FOREWORD INTRODUCTION

Calcium sulfate, dihydrate

CAS N°: 10101-41-4

SIDS Initial Assessment Report

For

SIAM 17

Arona, Italy, 11-14 November 2003

1. Chemical Name: Calcium sulfate, dihydrate

2. CAS Number: 10101-41-4

3. Sponsor Country: Republic of Korea

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4. Shared Partnership with:

5. Roles/Responsibilities of the Partners:

- Name of industry sponsor /consortium
- Process used

6. Sponsorship History

- How was the chemical or category brought into the OECD HPV Chemicals Programme ?

This substance is sponsored by Korea. The assessment process was started in 1999. Korea National Institute of Environmental Research conducted a literature search, reviewed of submitted data and prepared document for SIAM 17.

7. Review Process Prior to the SIAM: Korea National Institute of Environmental Research peer-reviewed the document and checked the quality.

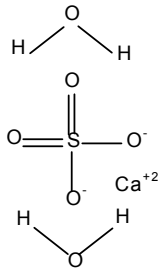
8. Quality check process: Korea National Institute of Environmental Research peer-reviewed selected endpoints and compared original studies with data in SIDS dossier.

9. Date of Submission: December 2003

10. Date of last Update:

11. Comments:

SIDS INITIAL ASSESSMENT PROFILE

CAS No.	10101-41-4
Chemical Name	Calcium sulfate, dihydrate
Structural Formula	

SUMMARY CONCLUSIONS OF THE SIAR

Human Health

There is no information on toxicokinetics, metabolism and distribution.

The acute oral toxicity study [OECD TG 420, Fixed dose procedure] of calcium sulfate, dihydrate showed that this chemical did not cause any changes even at 2,000 mg/kg b.w. Therefore, the oral LD_{50} value was more than 2,000 mg/kg b.w. for female rats without specific clinical signs.

Calcium sulfate, dihydrate was not irritating to the skin of rabbits at 1, 24, 48 and 72 hours after removal of the patches [OECD TG 404]. There is no indication of skin sensitisation in guinea pigs [OECD TG 406].

In a Combined Repeated Dose and Reproduction/Developmental Toxicity Screening Test in rats [OECD TG 422], calcium sulfate, dihydrate was administered by gavage at the dose levels of 0, 100, 300 and 1,000 mg/kg bw/day for more than 35 days and 41 ~ 45 days for male and female animals, respectively. Calcium sulfate, dihydrate had no critical influence on test items such as mortality, body weights (organ weight), food consumption, necropsy, reflex action, grip strength and behaviour of the animals. However, the values of total protein, albumin, blood urea nitrogen, aspartate aminotransferase, alanine aminotransferase and creatinine were decreased at 300 mg/kg bw/day and 1,000 mg/kg bw/day treatment for male animals showing that the test substance might affect the excretion process, distribution or metabolism of test substance in relation to the kidney. Based on these results, the LOAEL and NOAEL were determined to be 300 mg/kg bw/day and 100 mg/kg bw/day for male rats. In case of female rats, no effects were observed at the top dose tested (1,000 mg/kg bw/day).

In the above mentioned reproduction/developmental toxicity screening test [OECD TG 422], male and female rats, were dosed for 35 days and 41 ~ 45 days respectively and the pre-mating exposure period was 14 days. No adverse effects were observed in terms of fertility, delivery and nursing in parent animals during the test period. There were no signs of reproduction/developmental toxicity on the body weight, gestation index, sex ratio, clinical signs or viability up to 1,000 mg/kg/day (highest dose tested).
Bacterial gene reverse mutation tests in *Salmonella typhimurium* (strains TA98, TA100, TA1535 and TA1537) and *Escherichia coli* WP2 *uvr*A with and without metabolic activation gave negative results. An i*n vivo* mammalian erythrocyte micronucleus assay using male ICR mice [OECD TG 474], tested at the dose levels of 1,250, 2,500 and 5,000 mg/kg b.w, gave negative results. Accordingly calcium sulfate, dihydrate was not mutagenic *in vivo* and *in vitro.*

According to mutagenicity data, this substance would not be expected to be carcinogenic. There is no data available on carcinogenicity.

Environment

Calcium sulfate, dihydrate is a colorless solid inorganic substance with monoclinic and hygroscopic properties. It

has a water solubility of 2.05 g/L at 20 °C. Vapor pressure, n-octanol/water partition coefficient and stability in water are not applicable for the salt of an inorganic substance. Photodegradation, environmental fate modeling and biodegradation are not relevant for an inorganic compound. Bioaccumulation is not expected.

The following studies for aquatic organisms are available:
Green algae (*Selenastrum capricornutum)*: EC_{g50} (72 h) > 100 mg/L (growth rate),
EC_{b50} (72 h) > 100 mg/L (biomass)
Invertebrates (*Daphnia magna):* EC_{50} (48 h) > 100 mg/L.
Fish (*Oryzias latipes*): LC_{50} (96 h) > 100 mg/L.

No data are available on terrestrial organisms. Data from limit tests of 100 mg/L in fish, invertebrates and algae show no harmful effects..

Exposure

In Korea, the estimated production amounts of calcium sulfate, dihydrate were 1,447,000 tonnes in 2002. The total estimated amounts of import were about 59.1 tonnes from four countries in 2002 such as 46 tonnes from China, 3.6 tonnes from Nauru, 1.5 tonnes from South Africa and 8 tonnes from Morocco.

Calcium sulfate, dihydrate is produced in two companies as a waste-solid in the phosphatic fertilizer industry in Korea and this chemical is used as a primary material in gypsum industry, in which residues of calcium sulfate, dihydrate are recycled. Calcium sulfate, dihydrate is used in portland-cement retarders, tiles, polishing powders, paints, paper, dyes, metallurgy, wallboard, food additives and desiccants.

Releases of calcium sulfate, dihydrate into environment might be considered to be significant. As for human exposure, there is a potential for exposure to workers via dust inhalation and dermal routes at the manufacturing or using process. No data were available for workplace measurement of calcium sulfate, dihydrate but measured monitoring data for total dust in workplace was below the exposure limit value TWA of 15 mg/m^3.

RECOMMENDATION

The chemical is currently of low priority for further work.

RATIONALE FOR THE RECOMMENDATION AND NATURE OF FURTHER WORK RECOMMENDED

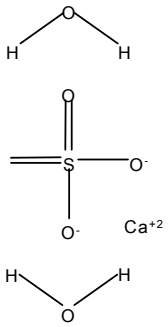
This substance is currently of low priority for further work because of its low hazard profile.

SIDS Initial Assessment Report

1 IDENTITY

1.1 Identification of the Substance

CAS Number: 10101-41-4
IUPAC Name: Calcium sulfate, dihydrate
Molecular Formula: $CaSO_4 \cdot 2H_2O$
Structural Formula:



Molecular Weight: 172.17
Synonyms: Alabaster
Annaline
C.I. Pigment white 25
Gypsum
Gypsum stone
Land and plaster
Light spar
Magnesia white
Mineral white
Native calcium sulfate
Precipitated calcium sulfate
Sainite
Satin spar
Sulfuric acid, calcium($^{2+}$) salt, dihydrate
Terra alba

1.2 Purity/Impurities/Additives

Purity:	> 90 %
Impurity:	< 1.3 % Phosphoric anhydrate (P_2O_5)
	< 0.07 % Magnesium oxide (MgO)
	< 0.01 % Silicon dioxide (SiO_2)
	< 0.02 % Iron(III) oxide (Fe_2O_3)
	< 8.6 % Crystalline water
Additives:	None

1.3 Physico-Chemical properties

Table 1-1 Summary of physico-chemical properties

Property	Value	Reference
Physical state	Solid	
Melting point	No available data.	
Boiling point	No available data.	
Density	2.32 g/cm^3	(1), (2), (3)
Vapour pressure	Not applicable for the salt of inorganic compounds	
Water solubility	2.05 g/L-at 20 °C	(3)
Partition coefficient n-octanol/water (log value)	Not applicable for the salt of inorganic compounds	

Calcium sulfate, dihydrate consists of colorless, monoclinic and hygroscopic crystals (2). Calcium sulfate exists in three different forms which are calcium sulfate ($CaSO_4$), calcium sulfate dihydrate ($CaSO_4 \bullet 2H_2O$) and calcium sulfate hemihydrate ($CaSO_4 \bullet 1/2H_2O$). Calcium sulfate (anhydrite) is the commonest form of the natural sulfates and gypsum, $CaSO_4 \bullet 2H_2O$ and contains 27 % of water. When calcined, gypsum loses 75% of its combined water and becomes the hemihydrate, $CaSO_4 \bullet 1/2H_2O$ (4).

Table 1-2 Hydrate form of calcium sulfate

Molecular formula	Chemical name	CAS No.	Molecular weight
$CaSO_4$	Calcium sulfate	7778-18-9	136.14
$CaSO_4 \bullet 0.5\ H_2O$	Calcium sulfate hemihydrate	10034-76-1	145.15
$CaSO_4 \bullet 2\ H_2O$	Calcium sulfate dihydrate	10101-41-4	172.17

2 GENERAL INFORMATION ON EXPOSURE

2.1 Production Volumes and Use Pattern

In 2002 the estimated production amounts of calcium sulfate, dihydrate were 1,447,000 tonnes/year in Korea. Calcium sulfate, dihydrate is produced as a by-product in the phosphatic fertilizer industry. Two companies of phosphatic fertilizer produce calcium sulfate, dihydrate in Korea. The total amounts of import were estimated at 59.1 tonnes/year for four countries in 2002. Imports of calcium sulfate, dihydrate to Korea were 46 tonnes/year from China, 3.6 tonnes/year from Nauru, 1.5 tonnes/year from South Africa and 8 tonnes/year from Morocco. In Nordic countries (Norway, Sweden, Denmark and Finland), the total use volume of the substance was 48,527.7 tonnes in 2001. In the EU, Calcium sulfate, dihydrate is not listed in product registers in 2003.

In phosphatic fertilizer industry phosphate rock ($Ca_3(PO_4)_2$) reacts with sulfuric acid (H_2SO_4) to produce hemi-slurry, a mixture of phosphate and calcium sulfate hemihydrate. The reaction product can be separated into phosphoric anhydrate (P_2O_5) and calcium sulfate, dihydrate in the filter system. Phosphoric anhydrate is recycled and calcium sulfate, dihydrate remains as waste-solid and

is transported to the gypsum industry. In the gypsum industry calcium sulfate, dihydrate is at the origin of gypsum boards, bonds and plasters.

The different uses of calcium sulfate, dihydrate are: Portland-cement retarder; tile and plaster; source of sulfur and sulfuric acid; polishing powders; paints (white pigment, filler, drier); paper (size filler, surface coating); dyeing and calico printing; metallurgy (reduction of zinc minerals); drying industrial gases, solids and many organic liquids; in granulated form as soil conditioner; quick-setting cements, molds and surgical casts; wallboard; food additive; desiccant.

The substance is used for food additives in soy manufacturing industry, primarily materials in gypsum industry and cement retarder in cement industry in Korea. In Nordic countries, the substance is mainly used in adhesives, binding agents, construction materials and manufacture of other non-metallic mineral product industries (5).

2.2 Environmental Exposure and Fate

Releases of calcium sulfate, dihydrate into the environment are expected to occur mainly during processing with wastewater in the food industry. In the food industry, calcium sulfate, dihydrate is used as a coagulant in soy processing. According to the producer, calcium sulfate, dihydrate reacts with bean protein and the residue of the reaction process is released to wastewater treatment plants. In the phosphatic fertilizer industry and gypsum industry, wastewater containing calcium sulfate, dihydrate is recycled into the manufacturing process. Thus there are no emissions of wastewater and exhaust gases to the environment from these industries (5).

Photodegradation and distribution modelling are not applicable since calcium sulfate, dehydrate is the salt of an inorganic substance. No data on biodegradation and bioaccumulation are applicable. Mixed with water, calcium sulfate, dihydrate becomes a paste that can be spread, cast, or molded and will then set to rocklike hardness when dry.

Calcium sulfate (anhydrite) is the commonest form of the natural sulfates and gypsum. $CaSO4 \bullet 2H2O$, contains 27 % water. Gypsum and anhydrite are evaporates, which accumulate in basins or on supratidal salt flats under arid conditions. Where evaporation exceeds inflow, calcium sulfate follows calcium carbonate in the theoretical sequence of precipitation of salts. From a thousand foot column of the seawater, only 0.4 foot of calcium sulfate is precipitated. Possibly numerous thin beds of gypsum were leached and the gypsum transported and redeposited in deeper basins. If calcium sulfate was originally deposited as gypsum, it would soon have altered to anhydrite, making up the bulk of deeply buried deposits. Gypsum had been formed by hydration of anhydrite along basin margins and at shallow depths (4). Another natural accumulation of gypsum and anhydrite is shown in salt domes, Wechstein 'gypshu' of Germany or the US Gulf Coast.

2.3 Human Exposure

2.3.1 Occupational Exposure

Workers could be exposed to calcium sulfate, dihydrate via dust inhalation and dermal routes during manufacturing or processing. No data were available for workplace measurement of calcium sulfate, dihydrate but measured monitoring data for total dust in workplace was below 15 mg/m^3 TWA of exposure limit value (5).

2.3.2 Consumer Exposure

Calcium sulfate, dihydrate is used for interior decorations in building, as food additives and surgical cements. The surgical cements are potentially used in bone cements, dental cements, bone graft materials, bone substitutes, bone fillers, drug delivery systems and binders for granule forms of bioceramic materials. In the processing of soy protein, calcium sulfate, dihydrate is added as a coagulator in soy protein, and it is reacted with soy protein. From the reaction, soy protein is curdled and there is no residue of calcium sulfate, dihydrate in food. The only consumer exposure of calcium sulfate, dihydrate is expected from interior decorations and surgical cements (5).

3 HUMAN HEALTH HAZARDS

3.1 Effects on Human Health

3.1.1 Toxicokinetics, Metabolism and Distribution

There is no information in terms of toxicokinetics, Metabolism and Distribution.

3.1.2 Acute Toxicity

One study on acute oral toxicity in animals is available.

After single oral administration of 2,000 mg/kg bw of the test substance to 4 female animals by gavage, the LD50 for rats was determined in accordance with an OECD TG 420, Acute Oral Toxicity-Fixed dose procedure. No dead animals were observed at the limit test exposed to 2,000 mg/kg, so oral LD50 for rats was greater than 2,000 mg/kg bw.

3.1.3 Irritation

One study on skin irritation in animals is available.

This test was carried out in accordance with OECD TG 404, Acute Dermal Irritation/ Corrosion. The test substance led to no erythema and oedema on the abraded and intact backs of rabbits after removal of the patches (after a 4 hour occlusive exposure), which included 500 mg of test material and about 0.1 ml of sterile distilled water for humidity. Weight loss was observed in 24 hours after the administration but this sign did not have any relationship with the spread of calcium sulfate, dihydrate because it was caused by physical stress from the fixed patch. Body weight almost recovered within 72 hours. There were no clinical signs in relation to the spread of calcium sulfate, dihydrate (7).

3.1.4 Sensitisation

One study on skin sensitization in animals is available.

The sensitizing test of calcium sulfate, dihydrate was carried out with male guinea pigs in accordance with OECD TG 406, Skin Sensitization. A patch including 0.4 g of test material was applied to the abraded and intact sites on the shaved backs of rabbits and was held in place for 6 hours. The skin of animals was examined in accordance with the sensitization grading system and scored at 1 and 24 hours after removal of the patches for induction; and 24 and 48 hours after removal of the patches for challenge. According to the result, skin sensitization was not observed with the test concentrations of calcium sulfate, dihydrate on the backs of guinea pigs. Emaciation, sores, lacrimation and dyspnea occurred sporadically in some animals that belong to the treatment

groups including the control groups and each case of death was observed at the treatment group and positive control group, respectively. However, these were not influenced by test substance because these were induced by stress of the fixed patches (8).

3.1.5 Repeated Dose Toxicity

One study on oral repeated dose toxicity in animals is available.

In a gavage study in Sprague-Dawley rats in accordance with OECD TG 422, Combined Repeated Dose Toxicity Study with the Reproduction/Developmental Screening Test was conducted. The rats were exposed to calcium sulfate, dihydrate at level of 0, 100, 300 and 1,000 mg/kg bw/day for more than 35 days and 41 - 45 days for male and female animals, respectively. For male animals, in the control group within the recovery group, a case of left and right caput epididymis cyst was observed and the 1,000 mg/kg bw/day recovery group had symptom of right caput epididymis cyst. For female animals, in the 300 mg/kg bw/day treatment group, one animal was died on day 7 and another on day 14 and in each case dark-red discolouration of the lung was observed, but white particles in a lobe of the lung were observed just in one dead animal. However, its frequency of occurrence was quite low. After all, calcium sulfate, dihydrate had no critical influence on test items such as mortality, body weights (organ weight), food consumption, necropsy and behaviour of the animals. However, the values of TP (Total Protein), ALB (Albumin), BUN (Blood Urea Nitrogen), and CREA (Creatinine) were decreased significantly at the 300 mg/kg bw/day and 1,000 mg/kg bw/day treatment for male animals in accordance with analysis of biochemical test of blood, for the test substance might affect the excretion process, distribution or metabolism of the test substance in relation to the kidney. On the other hand, no significant difference was found at every test item between female controls and treatment groups. There were some changed values in the female recovery group for AST, TCHO and GLU, but these were in the normal range and there was no dose-response relationship. Therefore, LOAEL and NOAEL for male animals were determined to be 300 mg/kg bw/day and 100 mg/kg bw/day, respectively. (9). For female rats, no effects were observed at the top dose tested (1,000 mg/kg bw/day).

3.1.6 Mutagenicity

In vivo and *in vitro* studies on mutagenicity are available.

In vitro Studies

Bacterial Test – Bacterial Reverse Mutation Test: A preliminary test was carried out to decide the appropriate starting dose level of the main study at the concentrations of 1.6, 8, 40, 200, 1,000 and 3,000 mg/plate. In the main study, calcium sulfate, dihydrate was negative in the bacterial reverse mutation assay with *Salmonella tryphimurium* (strains TA98, TA100, TA1535, and TA1537) and *Escherichia coli* WP2 *uvr*A with and without metabolic activation tested at concentrations of 12, 37, 111, 333, 1,000 and 3,000 mg/ plate in accordance with OECD TG 471 and 472. The number of revertant colonies in the plate was counted after 2 day-incubation at 37 °C. In conclusion, no mutation occurred with calcium sulfate, dihydrate with and without metabolic activation (11).

In vivo Studies

Mammalian erythrocyte micronucleus test: An *in vivo* mammalian erythrocyte micronucleus test with 6 mice yielded a negative response up to the test concentration of 5,000 mg/kg bw in accordance with OECD TG 474, Genetic toxicity: Micronucleus Test. The route of administration was oral feed and I.P for the test substance and the positive control, respectively. This test indicated

that calcium sulfate, dihydrate does not induce chromosomal aberrations up to the highest test concentration (10).

3.1.7 Carcinogenicity

There is no information available regarding of carcinogenicity.

3.1.8 Toxicity for Reproduction

In this study, Sprague-Dawley rats were treated orally (gavage) with calcium sulfate, dihydrate at doses of 0, 100, 300 and 1,000 mg/kg/day in accordance with OECD TG 422, combined repeated dose toxicity study with the reproduction/developmental toxicity screening test. Male and female animals were dosed for 35 days and 41 - 45 days, respectively and the pre-mating exposure period was 14 days. Some animals in the test groups including the control group had quite higher loss rates of the embryo prior to the implantation and the fetus after the implantation but a significant difference was not observed between the treatment and the control groups. These higher loss rates occurred spontaneously and there was no dose-response correlation. A case of salivation and bloody-like secretion and genitalia bloody-like secretion were observed in the male and female control group, respectively. However, the frequency of occurrence was low and there was no dose-response correlation. Therefore, there were no significant treatment-related changes up to 1,000 mg/kg/day (highest dose tested) in terms of pregnancy; index of copulation, fertility and gestation; examination of the external surface of pups; and clinical signs, etc. (9).

3.2 Initial Assessment for Human Health

There is no information on toxicokinetics, metabolism and distribution.

The acute oral toxicity study [OECD TG 420, Fixed dose procedure] of calcium sulfate, dihydrate showed that this chemical did not cause any changes even at 2,000 mg/kg b.w. Therefore, the oral LD_{50} value was more than 2,000 mg/kg b.w. for female rats without specific clinical signs.

Calcium sulfate, dihydrate was not irritating to the skin of rabbits at 1, 24, 48 and 72 hours after removal of the patches [OECD TG 404]. There is no indication of skin sensitisation in guinea pigs [OECD TG 406].

In a Combined Repeated Dose and Reproduction/Developmental Toxicity Screening Test in rats [OECD TG 422], calcium sulfate, dihydrate was administered by gavage at the dose levels of 0, 100, 300 and 1,000 mg/kg bw/day for more than 35 days and 41 ~ 45 days for male and female animals, respectively. Calcium sulfate, dihydrate had no critical influence on test items such as mortality, body weights (organ weight), food consumption, necropsy, reflex action, grip strength and behaviour of the animals. However, the values of total protein, albumin, blood urea nitrogen, aspartate aminotransferase, alanine aminotransferase and creatinine were decreased at 300 mg/kg bw/day and 1,000 mg/kg bw/day treatment for male animals showing that the test substance might affect the excretion process, distribution or metabolism of test substance in relation to the kidney. Based on these results, the LOAEL and NOAEL were determined to be 300 mg/kg bw/day and 100 mg/kg bw/day for male rats. In case of female rats, no effects were observed at the top dose tested (1,000 mg/kg bw/day).

In the above mentioned reproduction/developmental toxicity screening test [OECD TG 422], male and female rats, were dosed for 35 days and 41 ~ 45 days respectively and the pre-mating exposure period was 14 days. No adverse effects were observed in terms of fertility, delivery and nursing in parent animals during the test period. There were no signs of reproduction/developmental toxicity

on the body weight, gestation index, sex ratio, clinical signs or viability up to 1,000 mg/kg/day (highest dose tested).

Bacterial gene reverse mutation tests in *Salmonella typhimurium* (strains TA98, TA100, TA1535 and TA1537) and *Escherichia coli* WP2 *uvr*A with and without metabolic activation gave negative results. An i*n vivo* mammalian erythrocyte micronucleus assay using male ICR mice [OECD TG 474], tested at the dose levels of 1,250, 2,500 and 5,000 mg/kg b.w, gave negative results. Accordingly calcium sulfate, dihydrate was not mutagenic *in vivo* and *in vitro*.

According to mutagenicity data, this substance would not be expected to be carcinogenic. There is no data available on carcinogenicity.

4 HAZARDS TO THE ENVIRONMENT

4.1 Aquatic Effects

The following acute toxicity tests with aquatic organisms are available;

Table 4-1 Effects of calcium sulfate, dihydrate on aquatic organisms

Organisms	Species	Results	Test condition	Reference
Fish	*Oryzias latipes*	LC_{50} (96 h) > 100 mg/L	OECD TG 203 (static, nominal concentration)	(12)
Invertebrate	*Daphnia magna*	EC_{50} (48 h) > 100 mg/L	OECD TG 202 (static, nominal concentration)	(13)
Algae	*Selenastrum capricornutum*	EC_{r50} (72 h) > 100 mg/L EC_{b50} (72 h) > 100 mg/L $NOEC_r$ < 100 mg/L $NOEC_b$ < 100 mg/L	OECD TG 201 (static, nominal concentration)	(14)

All tests were conducted according to GLP and all values are related to nominal concentration. Analytical monitoring was not performed. In the algae toxicity test, growth inhibition of 18.2 % for growth rate and 43.0 % for biomass were observed at 100 mg/L.

In the limit tests at 100 mg/L with the two other aquatic organisms no harmful effect to calcium sulfate, dihydrate were observed.

In aqueous solution, calcium sulfate, dihydrate has the same behaviour as calcium sulfate. Toxicity of aquatic organisms for calcium sulfate are summarised in table 4-2. ;

Table 4-2 Effects of calcium sulfate on aquatic organisms

Organisms	Species	Results	Test condition	Reference
Fish	*Pimephales promelas*	LC_{50} (96 h) > 1,970 mg/L	EPA /600/4-90/027 & EPA /600/6-91/003 (static, nominal concentration)	(15)
	Lepomis macrochirus	LC_{50} (96 h) > 2,980 mg/L	Trama, F. B., 1954 (static, nominal concentration)	(16)
Invertebrate	*Daphnia magna*	LC_{50} (48 h) > 1,970 mg/L	EPA /600/4-90/027 & EPA /600/6-91/003 (static, nominal concentration)	(15)
Aquatic plant	*Navicula*	LC_{50} (120 h)	Patrick, R. J. *et al*, 1968	(17)

	linearis	> 3,200 mg/L	(static, nominal concentration)	

These results confirm the results from the limit tests with calcium sulfate, dihydrate.

4.2 Terrestrial Effects

No data are available on terrestrial organisms.

4.3 Other Environmental Effects

No data are available.

4.4 Initial Assessment for the Environment

Calcium sulfate, dihydrate is a colorless solid inorganic substance with monoclinic and hygroscopic properties. It has a water solubility of 2.05 g/L at 20 °C. Vapor pressure, n-octanol/water partition coefficient and stability in water are not applicable for the salt of an inorganic substance. Photodegradation, environmental fate modeling and biodegradation are not relevant for an inorganic compound. Bioaccumulation is not expected.

The following studies for aquatic organisms are available:

Green algae (*Selenastrum capricornutum)*: EC_{g50} (72 h) > 100 mg/L (growth rate),

EC_{b50} (72 h) > 100 mg/L (biomass)

Invertebrates (*Daphnia magna):* EC_{50} (48 h) > 100 mg/L.

Fish (*Oryzias latipes*): LC_{50} (96 h) > 100 mg/L.

No data are available on terrestrial organisms. Data from limit tests of 100 mg/L in fish, invertebrates and algae show no harmful effects.

5 RECOMMENDATIONS

This substance is currently of low priority for further work because of its low hazard profile.

6 REFERENCES

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SIDS DOSSIER ON THE HPV CHEMICAL

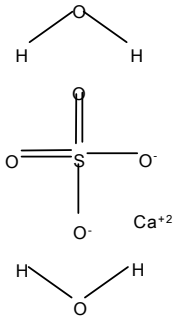
Calcium sulfate, dihydrate CAS No.: 10101-41-4

Sponsor Country: Republic of Korea

Date of submission to OECD: December 2003

1.01 SUBSTANCE INFORMATION

***A. CAS number** : 10101-41-4
B. Name (Primaryname) : Calcium sulfate, dihydrate
***C. Name (OECD name)** : Calcium sulfate, dihydrate
†D. CAS Descriptor :
E. EINECS-Number :
F. Molecular Formula : $CaSO_4 \cdot 2H_2O$
***G. Structural Formula** :



H. Substance Group :

I. Substance Remark (Indicate the substance remark as prescribed in the EINECS Inventory, if possible)

J. Molecular Weight : 172.17

1.02 OECD INFORMATION

A. Sponsor Country : Republic of Korea

B. Lead Organisation : National Institute of Environmental Research
Contact person : Hyun-Mi KIM, Ph. D.
Address : Environmental Research Complex
Street : Gyeongseo-dong, Seo-gu
Postal code : 404-708
Town : Incheon
Country : Republic of Korea
Tel : +82-(0)32-560-7124
Fax : +82-(0)32-560-7161
E-mail : hmikim@me.go.kr

C. Name of responder (Information on a responder should be provided when companies respond to Lead Organisation or SIDS Contact Points.)
Name : Same as above
Address : Same as above

1.1 GENERAL SUBSTANCE INFORMATION

A. Type of Substance : Inorganic

B. Physical State (at 20 °C and 1.013 hPa)
: Solid

C. **Purity** : > 90 %

Remark :

Molecular formula	Chemical name	CAS No.
$CaSO_4$	Calcium sulfate	7778-18-9
$CaSO_4 \cdot 0.5\ H_2O$	Calcium sulfate hemihydrate	10034-76-1
$CaSO_4 \cdot 2\ H_2O$	Calcium sulfate dihydrate	10101-41-4

Source : Namhae Chemical Company, Korea (2002)

1.2 SYNONYMS

: Alabaster
: Annaline
: C.I. Pigment White 25
: Gypsum
: Gypsum stone
: Land plaster
: Light spar
: Magnesia white
: Mineral white
: Native calcium sulfate
: Precipitated calcium sulfate
: Sainite
: Satin spar
: Sulfuric acid, calcium($^{2+}$) salt, dihydrate
: Terra alba

1.3 IMPURITIES

CAS No : 1314-56-3

EINECS No : 215-236-1
Name : Phosphoric anhydrate (P_2O_5)
Value : < 1.3 %
Remarks :

Source : Namhae Chemical Company, Korea (2002)

CAS No : 1309-48-4
EINECS No : 215-171-9
Name : Magnesium oxide (MgO)
Value : < 0.07 %
Remarks :

Source : Namhae Chemical Company, Korea (2002)

CAS No : 112926-00-8
EINECS No :
Name : Silicon dioxide (SiO_2)
Value : < 0.01 %
Remarks :

Source	:	Namhae Chemical Company, Korea (2002)
CAS No	:	1317-60-8
EINECS No	:	215-275-4
Name	:	Iron(III) oxide (Fe_2O_3)
Value	:	< 0.02 %
Remarks	:	
Source	:	Namhae Chemical Company, Korea (2002)
CAS No	:	
EINECS No	:	
Name	:	Crystalline water
Value	:	< 8.6 %
Remarks	:	
Source	:	Namhae Chemical Company, Korea (2002)

1.4 ADDITIVES

1.5 QUANTITY

Estimated production	:	Calcium sulfate, dihydrate of 1,447,000 tonnes was produced by estimate in 2002 in Korea. The total amounts of import were estimated as 59.1 tonnes from four countries in 2002 such as 46 tonnes from China, 3.6 tonnes from Nauru, 1.5 tonnes from South Africa and 8 tonnes from Morocco. In Nordic countries (Norway, Sweden, Denmark and Finland), total use volume of the substance was 48527.7 tonnes in 2001.
Remarks	:	

(1)

1.6.1 LABELLING

Labelling	:	As in Directive 67/548/EEC
Specific limits	:	
Symbols	:	Not available
Nota	:	
R-phrases	:	
S-phrases	:	
Remarks	:	

1.6.2 CLASSIFICATION

Classified	:	Not on the TSCA Inventory
Class of danger	:	
R-phrases	:	

1.7 USE PATTERN

Type	:	Type
Category	:	Non dispersive use
Type	:	Type
Category	:	Wide dispersive use
Type	:	Industrial
Category	:	Cement industry; Portland-cement retarder
Type	:	Industrial
Category	:	Food industry; food additives (coagulation agent)
Type	:	Industrial
Category	:	Gypsum industry; source of gypsum board, bond and plaster
Type	:	Industrial
Category	:	Source of sulfur and sulfuric acid
Type	:	Industrial
Category	:	Polishing powders
Type	:	Industrial
Category	:	Paints (white pigment, filler, drier)
Type	:	Industrial
Category	:	Paper (size filler, surface coating)
Type	:	Industrial
Category	:	Dyeing and calico printing
Type	:	Industrial
Category	:	Metallurgy (reduction of zinc minerals)
Type	:	Industrial
Category	:	Drying industrial gases, solids and many organic liquids

Type : Industrial
Category : In granulated form as soil conditioner

Type : Use
Category : Quick-setting cements, molds and surgical casts

Type : Use
Category : Desiccant

Type : Use
Category : Wallboard and interior decoration

1.8 OCCUPATIONAL EXPOSURE LIMIT VALUE

Exposure limit value
Type : ACGIH TLV
Value : TWA (nuisance particulate) 10 mg/m^3 of total dust
Reference : (2)

Exposure limit value
Type : OSHA PEL
Value : Total dust - 15 mg/m^3, Respirable dust - 5 mg/m^3
Reference : (2)

1.9 SOURCES OF EXPOSURE

Source : In the food industry
Remarks : Calcium sulfate, dihydrate is reacted with bean protein and the residue of reacting process release to waste water treatment plant.
(1)

Source : In the gymsum industry
Remarks : Wastewater contained calcium sulfate dihydrate is recycled in manufacturing process.
(1)

1.10 ADDITIONAL REMARKS

2.1 MELTING POINT

Value : Not available data
Reliability :

2.2 BOILING POINT

Value : Not available data
Reliability :

2.3 DENSITY(RELATIVE DENSITY)

Type : density
Value : 2.32 g/cm^3
Temperature :
Reliability : (2) Reliable with restrictions
Flag : Critical study for SIDS endpoint

(2), (3), (4)

2.4 VAPOUR PRESSURE

Value : Not applicable for the salt of inorganic compounds
Temperature :
Method :
Remarks :
Reliability :

2.5 PARTITION COEFFICIENT LOG$_{10}$ P$_{OW}$

Log P$_{ow}$: Not applicable for the salt of inorganic compounds
Temperature :
Method :
Remarks :
Reliability :

2.6 WATER SOLUBILITY

Value : 2.05 g/L
Temperature : 20 °C
Reliability : (2) Reliable with restrictions
: Handbook data
Flag : Critical study for SIDS endpoint

(3)

Value : 2.1 g/L
Temperature : 20 °C
Reliability : (4) Not assignable
: No data available

(5)

2.7 FLASH POINT

2.8 AUTO FLAMMABILITY

2.9 FLAMMABILITY

2.10 EXPLOSIVE PROPERTIES

Results : Noncombustible
Reliability : (2) Reliable with restrictions

(4)

2.11 OXIDIZING PROPERTIES

2.12 OXIDATION: REDUCTION POTENTIAL

2.13 ADDITIONAL DATA

Value : Loses 1.5 parts of water at 128 °C, becomes anhydrous at 163 °C
Reliability : (2) Reliable with restrictions

(4)

3.1 STABILITY

3.1.1 PHOTODEGRADATION

Remarks : Not applicable for the salt of inorganic compounds
Reliability :

3.1.2 STABILITY IN WATER

Type : Not applicable for the salt of inorganic compounds
Half-life at 25 °C :
Degradation % :
Method :
Year :
GLP :
Test substance :
Reliabilities :

Remarks : After mixing with water, this compound can be spread, cast, or molded and will be set to rocklike hardness.
Reliability : (2) Reliable with restrictions
(6)

Remarks : Neither the anhydrite nor the dihydrate form can set with water.

Reliability : (2) Reliable with restrictions
(4)

Remarks : Surgical cements are derived from calcium sulfate components in combination with cementing components and certain soluble salts as setting components. Any two or all of the cementing components, fillers and setting components can be premixed. To form cement, the premixed material containing all three materials is mixed with desired amount of water to make a paste. This paste becomes viscous and adhesive or cohesive. After a certain time, the paste sets and hardens. For an aging in a water environment, these setting cements maintained in its integrity. The following table showed the results of all the examples.

Example No.	Setting Components (g)	Strength Enhancing Component (g)	H_2O (ml)	Setting Time (min.)
1	0.5 g K citrate	0	0.6 0.7	2
2	2.0 g K citrate	0	0.7	7
3	0.7 g K citrate	0.3 g $(NH_4)_2HPO_4$		8
4	1.0 g K citrate 0.7 g ferric ammonium citrate			
	0		0.8	
5	0.5 g K citrate	1.0 g NaK tartrate	0.8	< 1
5	0.5 g Na citrate	0.5 g NaK tartrate	0.8	8
6	0.5 g K citrate	0.5 g K_2HPO_4	0.7	

7	0.7 g K citrate	0.5 g K_2HPO_4	0.7	< 1
8	0.8 g K citrate	0.3 g K_2HPO_4	0.7	7
9	0	0.2 g Na_2HPO_4	0.6	5
10		0.5 g $(NH_4)_2HPO_4$		1.5

* EACH OF THESE TESTS USED 2 G OF CALCIUM SULFATE, DIHYDRATE AS THE CEMENTING COMPONENT.

Reliability : (2) Reliable with restrictions

(7)

3.1.3 STABILITY IN SOIL

3.2 MONITORING DATA (ENVIRONMENT)

3.3 TRANSPORT AND DISTRIBUTION BETWEEN ENVIRONMENTAL COMPARTMENTS INCLUDING ESTIMATED ENVIRONMENTAL CONCENTRATIONS AND DISTRIBUTION PATHWAYS

3.3.1 TRANSPORT

Remarks : Calcium sulfate (anhydrite) is the commonest of the natural sulfates and gypsum, CaSO4 • 2H2O, contains 27 % water. When gypsum is calcined, it loses three-quarters of combined water to form the hemihydrate, CaSO4 • 1/2H2O. Gypsum and anhydrite are evaporites, which accumulate in basins or on supratidal salt flats under arid conditions. Where evaporation exceeds inflow, calcium sulfate follows calcium carbonate in the theoretical sequence of precipitaion of salts. From a thousandfoot column of the seawater, only 0.4 foot of calcium sulfate is precipitated. Possibly numerous thin beds of gypsum were leached and the gypsum transported and redeposited in a deeper basin. If calcium sulfate was originally deposited as gypsum, it must soon have altered to anhydrite, making up the bulk of deeply buried deposits. Gypsum had been formed by hydration of anhydrite along basin margins and at shallow depths. Another natural accumulation of gypsum and anhydrite are shown in salt domes, the Zechstein ‘gypshu’ of Germany or the US Gulf Coast.
Reliability : (2) Reliable with restrictions
Flag : Critical study for SIDS endpoint

(6)

3.3.2 THEORETICAL DISTRIBUTION (FUGACITY CALCULATION)

Remarks : Not applicable for the salt of inorganic compounds
Reliability :

3.4 IDENTIFICATION OF MAIN MODE OF DEGRADABILITY IN ACTUAL USE

3.5 BIODEGRADATION

Remarks : Not applicable for the salt of inorganic compounds
Reliability :

3.6 BOD5, COD OR RATIO BOD5/COD

3.7 BIOACCUMULATION

Remarks : Not applicable for the salt of inorganic compounds
Reliability :

3.8 ADDITIONAL REMARKS

4.1 ACUTE/PROLONGED TOXICITY TO FISH

Type	:	Static
Species	:	*Oryzias latipes*
Exposure period	:	96 hours
Unit	:	mg/L
Analytical monitoring	:	No
LC_{50}	:	> 100 mg/L
Method	:	OECD TG 203 "Fish, Acute Toxicity Test"
Year	:	2002
GLP	:	Yes
Test substance	:	Other TS: Calcium sulfate, dihydrate, purity = 99.9 % Sigma-Aldrich Corporation, Lot. No. – 109H0166
Remarks	:	- Test Organisms Age: 5 months Length: 2.7 ± 0.1 cm Weight: 0.15 ± 0.02 g Loading: 8.7 L aquarium per 7 fish Pretreatment: 55 fish were acclimated for 7 days before test. No food was fed before 1 day and during test. - Test Conditions Dilution water source: Tap water passed through activated carbon and membrane filter (1 μm), hardness: 54.5 mg/L as $CaCO_3$, alkalinity: 31.5 mg/L as $CaCO_3$, Water chemistry: DO: 81.9 ~ 105.3 %, pH: 7.41 ~ 7.95 Temperature: 24.2 ~ 24.8 °C Light: 1,628 ~ 1,816 Lux, Light periocity: 16/8 (light/dark) A group of 7 fish was used and no replicate.
Result	:	Nominal concentration was used. From the limit test at 100 mg/L, no mortality and visible abnormality were occurred.
Reliabilities	:	(1) Reliable without restrictions
Flag	:	Critical study for SIDS endpoint

(8)

4.2 ACUTE TOXICITY TO AQUATIC INVERTEBRATES

A. Daphnia

Type	:	Static
Species	:	*Daphnia magna*
Exposure period	:	48 hours
Unit	:	mg/L
EC_{50}	:	> 100 mg/L
Analytical monitoring	:	No
Method	:	OECD TG 202, "*Daphnia sp.*, Acute Immobilisation Test and Reproduction Test"
Year	:	2002
GLP	:	Yes
Test substance	:	Other TS: Calcium sulfate, dihydrate, purity = 99.9 % Sigma-Aldrich Corporation, Lot. No. – 109H0166
Remarks	:	- Test Organisms Age: juveniles within 24 hours old. Supplier: GSF Institute of Ecological Chemistry, Germany - Test Conditions Dilution water source: OECD M4 medium, hardness: 124 mg/L as $CaCO_3$, alkalinity: 42 mg/L as $CaCO_3$ Water chemistry: DO: 94 ~ 95 %, pH 7.90 ~ 7.98

Temperature: 20.1 ± 0.2 °C
Light: 1,221 ~ 1,996 Lux, Light precocity: 16/8 (light/dark)
3 replicates per 10 organisms were used and total 30 daphnids were exposed to 100 mg/L of test substance.

Result : Nominal concentration was used. According to the limit test at 100 mg/L, no immobilization and mortality were observed.
Reliabilities : (1) Reliable without restrictions
Flag : Critical study for SIDS endpoint

(9)

4.3 TOXICITY TO AQUATIC PLANTS

ALGAE

Species : *Selenastrum capricornutum*
Endpoint : Growth rate
Exposure period : 72 hours
Unit : mg/L
E_gC_{50} : > 100 mg/L
E_bC_{50} : > 100 mg/L
$NOEC_r$: < 100 mg/L
$NOEC_b$: < 100 mg/L

Analytical monitoring : No
Method : OECD TG 201, "Alga, Growth Inhibition Test"
Year : 2002
GLP : Yes
Test substance : Other TS: Calcium sulfate, dihydrate, purity = 99.9 %
Sigma-Aldrich Corporation, Lot. No. – 109H0166
Remarks : **- *Test organisms***
Laboratory culture: ATCC culture medium 625 Gorham's medium
Strain No.: ATCC 22662
Method of cultivation: sterilization
- *Test conditions*
Temperature: 22 ~ 23 °C
Dilution water source: OECD medium
Water chemistry: pH 7.97 ~ 8.03 at start and pH 8.03 ~ 8.20 at finish
Light level: 8,236 ~ 8,324 Lux
Initial cell density: 1 x 10^4 cells/mL
Test design: 3 replicates
Result : Nominal concentration of 100 mg/L was used.
Growth inhibition rate:

- Growth rate

Nominal Concentration (mg/L)	Growth rate	Relative growth rates (%)	Relative inhibition (%)
Control	0.074	-	-
100	0.061	81.8	18.2

- Areas under the curve

Nominal Concentration (mg/L)	Area under the curve	Relative growth rates (%)	Relative inhibition (%)
Control	27,222,000	-	-
100	15,504,000	57.0	43.0

: Significant difference in growth curve was not observed between test concentration and control group.
Reliabilities : (1) Reliable without restrictions.
Flag : Critical study for SIDS endpoint

(10)

4.4 TOXICITY TO MICROORGANISMS

4.5 CHRONIC TOXICITY TO AQUATIC ORGANISMS

4.5.1 CHRONIC TOXICITY TO FISH

4.5.2 CHRONIC TOXICITY TO AQUATIC INVERTEBRATES

4.6 TERRESTRIAL ORGANISMS

4.6.1 TOXICITY TO SOIL DWELLING ORGANISMS

4.6.2 TOXICITY TO TERRESTRIAL PLANTS

4.6.3 TOXICITY TO OTHER NON MAMMALIAN TERRESTRIAL SPECIES (INCLUDING AVIAN)

4.7 BIOLOGICAL EFFECTS MONITORING (INCLUDING BIOMAGNIFICATION)

4.8 BIOTRANSFORMATION AND KINETICS

4.9 ADDITIONAL REMARKS

Remarks : In aqueous solution, calcium sulfate, dihydrate has the same behaviour as calcium sulfate.
Toxicity of aquatic organisms for calcium sulfate are as followed. ;
Fish: *Pimephales promelas*, LC_{50} (96 h) > 1,970 mg/L
(EPA /600/4-90/027 & EPA /600/6-91/003, static, nominal concentration)
Lepomis macrochirus, LC_{50} (96 h) > 2,980 mg/L
(Trama, F. B., 1954, static, nominal concentration)
Invertebrates: *Daphnia magna* LC_{50} (48 h) > 1,970 mg/L
(EPA /600/4-90/027 & EPA /600/6-91/003, static, nominal concentration)

Aquatic plant: *Navicula linearis,* LC_{50} (120 h) > 3,200 mg/L
(Patrick, R.J. *et al*, 1968, static, nominal concentration)
Reliabilities : (2) Reliable with restrictions
Flag : Critical study for SIDS endpoint
Reference : (11), (12), (13)

5.1 ACUTE TOXICITY

5.1.1 ACUTE ORAL TOXICITY

Type	:	LD_{50}
Species/strain	:	Rat (Sprague-Dawley)
Sex	:	Female
Number of animals	:	7 animals (3 animals for sighting study, 4 animals for main study)
Vehicle	:	Not used
Value	:	50, 300 and 2,000 mg/kg for sighting study 2,000 mg/kg for main study
Route of administration	:	Oral (gavage)
Method	:	OECD Test Guideline 420 (Acute Oral Toxicity-Fixed dose procedure)
Method remark		- *Sighting study* In order to determine the appropriate starting dose for the main test, 50, 300 and 2,000 mg/kg of test substance were administered to each animal, but there were no toxic effects at least 2 days after the administration. - *Main study* 2,000 mg/kg of test substance was administered to 4 female rats. - *Administration* Test substance was dissolved in the distilled water on the day of administration. Animals were fasted the night before administration but fodder was offered 3 to 4 hours after the administration. - *Observation* Mortality, clinical signs, and toxic effects: these items were observed 0.5, 1, 2, 3 and 4 hours after the treatment on the day of administration, after that were observed at least once a day till necropsy. *Body weight*: Before and after the treatment, it was measured at 1, 7 and 14 day. *Necropsy*: on the day 14 after the administration, every survived animal was narcotized with CO_2 then cut the abdomen open to kill the animals by releasing blood from the aorta of abdomen. Finally, the internal organs were investigated with the unaided eye. - *A criterion*: OECD Series on testing and assessment No. 33, "Harmonized Integrated Classification System for Human Health and Environmental Hazards of Chemical Substances and Mixtures" Category 1: LD50 ≤ 5 mg/kg Category 2: 5 mg/kg < LD50 ≤ 50 mg/kg Category 3: 50 mg/kg < LD50 ≤ 300 mg/kg Category 4: 300 mg/kg < LD50 ≤ 2000 mg/kg Category 5: 2000 mg/kg < LD50 ≤ 5000 mg/kg
Year	:	2002
GLP	:	Yes
Test substance	:	Other TS: Calcium sulfate, dihydrate, purity = 99.9 %; Sigma-Aldrich Corporation, Lot No. - 109H0166
Test condition	:	Age: 9 ~ 11 weeks Body weight at study acute oral toxicity : 194.9 ~ 206.6 g (sighting study) : 194.9 ~ 203.6 g (main study) Doses per time period: single treatment Volume administered: 10 mL/kg Post dose observation period: 14 days

Result	:	No mortality was observed within every dose level. Therefore, calcium sulfate, dihydrate was classified into category 5 in accordance with an OECD Series on testing and assessment No. 33. There were no specific clinical signs during test period. No abnormal necropsy opinions in relation to administration of calcium sulfate, dihydrate. Rats showed normal body weight gain during test period.
Conclusion	:	All things being considered, no dead animals were observed at the limit test exposed to 2,000 mg/kg, so oral LD_{50} for rats was more than 2,000 mg/kg (category 5).
Reliability	:	(1)Reliable without restrictions
Flag	:	Critical study for SIDS endpoint

(14)

5.1.2 ACUTE INHALATION TOXICITY

.

5.1.3 ACUTE DERMAL TOXICITY

5.1.4 ACUTE TOXICITY, OTHER ROUTES OF ADMINISTRATION

5.2 CORROSIVENESS/IRRITATION

5.2.1 SKIN IRRITATION

Test type	:	*In vivo*
Species/strain	:	Rabbit (New Zealand White)
Results	:	Not irritating The skin on the backs of three rabbits appeared unaffected.
Method	:	OECD TG 404 (1991) “Acute Dermal Irritation/Corrosion”
Method remark		500 mg of test material with about 0.1 mL of sterile distilled water for humidity was applied to the abraded and intact sites on the shaved backs (2.5 x 2.5 cm) of rabbits. It was held in place for 4 hours with three fold gauze patches, which was applied in place with elasticity bandage then was fixed with non-irritating tape (3M paper-tape) to prevent leakage. After 4 hours, three gauze patches were removed and the exposed areas were washed using warm water without altering the existing response or the integrity of the epidermis. The skin of animals was examined in accordance with an OECD scoring method for signs of erythema and oedema and the responses scored at 1, 24, 48 and 72 hours after the patches removal. Mortality, clinical signs and body weight were also observed.
Year	:	2002
GLP	:	Yes
Test substance	:	Other TS: Calcium sulfate, dihydrate, purity = 99.9 %, Sigma-Aldrich Corporation, LOT No. - 109H0166
Test condition	:	Test organism - Age: 3 to 4 months old - Number of animals: 3 animals - Sex: Males weighting 2.1 kg ~ 2.4 kg Total dose: 500 mg/site/rabbit of calcium sulfate, dihydrate Vehicle: Not used

Result : Route of administration: With an occluded patch
Exposure time period: 4 hours
Scoring method used: OECD method (Grading of skin reaction)
- Not irritating: no erythema, no eschar and no oedema was observed at the skin on the backs of three rabbits.
- There were no clinical signs in relation to spread with calcium sulfate, dihydrate.
Weight loss was observed in 24 hours after the administration.
Body weight was almost recovered in 72 hours.

Evaluation of skin irritation

Right site: Calcium sulfate, dihydrate

Change	Erythema & Eschar							
Applicated area	Intact				Abraded			
Phase (hrs)	1	24	48	72	1	24	48	72
Animal ID	0	0	0	0	0	0	0	0
M01	0	0	0	0	0	0	0	0
M02	0	0	0	0	0	0	0	0
M03	0	0	0	0	0	0	0	0
Total	0	0	0	0	0	0	0	0
Mean	0	0	0	0	0	0	0	0
Total of mean	0							

- Erythema and Eschar formation

0 – No erythema

1 – Very slight erythema (barely perceptible)

2 – Well defined erythema

3 – Moderate to severe erythema

4 – Severe erythema (beef redness) to eschar formation preventing grading of erythema

Right site: Calcium sulfate, dihydrate

Change	Oedema							
Applicated area	Intact				Abraded			
Phase (hrs)	1	24	48	72	1	24	48	72
Animal ID	0	0	0	0	0	0	0	0
M01	0	0	0	0	0	0	0	0
M02	0	0	0	0	0	0	0	0
M03	0	0	0	0	0	0	0	0
Total	0	0	0	0	0	0	0	0
Mean	0	0	0	0	0	0	0	0
Total of mean	0							

- Oedema formation

0 – No oedema

1 – Very slight oedema (barely perceptible)

2 – Slight oedema (edges of area well defined by definite raising)

3 – Moderate oedema (raised approximately 1 mm)

4 – Severe oedema (raised more than 1 mm and extending beyond area of exposure)

Conclusion	:	Calcium sulfate, dihydrate did not make skin irritation at the test concentration
Reliability	:	(1) Reliable without restrictions
Flag	:	Critical study for SIDS endpoint

(15)

5.2.2 EYE IRRITATION/CORROSION

5.3 SKIN SENSITIZATION

Type	:	Buehler test
Species/strain	:	Guinea pig (Hartley)
Method	:	OECD TG 406 (1991) “Skin Sensitization”
Method remarks		A patch (Whatman # filter paper, 2 x 2 cm) including 0.4 g of test material, which was dissolved in 0.4 mL of sterile distilled water, was applied to the abraded and intact sites on the shaved backs (4 x 4 cm) of Guinea pig. It was held in place for 6 hours with three fold gauze patches, which were applied in place with elasticity bandage (6.4 cm width) to prevent leakage. After 6 hours, three fold gauze patches were removed and the exposed areas washed using warm water without altering the existing response or the integrity of the epidermis. The skin of animals was examined in accordance with the sensitization grading system and scored at 1 and 24 hours after the patches removal for induction; and 24 and 48 hours after the patches removal for challenge. The test of induction on the skin was performed 3 times on the day 0, 7 and 14 but the test of challenge was performed 2 weeks after the final test of induction.
Year	:	2002
GLP	:	Yes
Test substance	:	Other TS: Calcium sulfate dihydrate; purity = 99.9 %, Sigma-Aldrich Corporation, LOT No. - 109H0166

Test condition	:	Test organism - Sex: male - Age of animal at study sensitization: 5 to 6 weeks old - Weight at study sensitization: 306.4 ~ 457.9 g - Number of test animals: 40 animals Exposure time period: 6 hours Concentration - Induction: 0.4 g/0.4 mL (100 %); pre-treatment had conducted with 13 %, 25 %, 50 % and 100 % of test substance. - Challenge: 0.4 g/0.4 ml (100 %) Route of administration: topical with an occluded patch (whatman # 3 filter paper) Negative control: solvent only (sterile distilled water) Positive control: 0.1 % 1-Chloro-2,4-dinitrobenzene (solvent: 10 % Propylene Glycol) Volume of material dosed: 0.4 g/0.4 ml Duration of exposure for induction: 6 hours/week for 3 consecutive weeks Duration of exposure for challenge: 6 hours once in two weeks from induction Length of rest period: 2 weeks prior to analysis Grading system used: OECD method (Magnusson and kligman grading scale for the evaluation of challenge patch test reactions)
Result	:	- Clinical signs and mortality: Emaciation, sores, lacrimation and dyspnea were occurred sporadically in some animals that belong to the treatment groups including the control groups. Each case of death was observed at the treatment group and positive control group on the day 16 and 9, respectively. These deaths were induced by stress, so no relationship with substance could be assumed. - Body weight: No critical difference between negative control group and treatment group including positive control group. - Necropsy opinion: The symptom of multifocal hepatization of lung was observed from the carcass of treatment group. The symptom of left lobe hepatization of lung and multifocal white spot of liver were observed from the carcass of positive control group. These symptoms were induced by stress, so no relationship with substance could be assumed. - Skin sensitization: Not sensitizing All test groups except positive control group had sensitization score of 0 (No visible change) for both induction and challenge test.

- stimulation index(SI)

Animal number	Negative control	Calcium sulfate, dihydrate								CDNB (in 10 % PG)							
		Induction 1		Induction 2		Induction 3		Challenge		Induction 1		Induction 2		Induction 3		Challenge	
		100 %		100 %		100 %		100 %		0.1 %		0.1 %		0.1 %		0.1 %	
		1 h	24 h	1 h	24 h	1 h	24 h	24 h	48 h	1 h	24 h	1 h	24 h	1 h	24 h	24 h	48 h
1	0	0	0	0	0	0	0	0	0	0	1	2	2	2	3	2	2
2	0	0	0	0	0	0	0	0	0	2	2	2	3	2	3	3	3
3	0	0	0	0	0	0	0	0	0	1	2	2	3	2	3	3	3
4	0	0	0	0	0	0	0	0	0	1	2	2	2	1	2	2	2
5	0	0	0	0	0	0	0	0	0	2	3	2	3	2	3	3	3
6	0	0	0	0	0	0	0	0	0	2	2	1	2	2	3	3	3
7	0	0	0	0	0	0	0	0	0	1	2	2	3	2	3	3	3
8	0	0	0	0	0	0	0	0	0	2	2	2	3	1	3	3	3
9	0	0	0	0	0	0	0	0	0	2	3	2	3	1	2	2	2
10	0	0	0	0	0	0	0	0	0	0	1	1	2	-			
11		0	0	0	0	0	0	0	0								
12		0	0	0	0	0	0	0	0								
13		0	0	0	0	0	0	0	0								
14		0	0	0	0	0	0	0	0								
15		0	0	0	0	0	0	0	0								
16		0	0	0	0	0	0	0	0								
17		0	0	0	0	0	0	0	0								
18		0	0	0	0	0	0	0	0								
19		0	0	0	0	0	0	-									
20		0	0	0	0	0	0	0	0								

CDNB: 1-Chloro-2,4-Dinitrobenzene

PG: Propylene Glycol

- : Death

Magnusson and kligman grading scale for the evaluation of challenge patch test reactions

0 – No visible change
1 – Discrete or patchy erythema
2 – Moderate & confluent erythema
3 – Intense erythema & swelling

Conclusion : According to the result, skin sensitization was not observed with the test concentrations of calcium sulfate, dihydrate on the backs of guinea pigs.
Reliability : (1)Reliable without restrictions
Flag : Critical study for SIDS endpoint

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5.4 REPEATED DOSE TOXICITY

Species/strains : Rat (Sprague-Dawley)

Sex : Male/Female
Route of administration : Oral (Gavage)
Method : OECD TG No. 422 “Combined Repeated Dose Toxicity Study with the Reproduction/Developmental Toxicity Screening Test”
Year : 2002
GLP : Yes
Test substance : Other TS: Calcium sulfate, dihydrate, purity = 99.9 %, Sigma-Aldrich Corporation, LOT No. – 109H0166
Dose level : 0, 100, 300 and 1,000 mg/kg/day; pre-treatment (Test No. P705) had conducted with 0, 125, 250, 500 and 1,000 mg/kg/day of the test substance for 7 days to determine the appropriate starting dose level.

Exposure period	:	35 days for male animals and 41 to 45 days for female animals
Frequency of treatment	:	Daily
Control group	:	Yes (Concurrent no treatment)
Post exposure observation period	:	No data
Statistical methods	:	Statistical decision tree, but in case of recovery group, either two-side Student's t-test or two-side Aspin-Welch t-test was used. In case of categorical data, two-sided Fisher's exact test was used.
Test condition	:	Test organism - Sex: male/female - Age of animals at study: 8 weeks old for males and females - Weight at study repeated dose toxicity: 254.2 - 297.8 g for males and 182.7 - 208.2 g for females - Number of test animals: 60 animals for each sex - Group composition: twelve animals (6 male + 6 female) were allocated as a recovery group for the control (0 mg/kg/day) and T3 (100 mg/kg/day) group. Observation of F0 - *Clinical observations performed and frequency*: Clinical symptoms were observed once a day but were observed once a week in detail; a death rate was observed twice a day; and body weight was observed once a week and just before the necropsy, but in case of pregnant females, it was measured on the day 0, 7, 14, 20 of gestation period, date of delivery, and 4 days after the delivery; consumption rate of fodder was observed once a week except mating period. - *Tests for sensory organ and reflex action*: 5 animals were randomly selected from each test group. Both preyer reflex test and corneal reflex test were performed before necropsy and during lactation for males and females, respectively. - *Behaviour test*: 5 animals were randomly selected from each test group to do grip strength test in terms of behaviour test. This test was performed before necropsy and during lactation for males and females, respectively. - *Haematological and biochemical test of blood*: randomly selected 5 male and female animals from each test group were fasted a day before necropsy for both tests. Animals were anesthetized using ether and cut the abdomen open to collect blood. In case of the haematological test, blood coagulation preventative chemicals for the test of blood coagulation and the calculation of blood-corpuscles were 3.2 % sodium citrate and EDTA-2K, respectively. On the other hand, blood coagulation preventative chemical was not used for the biochemical test, but gathered blood was left itself in the room temperature then the sera were separated using a centrifuge. For haematological test, 6 following items were measured; Haematocrit, hemoglobin concentration, erythrocyte count, total and different leucocyte count, platelet count, prothrombin time, and active partial thromboplastin time. For biochemical test of blood, eleven following items were measured; sodium, potassium, glucose, total cholesterol, blood urea nitrogen, creatinine, total protein, albumin, alanine aminotransferase, aspatate aminotransferase, and total bilirubin.

Organs examined at necropsy:
Organ weight: testes, epididymider (all males) liver, kidney, adrenals, thymus, spleen, brain and heart (5 male and female animals from each test group).
Fixation: 22 kinds of tissues were fixed to do histopathologic tests such as testes, epididymides, ovaries, accessory sex organs for all animals, brain (including cerebrum, cerebellum and pons), spinal cord, stomach, small and large intestines (including peyer's patches), liver, kidneys, adrenals, spleen, heart, thymus, thyroid, trachea, lungs, uterus, urinary bladder, lymph nodes (cervical mesenteric), peripheral nerve (sciatic or tibial), and bone marrow.

NOAEL : 100 mg/kg/day for male, No effects for female.
LOAEL : 300 mg/kg/day for male, No effects for female
Results : Results for F0
- *Mortality*: There was one death at day 8 for male, and each death on the day 7 and 14 for female in the treatment group of 300 mg/kg/day. These were occurred during the administration process, so it did not have relationship with test substance.
- *Body weight*: In male groups, temporarily, a case of diminishment in the amount of body weight change was observed at week 2 within the control group in which some clinical signs were observed such as damage to esophagus. Body weight loss for female animals was observed several times during lactation period in every treatment group including the control group. However, these were occurred temporarily because of the lactation.
- *Clinical signs*: In male control group, a case of salivation and bloody-like secretion was observed on the day 11 and 12. In the 1,000 mg/kg/day treatment group, a case of depilation, dcab and pus was observed on the left cheek between the day 25 and the closing day. However, the frequency of occurrence was low and no dose-response correlation. Thus these symptoms were not influenced by test substance. In female control group, a case of genitalia bloody-like secretion was observed at day 29. In the 100 mg/kg/day treatment group, each case of hypoactivity and depilation was observed on the day 8 and 9, and between day 44 and the closing day, respectively. However, these symptoms were disappeared in short, thus these did not have relationship with test substance.
- *Amount of fodder consumption*: No crucial difference between the treatment group and the control group was observed for both male and female animals during test period. For recovery group, no significant change was observed within themselves.
- *Test of reflex action*: Five male and female animals were randomly selected from each test group, in which no specific reaction was observed.
- *Grip strength test*: For male animals, 6 animals were left out from the treatment group. For female animals, 5 animals were left out from the control group, and the treatment group. All things being considered, there was no dose-response correlation and was no illness at the related organs such as the cerebellum and muscle.
- *Organ weight*: Both absolute weight of the liver and the left kidney were increased at the recovery group with administration of 1,000 mg/kg/day as compared with that of the control group within the recovery group. There was no histopathological illness at the organs, so increased organ weight did not have relationship with test substance.

- *Necropsy opinions*: For male animals, in the control group within the recovery group, a case of left and right caput epididymis cyst was observed and the 1,000 mg/kg/day recovery group had symptom of right caput epididymis cyst. However, its frequency of occurrence was low and it was even observed at the control group within the recovery group, so it did not have relationship with test substance. For female animals, in the 300 mg/kg/day treatment group, each animal was dead on the day 7 and 14 and; each case of lung dark-red discolouration was observed, but white particle in a lobe of the lung was observed just from one of carcasses. A case of spleen white nodule was observed for an animal in the 300 mg/kg/day treatment group. There was a case of right adrenal gland white spots at the 1,000 mg/kg/day treatment group. In the control group within the recovery group, each case of right adrenal gland hemorrhagia and atrophy and liver adhesion with diaphragm was observed.
- *Analysis of haematological test of blood*: In the 1,000 mg/kg/day male recovery group, segments were increased ($p < 0.05$) in contrast with that of the control group within the recovery group. Prothrombin time (PT) was decreased in the 1,000 mg/kg/day female recovery group in comparison with that of the control group within the recovery group. However, these symptoms were not observed in the definitive test groups, so these symptoms were not influenced by test substance**.** In addition, level of WBC (white blood cell) was increased ($p < 0.001$) in the 100 mg/kg/day female treatment group in contrast with that of the control group. However, its increased value was in the normal range and no dose-response correlation, so it did not have relationship with test substance.
- *Analysis of biochemical test of blood*: In the 100 mg/kg/day treatment group for male animals, BUN (Blood urea nitrogen) was decreased as compared with that of the control group. The male treatment groups with both administration of 300 mg/kg/day and the 1,000 mg/kg/day decreased in TP (Total protein), ALB (Albumin), AST (Aspatate aminotransferase), ALT (Alanine aminotransferase), BUN (Blood urea nitrogen), CREA (Creatinine), Na (Sodium), TCHO (Total cholesterol), and Cl (Chloride) as compared with those of the control group. In case of the 1,000 mg/kg/day male recovery group, the value of AST was decreased significantly in contrast with that of the control group within the recovery group.
No significant difference was found at every test item between female control and treatment group. The female recovery group with administration of 1,000 mg/kg/day decreased in AST in contrast with that of the control group within the recovery group, but TCHO and GLU (Glucose) were increased.
In fact, decreased values of AST and ALT could be no toxicological effects. In addition, the changed values of AST, TCHO, and GLU in this test were in the normal range and no histopathological opinion in terms of related organs, so these changed values were not influenced by test substance. However, decreased values of TP, ALB, BUN, and CREA were possibly influenced by excretion process or metabolism of test substance in relation to the kidney, and these symptoms were possibly recovered in 2 weeks from reversible effects.
- *Histopathology*: For male animals, in the control group, each case of heart focal inflammatory cell infiltration, submadibular lymph node blood absorption, liver mononuclear cell foci, and adrenal gland cortical vacuolation was observed. In the 300 mg/kg/day treatment group, two cases of pancreas vacuolation, and a case of liver mononuclear cell foci were observed. In the treatment group with administration of 1,000 mg/kg/day, there were three cases of liver mononuclear cell foci; and a case of heart focal inflammatory cell infiltration was found.

For female animals, in the control group, two cases of liver mononuclear cell foci, a case of kidney cortical scaring, and a case of pancreas vacuolation were observed. In the treatment group with administration of 100 mg/kg/day, one case of esophagus submucosal gland proliferation was observed. In the 300mg/kg/day treatment group, a case of trachea submucosal gland proliferation was observed. In the 1,000 mg/kg/day treatment group, each case of pancreas vacuolation and liver mononuclear cell foci was observed. However, these symptoms for both sexes were just subtle level and were occurred spontaneously, so there was no significant difference between the treatment group and the control group.

Mortality of males (group): one animal was found dead at day 8 of treatment.

Group:	C	T1	T2	T3
Test article:	------	Calcium sulfate, dihydrate		-------
Dose level (mg/kg/day):	0	100	300	1,000

Group	Week				
	1	2	3	4	5
C	0	0	0	0	0
T1	0	0	0	0	0
T2	0	1	0	0	0
T3	0	0	0	0	0

Mortality of females (group): each animal was found dead at day 7 and day 14 of treatment, respectively.

Group:	C	T1	T2	T3
Test article:	------	Calcium sulfate, dihydrate		-------
Dose level (mg/kg/day):	0	100	300	1,000

Group	Week							
	1	2	3	4	5	6	7	8
C	0	0	0	0	0	0	0	0
T1	0	0	0	0	0	0	0	0
T2	1	1	0	0	0	0	0	0
T3	0	0	0	0	0	0	0	0

Grip strength of males (group)

Group:	C	T1	T2	T3
Test article:	------	Calcium sulfate, dihydrate		-------
Dose level (mg/kg/day):	0	100	300	1,000

Group	No. of animals	Success	Failure
C	5	5	0
T1	5	3	2
T2	5	4	1
T3	5	2	3

Grip strength of females (group)

Group:	C	T1	T2	T3
Test article:	------	Calcium sulfate, dihydrate		-------
Dose level (mg/kg/day):	0	100	300	1,000

Group	No. of animals	Success	Failure
C	5	4	1
T1	5	5	0
T2	5	3	2
T3	5	3	2

Histopathological findings of females (group)

Group:	C	T1	T2	T3
Test article:	-	Calcium sulfate, dihydrate		-
Dose level (mg/kg/day):	0	100	300	1,000
Group	C	T1	T2	T3
No. of animals examined	5	5	5	5
Observation(s)	No. of animals observed			
No significant findings	2	4	4	3
Trachea: submucosal gland proliferation	0	1	1	0
Liver: Mononuclear cell foci, minimal	2	0	0	1
Pancreas: vacuolation, minimal	1	0	0	1
Kidneys: cortical findings	1	0	0	0
No. of animals examined (reproductive organ)	12	12	9	12
Observation(s)	No. of animals observed			
No significant findings	11	11	9	12

Histopathological findings of males (group)

Group:	C	T1	T2	T3
Test article:	-	Calcium sulfate, dihydrate		-
Dose level (mg/kg/day):	0	100	300	1,000
Group	C	T1	T2	T3
No. of animals examined	5	5	5	5
Observation(s)	No. of animals observed			
No significant findings				
Heart: inflammatory cell infiltration, focal, minimal	2	5	5	2
Liver: Mononuclear cell foci, minimal	1	0	0	1
Pancreas: vacuolation, minimal	1	0	1	3
Submandibular lymph node: blood adsirption, minimal	0	0	2	0
Adrenal glands: cortical vacuolation, minimal	1	0	0	0
No. of animals examined (reproductive organ)	1	0	0	0
	11	12	11	12
Observation(s)	No. of animals observed			
No significant findings	11	12	11	12

Blood chemistry of females (group mean)

Treatment (mg/kg/day)	TP g/dL	ALB g/dL	AST IU/L	ALT IU/L	BUN mg/dL	CREA mg/dL	TCHO mg/dL	GLU mg/dL
0	5.6	2.3	137.1	77.2	15.5	1.2	96.0	77.4
100	6.0	2.6	123.4	59.9	18.1	1.1	75.4	92.8
300	5.7	2.4	128.5	65.9	15.4	1.0	91.0	89.6
1,000	5.8	2.4	103.5	59.6	16.6	1.1	84.4	116.6

Blood chemistry of males (group mean)

Treatment (mg/kg/day)	TP g/dL	ALB g/dL	AST IU/L	ALT IU/L	BUN mg/dL	CREA mg/dL	TCHO mg/dL	GLU mg/dL
0	5.7	2.3	177.3	35.4	16.5	0.9	58.2	
100	5.6	2.2	146.1	32.7	12.1	0.8	58.2	
300	4.0	1.5	112.1	22.2	11.6	0.6	42.8	
1,000	3.7	1.5	89.7	23.1	10.6	0.6	33.4	

Hematology of females (group mean)

Treatment (mg/kg/day)	WBC (10^3/mm^3)	RBC (10^6/mm^3)	HGB (g/dl)	HCT	PLT (10^3/mm^3)	Differential count (/100 WBCs)						PT	APTT
						Segs	Eos	Basos	Lymps	Monos	Bands		
0	5.6	7.3	14.1	41.3	1141.6	15.8	0.0	0.0	84.2	0.0	0.0	17.8	23.0
100	7.9	7.4	13.8	40.9	1305.5	18.3	0.0	0.0	81.8	0.0	0.0	17.2	20.8
300	5.5	6.9		37.8	1294.5	17.5	0.0	0.0	82.5	0.0	0.0	15.9	18.6
1,000	4.6	7.3	12.7	40.7	1222.0	19.8	0.0	0.0	80.2	0.0	0.0	17.3	20.0
			13.6										

Hematology of males (group mean)

Treatment (mg/kg/day)	WBC (10^3/mm^3)	RBC (10^6/mm^3)	HGB	HCT	PLT (10^3/mm^3)	Differential count (/100 WBCs)						PT	APTT
						Segs	Eos	Basos	Lymps	Monos	Bands		
0	7.7	8.3	15.2	44.6	836.0	20.8	0.0	0.0	79.2	0.0	0.0	16.4	18.4
100	9.3	8.2	15.1	44.6	835.0	18.2	0.0	0.0	81.8	0.0	0.0	16.8	20.9
300	8.7	8.1		43.7	928.2	21.6	0.0	0.0	78.4	0.0	0.0	16.8	19.2
1,000	9.5	8.4	14.8	45.4	938.0	17.8	0.0	0.0	82.2	0.0	0.0	17.0	20.2
			15.5										

Absolute (sex) organ weights of males (group mean)

Dose (mg/kg)	0	100	300	1,000	(+)	satellite	
						0	1,000
LT Testes (g)	1.680	1.581	1.639	1.657		1.646	1.569
RT Testes (g)	1.684	1.598	1.644	1.630		1.620	1.554
LT Epididymis (g)	0.571	0.544	0.552	0.592		0.621	0.610
RT Epididymis (g)	0.585	0.552	0.562	0.588		0.634	0.641
Liver (g)	10.561	10.248	9.997	10.542		11.123	10.924
Thymus (g)	0.403	0.407	0.409	0.416		0.392	0.418
LT Kidney (g)	1.305	1.304	1.349	1.316		1.241	1.201
RT Kidney (g)	1.345	1.339	1.289	1.310		1.242	1.211
LT Adrenal (g)	0.030	0.029	0.033	0.030		0.031	0.025
RT Adrenal (g)	0.026	0.028	0.030	0.030		0.026	0.025
Spleen (g)	0.818	0.744	0.690	0.755		0.836	0.740
Brain (g)	2.077	2.100	2.121	2.105		2.057	2.050
Heart (g)	1.303	1.282	1.275	1.266		1.322	1.349

Absolute organ weights of females (group mean)

Dose (mg/kg)	0	100	300	1,000	(+)	satellite	
						0	1,000
Liver (g)	8.952	8.062	8.451	8.479		6.097	7.043**
LT kidney (g)	0.885	0.848	0.836	0.818		0.745	0.824*
RT kidney (g)	0.893	0.880	0.813	0.837		0.773	0.825
LT adrenal (g)	0.039	0.037	0.037	0.040		0.033	0.032
RT adrenal (g)	0.039	0.034	0.036	0.040		0.030	0.030
Thymus (g)	0.249	0.319	0.284	0.271		0.321	0.348
Brain (g)	1.930	1.960	1.846	1.905		1.889	1.936
Spleen (g)	0.547	0.506	0.484	0.573		0.512	0.569
Heart (g)	0.996	0.888	0.858	0.884		0.825	0.888

* $p < 0.05$, ** $p < 0.01$, student's t-test

Conclusion : There was no specific opinion about test items such as clinical symptoms, body weight change, food consumption, reflex action, and necropsy, etc. under the influence of test substance. However, in case of male animals, the repeated dose toxicity test of more than 35 days affect at the kidney subtle level, so LOAEL and NOAEL were determined as 300 mg/kg/day and 100 mg/kg/day, respectively. In case of female animals, no effects were observed at the top dose tested.

Reliability : (1) Reliable without restrictions
Flag : Critical study for SIDS endpoint

(17)

5. 5 GENETIC TOXICITY *IN VITRO*

A. BACTERIAL TEST

Type : Bacterial reverse mutation assay

Species/Strain : *Salmonella typhimurium* (strains TA 98, TA 100, TA 1535 and TA 1537) and *Escherichia coli* WP2 *uvr*A

Method : OECD TG 471, 472
System of testing : Bacterial

Year : 2001
GLP : Yes
Metabolic activation : - Species and cell type: Rat (Sprague-Dawley strain), male, liverhomogenate

- Quantity: 5 % v/v S-9 in the S-9 mix

- Induced: Aroclor-1254 induced

Concentrations tested : 12, 37, 111, 333, 1,000 and 3,000 μg/plate

Statistical Methods : Not used

Test substance : Other TS: Calcium sulfate dihydrate, purity = 99.9 %, Sigma-Aldrich Corporation, LOT No. - 06316BO

Test condition : Number of replicates: one
Frequency of dosing: 2 plates/dose
Positive and negative control groups and treatment: Negative control-solvent control (sterile distilled water), positive control: 2-aminoanthracene with S9, Sodium azide, 4-nitroquinoline-1-oxide, 9-aminoacridine
Number of metaphases analyzed: Not analyzed
Solvent: sterile distilled water
Description of follow up repeated study: Preliminary test had carried out to decide the appropriate starting dose level of the main study at the concentration of 1.6, 8, 40, 200, 1,000 and 3,000 μg/plate.
Criteria for evaluating results: the number of revertant colonies in the plate was counted after 2 days incubation at 37 °C.
The direct incorporation method: For test without metabolic activation, the test substance and 0.1 ml of fresh bacterial culture were added to 2.0 ml of overlay agar. For tests with metabolic activation, 0.5 ml of metabolic activation mixture containing an adequate amount of post-mitochondrial fraction was added to the overlay agar after the addition of the bacteria and test substance. All plates in a given test should be incubated for the same time period.

Results :
Cytotoxicity conc With metabolic activation: not observed
Without metabolic activation: not observed
Genotoxic effects With metabolic activation: negative
Without metabolic activation: negative

Result of bacterial reverse mutation assay with calcium sulfate, dihydrate

Tester strain	Chemical treated	Dose (μg/plate)	Colonies/plate (mean)[Factor]	
			Without S-9 mix	With S-9 mix
TA100	Test item	0	132	114
		12	139 [1.0]	115 [1.0]
		37	143 [1.1]	122 [1.1]
		111	125 [0.9]	115 [1.0]
		333	129 [1.0]	125 [1.0]
		1,000	124 [0.9]	106 [1.0]
		3,000	124 [0.9]	115 [1.0]
TA1535	Test item	0	13	10
		12	20 [1.5]	11 [1.1]
		37	22 [1.7]	12 [1.2]
		111	17 [1.3]	13 [1.3]
		333	16 [1.2]	14 [1.4]
		1,000	17 [1.3]	13 [1.3]
		3,000	14 [1.1]	9 [0.9]
TA98	Test item	0	22	34
		12	22 [1.0]	28 [0.8]
		37	21 [0.9]	26 [0.8]
		111	29 [1.3]	37 [1.1]
		333	25 [1.1]	31 [0.9]
		1,000	23 [1.0]	33 [1.0]
		3,000	22 [1.0]	36 [1.0]
TA 1537	Test item	0	15	17
		12	16 [1.0]	17 [1.0]
		37	11 [0.7]	22 [1.3]
		111	15 [1.0]	19 [1.1]
		333	14 [0.9]	17 [1.0]
		1,000	13 [0.9]	16 [0.9]
		3,000	12 [0.8]	16 [0.9]

E.coli WP2 *uvr*A	Test item	0 12 37 111 333 1,000 3,000	8 7 [0.9] 6 [0.8] 8 [1.0] 8 [1.0] 6 [0.8] 6 [0.8]	12 8 [0.7] 13 [1.1] 8 [0.7] 8 [0.7] 9 [0.8] 9 [0.8]
Positive controls				
TA100	SA	0.5	493 [3.7]	
TA1535	SA	0.5	371 [28.5]	
TA98	4NQO	0.5	426 [19.4]	
TA1537	9-AA	50	740 [49.3]	
WP2 *uvr*A	4NQO	0.5	377 [47.1]	
TA100	2-AA	0.4		491 [4.3]
TA1535	2-AA	2		394 [39.4]
TA98	2-AA	0.4	14 [0.6]	289 [8.5]
TA1537	2-AA	2		326 [19.2]
WP2 *uvr*A	2-AA	4		311 [25.9]

[Factor]: No. of colonies of treated plate/No. of colonies of negative control plate
SA: Sodium azide 9-AA: 9-Amino acridine
4NQQ: 4-nitroquinoline-1-oxide 2-AA: 2-aminoanthracene

Conclusion : The mutation in the *Salmonella tryphimurium* (strains TA 98, TA 100, TA 1535, and TA 1537) and in the *Escherchia coli* WP2 *uvr*A did not occur with calcium sulfate, dihydrate
Reliability : (1) Reliable without restrictions
Flag : Critical study for SIDS endpoint

(18)

B. NON-BACTERIAL TEST

5. 6 GENETIC TOXICITY *IN VIVO*

Type : Mammalian erythrocyte micronucleus test

Species/Strains : Mouse/ICR

Sex : Male

Method : OECD TG No.474 “Genetic Toxicity: Micronucleus Test”
- Calcium sulfate, dihydrate was dissolved in 1 % CMC (Sodium carboxymethyl Cellulose) and supersonic wave was used to prepare the highest dose concentration.
- To observe the cell multiplication of bone mallow, a specimen was fixed with methanol. And 4 % Giemsa solution was used for dyeing to observe the ratio of polychromatic erythrocytes. To observe the micronucleus in the polychromatic erythrocytes, 40 μg/ml acridine was dropped for dyeing.

Year : 2002

GLP : Yes

Route of administration : Test substance: oral feed
Positive control: i.p

Dose : 1,250, 2,500 and 5,000 mg/kg b.w

Exposure period	:	24 hours
Statistical methods	:	ANOVA (Using Sigmastat 2.0 statistic programme)
Exposure period	:	24 hours
Doses	:	1,250, 2,500 and 5,000 mg/kg b.w
Test substance	:	Other TS: Calcium sulfate, dihydrate, purity = 99.9 %, Sigma-Aldrich Corporation, LOT No. - 109H0166
Test condition	:	- Age at study initiation: 8 weeks - No. of animals per dose: 6 - Vehicle: 1 % CMC (Sodium Carboxymethyl Cellulose) - Duration of test: 1 day - Frequency of treatment: single treatment - Sampling times and number of samples: 24 hours after administration - Control groups and treatment: Negative control (1 % CMC (Sodium Carboxymethyl Cellulose)), Positive control (0.5 and 1.0 mg/kg of Mitomycin C) - Clinical observations performed: None - Organs examined at necropsy: not examined - Criteria for evaluating results: at least 2,000 polychromatic erythrocytes per animals were scored for the incidence of micronuclei. - Criteria for selection of maximum tolerated dose (M.T.D): preliminary test had conducted with with 1,250, 2,500 and 5,000 mg/kg b.w. to determine appropriate starting dose level.
Results	:	All things being considered, calcium sulfate, dihydrate showed negative result in micronucleus test in vivo up to the test concentration of 5,000 mg/kg b.w.

Effect on mitotic index or PCE/NCE ratio by dose level

Dose (mg/kg)	Group mean (PCE/(PCE+NCE)) (%)	Group mean frequency of MNPCE (per 1,000)
Vehicle	60.49 ± 7.77	6.5
1,250	56.58 ± 9.07	7.0
2,500	54.61 ± 6.13	7.7
5,000	54.48 ± 9.02	8.0
Positive control (0.5mg/kg)	46.58 ± 10.76	19.2
Positive control (1.0mg/kg)	46.96 ± 7.08	44.8

Genotoxic effects	:	Negative - Statistical results: only positive control group showed statistically increased frequency of micronucleated cells.
Conclusion	:	Calcium sulfate, dihydrate showed negative result in the micronucleus test *in vivo* up to the test concentration of 5,000 mg/kg.
Reliability	:	(1) Reliable without restrictions
Flag	:	Critical study for SIDS endpoint

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5. 7 CARCINOGENICITY

5. 8 TOXICITY TO REPRODUCTION

Species/strains	:	Rat (Sprague-Dawley)
Sex	:	Male/Female
Method	:	OECD TG No. 422 “Combined Repeated Dose Toxicity Study with the Reproduction/Developmental Toxicity Screening Test”
Year	:	2002
GLP	:	Yes
Route of administration	:	Oral (Gavage)
Dose level	:	0, 100, 300 and 1,000 mg/kg/day; pre-treatment (Test No. P705) had conducted with 0, 125, 250, 500 and 1,000 mg/kg/day of test substance for 7 days to determine the appropriate starting dose level.
Exposure period	:	35 days for male animals and 41 to 45 days for female animals
Frequency of treatment	:	Daily
Control group	:	Yes (Concurrent no treatment)
Post exposure observation period	:	
Premating exposure period	:	2 weeks
Statistical methods	:	Statistical decision tree, but in case of recovery group, either two-side Student’s t-test or two-side Aspin-Welch t-test was used. In case of categorical data, two-sided Fisher’s exact test was used.
Test substance	:	Other TS: Calcium sulfate, dihydrate, purity = 99.9 %, Sigma-Aldrich Corporation, LOT No. - 109H0166

Test condition	:	Test organism - Sex: male/female - Age of animals at study: 8 weeks old for males and females - Weight at study repeated dose toxicity: 254.2 - 297.8 g for males and 182.7 - 208.2 g for females - Number of test animals: 60 animals for each sex Observation of F0 - *A number of implantation and corpus luteum*: while female animals were necropsied, the number of corpus leteum and implantation were counted; and the former was measured in the ovary and the latter was measured in the uterus. - *Mating*: each male and female animal was selected from the same test group in order to copulate. It spent 4 days in terms of mating. The day after the copulating, mating would be determined through the observation of sperm in a vaginal rinse. - *Pregnancy and delivery*: a period of pregnancy was calculated from mating date (day 0). - *Clinical observations performed and frequency*: Clinical symptoms were observed once a day but were observed once a week in detail; a death rate was observed twice a day; and body weight was observed once a week and just before the necropsy, but in case of pregnant females, it was measured on the day 0, 7, 14, 20 of gestation period, date of delivery, and 4 days after the delivery; consumption rate of fodder was observed once a week except mating period. Observation of F1 - The number of survivors and deaths during delivery - Body weight and Survival rate: measured on the day 0 and 4 after the delivery Organs examined at necropsy: - *Organ weight*: testes, epididymider (all males) liver, kidney, adrenals, thymus, spleen, brain, and heart (5 male and female animals from each test group). - *Fixation*: 22 kinds of tissues were fixed to do histopathologic tests such as testes, epididymides, ovaries, accessory sex organs for all animals, brain (including cerebrum, cerebellum and pons), spinal cord, stomach, small and large intestines (including peyer's patches), liver, kidneys, adrenals, spleen, heart, thymus, thyroid, trachea, lungs, uterus, urinary bladder, lymph nodes (cervical mesenteric), peripheral nerve (sciatic or tibial), bone marrow.
NOAEL parental	:	The highest test dose (1000 mg/kg/day)

Results : Results for F0
- *Pregnancy and delivery*: There was no significant difference between the treatment groups and the control group in terms of delivery and; the number of corpus luteum and implantation. Some animals in the test groups including the control group had quite higher loss rate of the embryo prior to the implantation and the fetus after the implantation but significant difference was not observed between the treatment group and the control group. These higher loss rate were occurred spontaneously and no dose-response correlation, thus no influence under test substance.
- *Index of copulation, fertility and gestation*: Every test group including control group was succeeded in the mating, but each animal from every group was not succeeded in the gestation. However, all pregnant female animals were succeeded in the delivery. Therefore, no significant difference between the treatment group and the control group was found.
- *Clinical signs*: In male control group, a case of salivation and bloody-like secretion was observed on the day 11 and 12. In the 1,000 mg/kg/day treatment group, a case of depilation, dcab and pus was observed on the left cheek between the day 25 and the closing day. However, the frequency of occurrence was low and no dose-response correlation. Thus these symptoms were not influenced by test substance. In female control group, a case of genitalia bloody-like secretion was observed at day 29. In the 100 mg/kg/day treatment group, each case of hypoactivity and depilation was observed on the day 8 and 9, and between day 44 and the closing day, respectively. However, these symptoms were disappeared in short, thus these symptoms did not have relationship with test substance.
- *Necropsy opinions*: For male animals, in the control group within the recovery group, a case of left and right caput epididymis cyst was observed and the 1,000 mg/kg/day recovery group had symptom of right caput epididymis cyst. However, its frequency of occurrence was low and it was even observed at the control group within the recovery group, so it did not have relationship with test substance.
For female animals, in the 300 mg/kg/day treatment group, each animal was dead on the day 7 and 14 and; each case of lung dark-red discolouration was observed, but white particles in a lobe of the lung was observed just from one of carcasses. A case of spleen white nodule was observed for an animal in the 300 mg/kg/day treatment group. There was a case of right adrenal gland white spots at the 1,000 mg/kg/day treatment group. In the control group within the recovery group, each case of right adrenal gland hemorrhagia and atrophy and liver adhesion with diaphragm was observed. However, their frequencies of occurrence were low and no dose-response correlation, so these did not have relationship with test substance.

Results for F1
- *Number of pups born, viability and sex ratio*: No significant difference was observed between the treatment group and the control group at the time of the delivery and on the day 4 after the delivery. There were re-confirmed of sex ratio at the day 7 after the delivery since total 8 cases of sex were decided again. For instance, each 2 cases of mis-confirmation of sex was found at the following three treatment groups such as 100, 300, 1,000 mg/kg/day as their sexes were replaced from male to female; and each case of mis-confirmation of sex was found at the 300 mg/kg/day and 1,000 mg/kg/day, for their sexes were replaced to male.

DOSE: (mg/kg)	0	100	300	1,000
No. of mated males	12	12	10	12
Copulation index (%)	100.0	100.0	100.0	100.0
Fertility index (%)	91.7	91.7	90.0	91.7
No. of mated females	12	12	10	12
Copulation index (%)	100.0	100.0	100.0	100.0
Fertility index (%)	91.7	91.7	90.0	91.7
Gestation index (%)	100.0	100.0	100.0	100.0
No. of corpora lutea	17.2	17.0	17.4	17.2
Mean ± S.D	2.6	3.4	3.5	1.9
No. of implantations	15.1	13.6	15.7	15.4
Mean ± S.D	2.5	4.1	1.9	4.3
Mean % preimplantation loss	11.6	20.2	9.0	10.3
No. of embryo/fetal death	1.5	1.0	0.7	0.7
No. of live pups born	13.5	12.6	15.0	14.6
Mean ± S.D	2.2	4.0	1.8	4.5
Mean pregnancy period (day)	21.8	21.7	22.0	22.0
Viability index on day at birth(%)	99.0	99.4	98.0	100.0
Viability index on day 4 pp (%)	98.0	98.3	97.8	97.6
Body weights of pups (g)				
Male (at birth)	6.49	6.42	6.56	6.55
4 DAY	9.78	9.86	9.70	9.52
Female (at birth)	6.19	6.06	6.23	6.26
4 DAY	9.44	9.13	9.37	8.74

Conclusion : According to the result of reproductctive toxicity test, the NOAEL could be the highest test dose (1,000 mg/kg/day). In addition, the LOAEL was above the highest test dose (> 1,000 mg/kg/day).

Reliability : (1) Reliable without restrictions

Flag : Critical study for SIDS endpoint

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5.9 DEVELOPMENTAL TOXICITY/TERATOGENICITY

Species/strains : Rat (Sprague-Dawley)

Sex : Male/Female

Route of administration : Oral (Gavage)

Method : OECD TG No. 422 “Combined Repeated Dose Toxicity Study with the Reproduction/Developmental Toxicity Screening Test”

Year : 2002

GLP : Yes

Dose level : 0, 100, 300 and 1,000 mg/kg/day; pre-treatment (Test No. P705) had conducted with 0, 125, 250, 500 and 1,000 mg/kg/day of test substance for 7 days to determine the appropriate starting dose level.

Exposure period : 35 days for male animals and 41 to 45 days for female animals

Frequency of treatment : Daily

Control group : Yes
Concurrent no treatment

Post exposure observation period :

Statistical methods	:	Statistical decision tree, but in case of recovery group, either two-side Student's t-test or two-side Aspin-Welch t-test was used. In case of categorical data, two-sided Fisher's exact test was used.
NOAEL for developmental	:	The highest test dose (1,000 mg/kg/day) for male and female animals
Test conditions	:	Test organism - Sex: male/female - Age of animals at study: 8 weeks old for males and females - Weight at study repeated dose toxicity: 254.2 - 297.8 g for males and 182.7 - 208.2 g for females - Number of test animals: 60 animals for each sex Observation of F0 - *Mating procedure*: each male and female animal was selected from the same test group in order to copulate. It spent 4 days in terms of mating. The day after the copulating, mating would be determined through the observation of sperm in a vaginal rinse. - *Clinical observations performed and frequency*: Clinical symptoms were observed once a day but were observed once a week in detail; a death rate was observed twice a day; and body weight was observed once a week and just before the necropsy but in case of pregnant females, it was measured on the day 0, 7, 14, 20 of gestation period, date of delivery, and 4 days after the delivery; consumption rate of fodder was observed once a week except mating period. Organs examined at necropsy: Organ weight: testes, epididymider (all males) liver, kidney, adrenals, thymus, spleen, brain, and heart (5 male and female animals from each test group). Fixation: 22 kinds of tissues were fixed to do histopathologic tests such as testes, epididymides, ovaries, accessory sex organs for all animals, brain (including cerebrum, cerebellum and pons), spinal cord, stomach, small and large intestines (including peyer's patches), liver, kidneys, adrenals, spleen, heart, thymus, thyroid, trachea, lungs, uterus, urinary bladder, lymph nodes (cervical mesenteric), peripheral nerve (sciatic or tibial), bone marrow.
Test substance	:	Other TS: Calcium sulfate, dihydrate, purity = 99.9 %, Sigma-Aldrich Corporation, LOT No. - 109H0166
Results	:	Results for F0 - *Pregnancy and delivery*: There was no significant difference between the treatment and the control group in terms of delivery and; the number of corpus luteum and implantation. Some test groups including the control group had quite higher loss rate of the embryo prior to the implantation and the fetus after the implantation but significant difference was not observed between the treatment and the control group. These higher loss rate were occurred spontaneously and no dose-response correlation. Thus no influence under test substance. In addition, there were no premature pups. - *Clinical signs*: In male control group, a case of salivation and bloody-like secretion was observed on the day 11 and 12. In the 1,000 mg/kg/day treatment group, a case of depilation, dcab and pus was observed on the left cheek between the day 25 and the closing day. However, the frequency of occurrence was low and no dose-response correlation, thus these symptoms were not influenced by test substance. In female control group, a case of genitalia bloody-like secretion was observed at day 29. In the 100 mg/kg/day treatment group, each case of hypoactivity and depilation was observed on the day 8 and 9, and between day 44 and the closing day, respectively. However, these symptoms were disappeared in short, thus these did not have relationship with test substance.

- *Necropsy opinions*: For male animals, in the control group within the recovery group, a case of left and right caput epididymis cyst was observed and the 1,000 mg/kg/day recovery group had symptom of right caput epididymis cyst. However, its frequency of occurrence was low and it was even observed at the control group within the recovery group, so it did not have relationship with test substance.
For female animals, in the 300 mg/kg/day treatment group, each animal was dead on the day 7 and 14 and; each case of lung dark-red discolouration was observed, but white particles in a lobe of the lung was observed just from one of carcasses. A case of spleen white nodule was observed for an animal in the 300 mg/kg/day treatment group. There was a case of right adrenal gland white spots at the 1,000 mg/kg/day treatment group. In the control group within the recovery group, each case of right adrenal gland hemorrhagia and atrophy and liver adhesion with diaphragm was observed. However, their frequencies of occurrence were low and no dose-response correlation, so these did not have relationship with test substance.

Results for F1
- *Examination of the external surface of pups*: At the time of the delivery and on the day 4, in the every test group including the control group, no observation in relation to runt, malformation, and variance was found. A case of malrotated limb was observed at the 1,000 mg/kg/gay treatment group but its frequency was insignificant and no relation with test substance.
- *Body weight of pups*: In the male pups, total 3 cases of underweight were observed from the control group and the treatment group with administration of 100 mg/kg/day, but no significant difference was found between the two. On the day 4 after the delivery, in the nursing pups, 1, 1, 2 cases of underweight were observed for the control group, the 100 mg/kg/day treatment group and the 1,000 mg/kg/day treatment group, respectively, and no significant differences was found between the control group and the treatment group.
In the female pups, total 6 cases of underweight were observed from the following three groups such as the control group, the 100 mg/kg/day treatment group and the 1,000 mg/kg/day treatment group. On the day 4 after the delivery, in the nursing pups, 1, 2, 3 cases of underweight were observed for the control group, the 100 mg/kg/day treatment group and the 1,000 mg/kg/day treatment group, respectively. In addition, the both 100 mg/kg/day and 1,000 mg/kg/day treatment groups had lower body weight than that of the control group. However, their weights were in the normal range of pups.

Reliability : (1) Reliable without restrictions

Flag : Critical study for SIDS endpoint

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5.10 OTHER RELEVANT INFORMATION

A. Specific toxicities

B. Toxicodynamics, toxicokinetics

5.11 EXPERIENCE WITH HUMAN EXPOSURE

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