Calcium sulphate

(CAS No: 7778-18-9)

Health-based reassessment Administrative
Occupational Exposure Limit

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 sulphate by the Committee on Updating 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 Institute, Zeist, the Netherlands).

The evaluation of the toxicity of calcium sulphate has been based on the review by the American Conference of Governmental Industrial Hygienists (ACGIH) (ACG91). Where relevant, the original publications were reviewed and evaluated as will be indicated in the text. In addition, literature was retrieved from the online databases Medline, Toxline, and Chemical Abstracts, covering the periods 1966 to 29 May 1998, 1965 to 24 February 1998, and 1967 to 2 June 1998, respectively, and using the following key words: calcium sulfate, gypsum, calcinosis, and 7778-18-9, 10101-41-4, 10034-76-1, 26499-65-0, and 13397-24-5. HSDB and RTECS, databases available from CD-ROM, were consulted as well (NIO98, NLM98). The final search was performed in June 1998.

In December 1998, the President of the Health Council released a draft of the document for public review. Comments were received by the following individuals and organisations: P Wardenbach, Ph.D.(Bundesanstalt für Arbeitsschutz und Arbeitsmedizin, Dortmund, Germany) and ir G. Wieling (Avios arbo, Rotterdam, the Netherlands). These comments were taken into account in deciding on the final version of the document.

An additional literature search in May 2002 did not result in information changing the committee's conclusions.

2 Identity

name	:	calcium sulphate
synonyms	:	anhydrite, anhydrous calcium sulphate, anhydrous sulphate of lime; gypsum; plaster of Paris
molecular formula	:	$CaSO_4$
structural formula	:	-
CAS number	:	7778-18-9 ($CaSO_4$); 10101-41-4 ($CaSO_4 \cdot 2H_2O$); 13397-24-5 (gypsum)

Data from ACG91, Ric93.

3 Physical and chemical properties

molecular weight	:	136.14
boiling point	:	1360-1450°C
melting point	:	-
flash point	:	-
vapour pressure	:	-
solubility in water	:	0,2 g/100 mL at 25°C
Log $P_{octanol/water}$	:	-0.17 (estimated)
conversion factors (20°C, 101.3 kPa)	:	-

Data from ACG91, NLM98, Ric93, http://esc.syrres.com.

Calcium sulphate occurs in nature as the mineral anhydrite ($CaSO_4$) and as the dihydrate, gypsum ($CaSO_4$ $2H_20$). These are commonly found together in nature. The mineral anhydrite exists as varied coloured orthorombic crystals. A controlled modest amount of heat is used to convert gypsum to the hemihydrate, plaster of Paris ($(CaSO_4)_2$ H_20), a fine powder that is tasteless and odourless. An insoluble anhydrite with the same crystalline structure as the mineral anhydrite is obtained from the complete dehydration of gypsum above 650°C, while a soluble anhydrite powder is obtained from the complete dehydration of gypsum in an electric oven at a temperature below 300°C. Synthetic gypsums are available from several chemical processes (ACG91).

4 Uses

The insoluble anhydrite is used in cement formulations and as paper filler, whereas the soluble anhydrite has a strong tendency to absorb moisture and is used as a drying agent known under the name Drierite®. The hemihydrate is used for wall plaster and wall board. Gypsum is used in soil treatment, in the manufacture of plaster of Paris and Portland cement, in the production of heavy chemicals, and in water clarification and animal feed. Food and pharmaceutical-grade gypsum is used as a source of calcium in foods (ACG91).

5 Biotransformation and kinetics

The committee did not find data on the toxicokinetics of calcium sulphate.

Gypsum dust is rapidly cleared from the lung both by dissolution and by the mechanisms of particle clearance (Clo97, Clo98).

6 Effects and mechanism of action

Human data

Gypsum dust has an irritant action on mucous membranes of the respiratory tract and eyes (NLM98).

Severe hand burns were reported in 4 students after making molds of theirs hands with dental plaster substituted for plaster of Paris. The dental plaster, known as Stone, was a special form of calcium sulphate hemihydrate, containing α-hemihydrate crystals that provide high compression strength to the molds. β-Hemihydrate, normal plaster of Paris, has not caused skin burns in similar procedures (ACG91). Prolonged eye exposure may cause conjunctivitis (Ric93).

Acute effects may include damage to upper airways because of local dehydration (Gre96) or gastric irritation due to osmotic disturbances after ingestion (Ric93).

Prolonged exposure may cause unpleasant nasal passage deposits, coughing, chronic rhinitis, laryngitis, pharyngitis, impaired sense of taste and smell, epistaxis, and reactions from tracheal and bronchial membranes in exposed workers (NLM98, Ric93).

Airborne calcium sulphate (concentration not known) emitted from coal-fired power plants was a suspected causative agent of acute asthma in Derby, UK (Bro87).

Calcium sulphate did not cause lung disease in calcium sulphate miners (ACG91). In a study of 241 gypsum mine workers, chest X-rays, lung function tests, respiratory symptom questionnaires, and work histories were evaluated. The existence of a dust hazard in the past (mild pneumoconiotic changes in chest X-rays) in 4 British mines in Nottinghamshire and Sussex was ascribed to quartz (silicon oxide) rather than to gypsum. Exposures in the highest exposure jobs (crusher) were estimated to average 6 mg/m^3 respirable dust and 0.07

mg/m^3 respirable quartz for Nottinghamshire and 2.8 mg/m^3 respirable dust and 0.12 mg/m^3 respirable quartz for Sussex (Oak82).

Animal data

Calcium sulphate applied to the eyes of rabbits was found to be innocuous (NLM98).

In a nose-only facility, male F344 rats (n=36/group) were exposed to an aerosol of calcium sulphate at 100 mg/m^3 for 3 weeks (6 hours/day, 5 days/week), either or not followed by a subsequent 3-week recovery period. Controls were exposed to air only. No effects were found on the number of macrophages per alveolus, bronchoalveolar lavage fluid (BALF) protein concentrations, or BALF γ-glutamyl transpeptidase (γ-GT) activity. Non-protein thiol levels (NPSH; mainly glutathione) were increased in animals exposed to calcium sulphate after 3 weeks of non-exposure. The viability and alkaline phosphatase-staining of type II pneumocytes from rats pre-exposed to calcium sulphate was unchanged compared to cells from unexposed controls (Clo96).

In subsequent experiments, male F344 rats (n=36/group) were exposed to an aerosol of anhydrous calcium sulphate for 3 weeks (6 hours/day, 5 days/week) at a concentration of approximately 15 mg/m^3 (fibers; Clo98) and 60 mg/m^3 (fibers and milled fibers; Clo97). Negative controls were similarly exposed to air. At the end of the exposure period, half of the animals were sacrificed immediately and the remaining animals were kept for 3 (high dose) or 4 weeks (low dose) without exposure before sacrifice. In all exposed groups, calcium levels in the lung were comparable to air-exposed controls, although histologically gypsum fibers were detected in the lungs of calcium sulphate-exposed animals. The number of lung macrophages and protein levels in lung macrophages and BALF were unaffected. However, NPSH levels in BALF were significantly increased in animals killed immediately after exposure (both dose groups), and in recovery animals exposed to 60 mg/m^3 calcium sulphate fibers. Macrophages from both recovery and non-recovery animals had lost almost all of their NPSH (only examined in low dose animals). There was a significant decrease in extracellular γ-GT activity after recovery of exposure to 15 mg/m^3 calcium sulphate. γ-GT activity in lung macrophages was significantly increased after exposure to 60 mg/m^3 calcium sulphate fibers. The latter finding was hypothesised to be a compensatory response, because membrane-bound γ-GT enables cells to take up extracellular glutathione. The authors considered the combination of increased (cellular) γ-GT activity and

changing NPSH levels a protective response by the lung. Systemic effects were not studied (Clo97, Clo98). Since decreased NPSH levels would render the lungs more vulnerable to subsequent damage by other agents, the noted effects of inhaled calcium sulphate are considered to be of relevance. The effects are however not considered to be of a chemical nature but are considered to be non-pathological local effects due to physical factors related to the shape of the gypsum fibers and not to calcium sulphate *per se*.

Carcinogenicity

Two years after a weekly intratracheal administration of 2 mg man-made calcium sulphate fibres for 5 weeks, 3 out of 20 female Syrian hamsters developed tumours (in heart (anaplastic carcinoma), rib (unspecified cell types), or kidney (dark cell carcinoma)), in contrast to none out of 20 control animals (Ada91). Calcium sulphate fibres did not induce oxidative damage in calf thymus DNA *in vitro* (Ada92). In addition, chronic alveolitis with macrophage and neutrophil aggregation were detected in the above mentioned hamsters exposed to calcium sulphate fibre (Ada91).

Three to 6 months after a single intratracheal administration of 35 mg pure anhydrite in female Wistar rats, wet weights and lipid content of the lungs were not affected. Aspecific reactions (such as bronchitis or alveolitis without collagen increase) were observed 6 months after intratracheal application of gypsum, although already after 2 months dusts were no longer detectable in lungs and lymph nodes (Gre96). After long-term inhalation of 1.6×10^4 particles of burned gypsum/mL (44 hours/week in 5½ days, for 2 years; average particle size 5 µm, range 1-40 µm), either or not followed by a dust-free period of up to 22 months, guinea pigs showed only marginal changes in their lungs. Twelve out of 20 and 4 out of 10 animals, respectively, died intercurrently, mostly from pneumonia. Other effects were not addressed in this study (Sche55).

Intraperitoneal injections of gypsum into guinea pigs caused absorption reactions, after which the gypsum was dissolved in surrounding tissues (Gre96). Granulomas were induced in female Sprague-Dawley rats after intraperitoneal injection of natural anhydrite dusts, derived from German coal mines. It was not clear whether this was caused by gypsum or unknown pollutants (Gre96). After 4 intraperitoneal injections of 25 mg fibre gypsum, the incidence of mesotheliomas or sarcomas in the peritoneal cavity was not significantly increased (Gre96).

Mutagenicity and genotoxicity

Calcium sulphate (up to 2.5%) was negative, with and without metabolic activation, in *in vitro* genotoxicity tests in *S. typhimurium* strains TA1535, TA1537, and TA1538, and in yeast *S. cerevisiae* strain D4. At higher concentrations of the test substance, survival of bacteria and yeast was severely impaired (Lit75).

Reproduction toxicity

The teratological potential of calcium sulphate was assessed in CD-1 mice, Wistar rats, and Dutch-belted rabbits by oral (gavage) exposure of pregnant animals from gestational days 6 to 15 (mice and rats) or gestational days 6 to 18 (rabbits). Administration of 16-1600 mg/kg bw/day of calcium sulphate (as a water solution at 10 mL/kg bw) did not affect maternal body weights. No clearly discernible effect was observed on nidation or on maternal or fetal survival. The number of abnormalities seen in either soft or skeletal tissues of the test groups did not differ from the number occurring spontaneously in the sham-treated controls (Foo74).

In contrast to mineral fibers (asbestos, ceramic fibers), gypsum (up to 10 $\mu g/cm^2$) failed to induce apoptosis in Syrian hamster embryo cells (Dop95).

7 Existing guidelines

The current administrative occupational exposure limit (MAC) for calcium sulphate in the Netherlands is 10 mg/m^3 (total inhalable dust), 8-hour TWA.

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

8 Assessment of health hazard

Inhaled calcium sulphate is rapidly cleared from the lung.

Acute effects may include irritation of upper airways upon inhalation or gastric irritation upon ingestion. It also has an irritant action on the eyes.

In a study of 241 gypsum mine workers, chest X-rays, lung function tests, respiratory symptom questionnaires, and work histories were evaluated. The existence of a dust hazard in the past in 4 British mines in Nottinghamshire and Sussex was ascribed to quartz (silicon oxide) rather than to gypsum. Exposures

in the highest exposure jobs were estimated to be on average 6 mg/m^3 respirable dust and 0.07 mg/m^3 respirable quartz for Nottinghamshire and 2.8 mg/m^3 respirable dust and 0.12 mg/m^3 respirable quartz for Sussex. The committee considers this study in itself insufficient to derive a health-based occupational exposure limit, but it will be considered supplementary.

In a previous evaluation of the health effects of nuisance dusts, the Dutch Expert Committee on Occupational Standards (DECOS) considered calcium sulphate dusts as inert (Zie90). Despite the relatively low solubility of calcium sulphate, it is not expected to persist long in tissues. A prolonged inhalation exposure may lead to aspecific dust reactions in lung tissue. However, calcium sulphate-specific tissue reactions are not likely.

In rats, a 3-week inhalation exposure to 15 or 60 mg/m^3 calcium sulphate fibers (6 hours/day, 5 days/week) resulted in decreased non-protein thiol (NPSH, mainly glutathione) levels in lung macrophages and in increased NPSH levels in bronchoalveolar lavage fluid (BALF). In addition, γ-glutamyl transpeptidase activity in lung macrophages was increased. This latter finding may be regarded as a compensatory response of macrophages to the loss of NPSH. The 15 mg/m^3 exposure level was considered to be a 'lowest observed adverse effect level' (LOAEL) because decreased NPSH levels may render the lungs more vulnerable to subsequent damage. The effects are, however, not considered to be of a chemical nature but as non-pathological local effects due to physical factors related to the shape of the gypsum fibers and not to calcium sulphate *per se*.

In a chronic carcinogenicity study with man-made monocrystalline fibers of calcium sulphate, malignant tumours were observed in 3 out of 20 hamsters exposed to the test materials and in none of 20 control hamsters. The type of tumours (tumour in the heart, kidney, and rib) are extremely rare in hamsters, i.e., have not been reported in the literature. Because of the high incidence of tumour-bearing animals and the rarity of the type of tumours observed, a relationship between the occurrence of the tumours and the exposure to the fibers can not be excluded. In subsequent *in vitro* experiments, this carcinogenic effect could not be explained by the induction of oxidative DNA damage. Although calcium sulphate fibres as such may pose a hazard, several restraints make the relevance of these experiments for the human situation questionable. First, the size and shape of the man-made calcium sulphate fibres are quite different from those of naturally occurring crystals of calcium sulphate. Secondly, because of the intratracheal route of administration, the deposition of fibres in the airways may be different compared to the occupational situation.

Finally, there are no reports on fibrous effects produced by natural dusts of calcium sulphate. Changes in lung tissues of animals and humans occurred only when calcium sulphate was contaminated with silicon oxide.

Genotoxicity tests with *S. typhimurium* and *S. cerevisiae* with and without metabolic activation were negative.

There were no data on reproduction toxicity of calcium sulphate. Calcium sulphate did not induce developmental toxicity after oral exposure to concentrations as high as 1600 mg/kg bw/d in mice, rats, or rabbits.

Though there is no apparent direct relationship between changes in NPSH levels in the lung, as observed in the 3-week rat inhalation study, and altered lung function or respiratory symptoms, as observed in the study in British mine workers, it can not be excluded that lung effects as observed in the rat may have been present in the miners. For this reason, the committee starts from the LOAEL of 15 mg/m^3 to derive a health-based recommended occupational exposure limit (HBROEL). For the extrapolation to a HBROEL, an overall factor of 30 is established. This factor covers the following aspects: the absence of a NOAEL, inter- and intraspecies variations, and differences between experimental conditions and the exposure pattern of the worker in duration. Thus, applying this factor and the preferred value approach, a health-based occupational exposure limit of 0.5 mg/m^3 is recommended for calcium sulphate respirable fibers, based on local effects in the lung. Assuming a respiratory volume of 10 m^3 per working day, this results in a total exposure of 5 mg per day for a worker. Calcium sulphate exposure at this level is not considered to result in adverse systemic effects in view of the ion levels already present in the body.

The committee recommends a health-based occupational exposure limit (HBROEL) of 0.5 mg/m^3 for calcium sulphate respirable fibers, as an 8-hour time-weighted average (TWA). Data on respirable dust are considered insufficient to justify recommendation of a HBROEL for calcium sulphate dust.

References

ACG91 American Conference of Governmental Industrial Hygienists (ACGIH). Documentation of the threshold limit values and biological exposure indices. 6th ed. Cincinnati OH, USA; ACGIH, 1991: 204-5.

ACG02a American Conference of Governmental Industrial Hygienists (ACGIH). Guide to occupational exposure values -2002. Cincinnati OH, USA: ACGIH®, Inc, 2002: 20.

ACG02b American Conference of Governmental Industrial Hygienists (ACGIH). 2002 TLVs® and BEIs®. Threshold Limit Values for chemical substances and fysical agents. Biological Exposure Indices. Cincinnati OH, USA: ACGIH®, Inc, 2002: 20.

Ada91 Adachi S, Takemoto K, Kimura K. Tumorigenicity of fine man-made fibers after intra tracheal administrations to hamsters. Environ Res 1991; 54: 52-73.

Ada92 Adachi S, Kawamura K, Yoshida S, et al. Oxidative damage on DNA induced asbestos and man-made fibers in vitro. Int Arch Occup Environ Health 1992; 63: 553-7.

Arb00a Arbejdstilsynet. Grænseværdier for stoffer og materialer. Copenhagen, Denmark: Arbejdstilsynet, 2000; At-vejledning C.0.1.

Arb00b Arbetarskyddsstyrelsen. Hygieniska gränsvärden och åtgärder mot luftföroreningar. Solna, Sweden: Arbetarskyddsstyrelsen, 2000; Ordinance AFS 2000/3.

Bro87 Brown HM, Jackson FA. Airborne crystals of anhydrous calcium sulphate - A new air pollutant. EXS 1987; 51: 261-6.

CEC00 Commission of the European Communities (CEC). Commission Directive 2000/39/EC of 8 June 2000 establishing a first list of indicative occupational exposure limit values in implementation of Council Directive 98/24/EC on the protection of the health and safety of workers from the risks related to chemical agents at work. Official Journal of the European Communities 2000; L142 (16/06/2000): 47-50.

Clo96 Clouter A, Houghton CE, Bowskill CA, et al. An in vitro/in vivo study into the short term effects of exposure to mineral fibres. Exp Toxicol Pathol 1996; 48: 484-6.

Clo97 Clouter A, Houghton CE, Bowskill CA, et al. Effect of inhaled fibers on the glutathione concentration and -glutamyl transpeptidase activity in lung type II epithelial cells, macrophages and bronchoalveolar lavage fluid. Inhal Toxicol 1997; 9: 351-67.

Clo98 Clouter A, Houghton CE, Hibbs LR, et al. Effect of inhalation of low doses of crocidolite and fibrous gypsum on the glutathione concentration and -glutamyl transpeptidase activity in macrophages and bronchoalveolar lavage fluid. Inhal Toxicol 1998; 10: 3-14.

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: 34 (rep no 38).

Dop95 Dopp E, Nebe B, Hahnel C, et al. Mineral fibers induce apoptosis in Syrian hamster embryo fibroblasts. Pathobiology 1995; 63: 213-21.

Foo74 Food and Drug Research Laboratories, Inc. Teratologic evaluation of FDA 71-86 (calcium sulfate) in mice, rats and rabbits. Waverly NY, USA: 1974 (report available from the National Technical Information Service, Springfield VA, USA; rep no PB-234 873).

Gre96 Greim H, ed. In: Gesundheitsschädliche Arbeitsstoffe. Toxikologisch-arbeitsmedizinische Begründungen von MAK-Werten (Maximale Arbeitsplatzkonzentrationen). 1st-23st ed. Weinheim, FRG: VCH Verlagsgesellschaft mbH, 1996.

HSE02 Health and Safety Executive (HSE). EH40/2002. Occupational exposure limits 2002. Sudbury (Suffolk), England: HSE Books, 2002: 19, 24.

Lit75 Litton Bionetics, Inc. Mutagenic evaluation of compound FDA 71-86, calcium sulfate. Kensington MD, USA: Litton Bionetics, Inc, 1975 (report available from the National Technical Information Service, Springfield VA, USA; rep no PB-245481).

NIO98 US National Institute of Occupational Safety and Health (NIOSH), ed. Registry of Toxic Effects of Chemical Substances (RTECS) [CD-ROM], issue April 1998. SilverPlatter International, 1998 (last update calcium sulphate file: January 1997 for CAS no 10101-41-4 and December 1997 for 7778-18-9).

NLM98 US National Library of Medicine (NLM), ed. Hazardous Substances Data Bank (HSDB) [CD-ROM], issue April 1998. SilverPlatter International, 1998 (last update calcium sulphate file: February 1998).

Oak82 Oakes D, Douglas R, Knight K, et al. Respiratory effects of prolonged exposure to gypsum dust. Ann Occup Hyg 1982; 26: 833-40.

Ric93 Richardson ML, Gangolli S, eds. C42 Calcium sulfate. In: The dictionary of substances and their effects. Cambridge, UK: Royal Society of Chemistry, 1993: 66-7 (Vol 2).

Sche55 Schepers GWH, Durkan TM, Delahant AB. The biological effects of calcined gypsum dust. Arch Ind Health 1955; 12: 329-47.

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.

Zie90 Zielhuis RC. Fijn hinderlijk stof; gezondheidskundige aspecten van bijlage 3 bij de Nationale MAC-lijst 1989. The Hague, the Netherlands: Sdu Uitgeverij, 1990: 34, 43 (rep no RA9/90).

Annex

Occupational exposure limits for calcium sulphate 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	-	6[d]	8 h			TRG00
- DFG MAK-Kommission	-	6[d]	8 h			DFG02
Great Britain						
- HSE	-	10[c,e]	8 h	OES		HSE02
		4[d,e]	8 h			
Sweden	-	-				Arb00b
Denmark	-	-				Arb00a
USA						
- ACGIH	-	10[f]	8 h	TLV		ACG02b
- OSHA	-	15[c]	8 h	PEL		ACG02a
	-	5[d]				
- NIOSH	-	10[c]	10h	REL		ACG02a
	-	5[d]				
European Union						
- SCOEL	-	-				CEC00

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

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

[c] Total inhalable dust.

[d] Respirable dust.

[e] Value indicated for gypsum and plaster of Paris, $(CaSO_4)_2 \cdot 2H_2O$.

[f] Particulate matter containing no asbestos and <1% crystalline silica.