommission zur Prüfung gesundheitsschädlicher Arbeitsstoffe. MAK- und BAT-Werte-Liste 2002. Maximale Arbeitsplatzkonzentrationen und Biologische Arbeitsstofftoleranzwerte. Weinheim, FRG: Wiley-VCH, 2002; rep no 38.
- EC02 European Commission (EC): Directorate General for Employment and Social Affairs. Occupational exposure limits (OELs). http://europe.eu.int/comm/employment_social/h&s/areas/oels_en.htm.
- Fou94 Fournier A, Moriniere Ph, Hamida B, *et al.* CaCO₃: an inefficient and unsafe phosphate binder? *Nephrol Dial Transplant* 1994; 9: 335-6.
- Gor89 Gora ML, Seth SK, Bay WH, *et al.* Milk-alkali syndrome associated with use of chlorothiazide and calcium carbonate. *Clin Pharmacy* 1989; 8: 227-9.
- HSE02 Health and Safety Executive (HSE). EH40/2002. Occupational exposure limits 2002. Sudbury (Suffolk), England: HSE Books, 2002: 14.
- Iva67 Ivanovich P, Fellows H, Rich C. The absorption of calcium carbonate. *Ann Intern Med* 1967; 66: 917-23.
-

- Jen87 Jenkins JK, Best TR, Nicks SA, *et al.* Milk-alkali syndrome with a serum calcium level of 22 mg/dl and J waves on the ECG. *Southern Med J* 1987; 80: 1444-9.
- Jie87 Jiemsripong K, Somsup C, Promkutkao C, *et al.* Respiratory survey of lime workers at Pong Village Chiang Mai Province. *J Med Assoc Thai* 1987; 70: 85-9.
- Kle91 Kleinman GE, Rodriquez H, Good MC, *et al.* Hypercalcemic crisis in pregnancy associated with excessive ingestion of calcium carbonate antacid (milk-alkali syndrome): Successful treatment with hemodialysis. *Obstet Gynecol* 1991; 78: 496-9.
- Lie89 Liebgott B, Srebrolow G. Fetal toxicity caused by excessive maternal dietary calcium. *J Can Dent Assoc* 1989; 55: 129-33.
- Mey75 Meyers D. Mortality and water hardness. *Lancet* 1975; 1: 398-9.
- Mul96 Muldowney WP, Mazbar SA. Roloids-Yoghurt Syndrome: A 1990s version of the milk-alkali syndrome. *Am J Kidney Dis* 1996; 27: 270-2.
- NIO98 US National Institute of Occupational Safety and Health (NIOSH). Registry of Toxic Effects of Chemical Substances (RTECS) [CD-ROM], issue April 1998. SilverPlatter International, 1998 (last update calcium carbonate file: December 1997).
- NLM98 US National Library of Medicine (NLM). Hazardous Substances Data Bank (HSDB) [CD-ROM], issue April 1998. SilverPlatter International, 1998 (last update calcium carbonate file: February 1998).
- Oht95 Ohtsuka Y, Munakata M, Homma Y, *et al.* Three cases of idiopathic interstitial pneumonia with bullae seen in schoolteachers. *Am J Ind Med* 1995; 28: 425-35.
- Par97 Park HS, Kim MS. The inflammatory potential of surgical glove lubricants: Biosorb[®], Keoflo[®], calcium carbonate and Hydrocote[™] after intravitreal injection. *Korean J Ophthalmol* 1997; 11: 51-9.
- Pel86 Pelling D, Evans JG. Long-term peritoneal tissue response in rats to mould-release agents and lubricant powder used on surgeons' gloves. *Food Chem Toxicol* 1986; 24: 425-30.
- Pip71 Piper DW. Calcium carbonate, hypercalcemia, and peptic ulcer. *Br Med J* 1971; 2: 774
- Pon75 Pond WG, Walker EF. Effect of Ca and Cd level of pregnant rats on reproduction and on dam and progeny tissue mineral concentrations. *Proc Soc Exp Biol Med* 1975; 148: 665-8.
- Ric93 Richardson ML, Gangolli S, eds. C23 Calcium carbonate. In: *The dictionary of substances and their effects*. Cambridge, UK: Royal Society of Chemistry, 1993: 43-4 (Vol 2).
- Sha93 Shackleford ME, Collins TFX, Welsh JJ, *et al.* Foetal development in rats fed AIN-76A diets supplemented with excess calcium. *Food Chem Toxicol* 1993; 31: 953-61.
- Spe93 Sperschneider H, Günther K, Marzoll I, *et al.* Calcium carbonate (CaCO₃): an efficient and safe phosphate binder in haemodialysis patients? A 3-year study. *Nephrol Dial Transplant* 1993; 8: 530-4.
- Swe00 Swedish National Board of Occupational Safety and Health. Occupational exposure limit values and measures against air contaminants. Solna, Sweden: National Board of Occupational Safety and Health, 2000; Ordinance AFS 2000:3.
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- SZW02 Ministerie van Sociale Zaken en Werkgelegenheid (SZW). Nationale MAC-lijst 2002. The Hague, the Netherlands: Sdu, Servicecentrum Uitgevers, 2002: 20.
- TRG00 TRGS 900. Grenzwerte in der Luft am Arbeitsplatz; Technische Regeln für Gefahrstoffe. BArbBl 2000; 2.

Annex

Occupational exposure limits for calcium carbonate in various countries.

country organisation	occupational exposure limit		time-weighted average	type of exposure limit	note ^a	reference ^b
	ppm	mg/m ³				
the Netherlands						
- Ministry of Social Affairs and Employment	-	10 ^c	8 h	administrative		SZW02
Germany						
- AGS	-	-				TRG00
- DFG MAK-Kommission	-	-				DFG02
Great Britain						
- HSE	-	10 ^c	8 h	OES		HSE02
		4 ^d	8 h	OES		
Sweden	-	-				Swe00
Denmark	-	-				Arb02
USA						
- ACGIH	-	10 ^c	8 h	TLV		ACG02b
- OSHA	-	15 ^c	8 h	PEL		ACG02a
	-	5 ^d		PEL		
- NIOSH	-	10 ^c	10h	REL		ACG02a
	-	5 ^d		REL		
European Union						
- SCOEL	-	-				EC02

^a S = skin notation; which mean that skin absorption may contribute considerably to body burden; sens = substance can cause sensitisation.

^b Reference to the most recent official publication of occupational exposure limits.

^c Total inhalable dust.

^d Respirable dust.

^e Particulate matter containing no asbestos and <1% crystalline silica.

