Calcium Carbonate (CAS# 471-34-1) GreenScreen® for Safer Chemicals (GreenScreen®) Assessment

Prepared for:

Lauren Heine Group

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TOXSERVICES
TOXICOLOGY RISK ASSESSMENT CONSULTING
1367 Connecticut Ave., N.W., Suite 300
Washington, D.C. 20036

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GreenScreen® Executive Summary for Calcium Carbonate (CAS #471-34-1)

Calcium carbonate is a chemical that functions as a nutrient supplement, pH control/buffering agent, anti-caking agent, stabilizer and thickener, and is used in the production of paint, adhesives, plastics, paper, rubber, textiles, inks, and chalk.

Calcium carbonate was assigned a **GreenScreen Benchmark™ Score of 3** ("Use but Still Opportunity for Improvement"). This score is based on the following hazard score:

- Benchmark 3c
    - Moderate Group II Human Toxicity (single dose systemic toxicity (STs))

Data gaps (DG) exist for endocrine activity (E) and respiratory sensitization (SnR*). As outlined in CPA (2013) Section 12.2 (Step 8 – Conduct a Data Gap Analysis to assign a final Benchmark score), calcium carbonate meets requirements for a GreenScreen® Benchmark Score of 3 despite the hazard data gaps. In a worst-case scenario, if calcium carbonate were assigned a High score for the data gaps endocrine activity (E) or respiratory sensitization (SnR*), it would be categorized as a Benchmark 1 Chemical.

GreenScreen® Benchmark Score for Relevant Route of Exposure:
As a standard approach for GreenScreen® evaluations, all exposure routes (oral, dermal and inhalation) were evaluated together, so the GreenScreen® Benchmark Score of 3 ("Use but Still Opportunity for Improvement") is applicable for all routes of exposure.

GreenScreen® Hazard Ratings for Calcium Carbonate

Group I Human					Group II and II* Human									Ecotox		Fate		Physical	
C	M	R	D	E	AT	ST		N		SnS*	SnR*	IrS	IrE	AA	CA	P	B	Rx	F
						single	repeated*	single	repeated*										
L	**L**	**L**	**L**	DG	**L**	*M*	**L**	**L**	**L**	**L**	DG	**L**	**L**	**L**	**L**	*vH*	*L*	*L*	**L**

Note: Hazard levels (Very High (vH), High (H), Moderate (M), Low (L), Very Low (vL)) in *italics* reflect estimated (modeled) values, authoritative B lists, screening lists, weak analogues, and lower confidence. Hazard levels in **BOLD** font are used with good quality data, authoritative A lists, or strong analogues. Group II Human Health endpoints differ from Group II* Human Health endpoints in that they have four hazard scores (i.e., vH, H, M, and L) instead of three (i.e., H, M, and L), and are based on single exposures instead of repeated exposures. Please see Appendix A for a glossary of hazard acronyms.

GreenScreen® Assessment for Calcium Carbonate (CAS #471-34-1)

Method Version: GreenScreen® Version 1.2[1]
Assessment Type[2]: Certified

Chemical Name: Calcium Carbonate

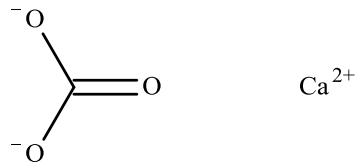
CAS Number: 471-34-1

GreenScreen® Assessment Prepared By:
Name: Zach Guerrette, Ph.D.
Title: Toxicologist
Organization: ToxServices LLC
Date: June 19, 2015
Assessor Type: Licensed GreenScreen® Profiler

Quality Control Performed By:
Name: Bingxuan Wang, Ph.D.
Title: Toxicologist
Organization: ToxServices LLC
Date: June 23, 2015

Confirm application of the *de minimus* rule[3]: N/A

Chemical Structure(s):



Also called:
Carbonic acid, calcium salt (1:1); CI 77220; Pigment white 18; Precipitated calcium carbonate; Precipitated chalk; C.I. Pigment White 18; Calcium monocarbonate; Carbonic acid calcium salt (1:1); EINECS 207-439-9; Levigated chalk; Marble white; Monocalcium carbonate; Carbonic acid calcium salt (1:1) (ChemIDplus 2015)

Identify Applications/Functional Uses (HSDB 2014)**:**
1. Nutrient supplement
2. pH control/buffering agent
3. Anti-caking agent
4. Stabilizer and thickener
5. Used in the production of paint, adhesives, plastics, paper, rubber, textiles, inks, and chalk

[1] Use GreenScreen® Assessment Procedure (Guidance) V1.2
[2] GreenScreen® reports are either "UNACCREDITED" (by unaccredited person), "AUTHORIZED" (by Authorized GreenScreen® Practitioner), "CERTIFIED" (by Licensed GreenScreen® Profiler or equivalent) or "CERTIFIED WITH VERIFICATION" (Certified or Authorized assessment that has passed GreenScreen® Verification Program)
[3] Every chemical in a material or formulation should be assessed if it is:
1. intentionally added and/or
2. present at greater than or equal to 100 ppm

GreenScreen® Summary Rating for Calcium Carbonate[4]:

Calcium carbonate was assigned a **GreenScreen Benchmark™ Score of 3** ("Use but Still Opportunity for Improvement") (CPA 2014). This score is based on the following hazard score:

- Benchmark 3c
    - Moderate Group II Human Toxicity (single dose systemic toxicity (STs))

Data gaps (DG) exist for endocrine activity (E) and respiratory sensitization (SnR*). As outlined in CPA Section 12.2 (Step 8 – Conduct a Data Gap Analysis to assign a final Benchmark score), calcium carbonate meets requirements for a GreenScreen® Benchmark Score of 3 despite the hazard data gaps. In a worst-case scenario, if calcium carbonate were assigned a High score for the data gaps endocrine activity (E) or respiratory sensitization (SnR*), it would be categorized as a Benchmark 1 Chemical.

Figure 1: GreenScreen® Hazard Ratings for Calcium Carbonate

Group I Human					Group II and II* Human									Ecotox		Fate		Physical	
C	M	R	D	E	AT	ST		N		SnS*	SnR*	IrS	IrE	AA	CA	P	B	Rx	F
						single	repeated*	single	repeated*										
L	L	L	L	DG	L	*M*	L	L	L	L	DG	L	L	L	L	*vH*	*L*	*L*	L

Note: Hazard levels (Very High (vH), High (H), Moderate (M), Low (L), Very Low (vL)) in *italics* reflect estimated (modeled) values, authoritative B lists, screening lists, weak analogues, and lower confidence. Hazard levels in **BOLD** font are used with good quality data, authoritative A lists, or strong analogues. Group II Human Health endpoints differ from Group II* Human Health endpoints in that they have four hazard scores (i.e., vH, H, M, and L) instead of three (i.e., H, M, and L), and are based on single exposures instead of repeated exposures. Please see Appendix A for a glossary of hazard acronyms.

Transformation Products and Ratings:

Identify feasible and relevant fate and transformation products (i.e., dissociation products, transformation products, valence states) **and/or moieties of concern**[5]

No transformation products were identified for calcium carbonate. Calcium carbonate is an inorganic chemical that does not undergo biodegradation. Calcium carbonate is the major component of limestone and marble. In the natural environment, carbonate stone weathering can occur slowly in slightly acidic environment, which can be accelerated by acidic rain. This process causes calcium carbonate to convert to calcium ion and carbon dioxide gas (USGS 1998). As weathering is a natural process and the transformation products produced are naturally occurring in the environment, ToxServices did not consider them relevant to this evaluation. Therefore, the Benchmark Score for calcium carbonate was not modified by transformation products.

Introduction

Calcium carbonate is used as a nutrient supplement, pH control/buffering agent, anti-caking agent, stabilizer and thickener, and used in the production of paint, adhesives, plastics, paper, rubber, textiles, inks, and chalk (HSDB 2014). It is produced via the reaction of calcium chloride and

[4] For inorganic chemicals with low human and ecotoxicity across all hazard endpoints and low bioaccumulation potential, persistence alone will not be deemed problematic. Inorganic chemicals that are only persistent will be evaluated under the criteria for Benchmark 4.

[5] A moiety is a discrete chemical entity that is a constituent part or component of a substance. A moiety of concern is often the parent substance itself for organic compounds. For inorganic compounds, the moiety of concern is typically a dissociated component of the substance or a transformation product.

sodium or ammonium carbonate or refined from deposits of limestone, marble, or chalk (HSDB 2014). Calcium carbonate is listed as Generally Recognized As Safe (GRAS) by the U.S. FDA (2013).

ToxServices assessed calcium carbonate against GreenScreen® Version 1.2 (CPA 2013) following procedures outlined in ToxServices' SOP 1.37 (GreenScreen® Hazard Assessment) (ToxServices 2013).

GreenScreen® List Translator Screening Results

The GreenScreen® List Translator identifies specific authoritative or screening lists that should be searched to identify GreenScreen® benchmark 1 chemicals (CPA 2012a). Pharos (Pharos 2015) is an online list-searching tool that is used to screen chemicals against the List Translator electronically. The output indicates benchmark or possible benchmark scores for each human health and environmental endpoint. The output for calcium carbonate can be found in Appendix C~~B~~ and a summary of the results can be found below:

- Medium Hazard
  - Eye Irritation
    - GHS New Zealand Category 6.4A (GHS Category 2) – Irritating to the eye.

Physiochemical Properties of Calcium Carbonate

Calcium carbonate is a white powder under standard temperature and pressure. It is slightly soluble in water. It is not expected to be volatile as an inorganic solid. A partition coefficient is not applicable to inorganic compounds. Calcium carbonate can be bioavailable through the GI tract.

Table 1: Physical and Chemical Properties of Calcium Carbonate (CAS #471-34-1)

Property	Value	Reference
Molecular formula	C-H2-O3.Ca	ChemIDplus 2015
SMILES Notation	C(=O)([O-])[O-].[Ca+2]	ChemIDplus 2015
Molecular weight	100.086 g/mol	ChemIDplus 2015
Physical state	Solid	ECHA 2015
Appearance	White powder	ECHA 2015
Melting point	825-1,339°C	ECHA 2015
Vapor pressure	Not identified	
Water solubility	16.6 mg/L at 20°C (OECD 105) Practically insoluble in water	ECHA 2015 HSDB 2014~~5~~
Dissociation constant	Not identified	
Density/specific gravity	Specific gravity = 2.70-2.95 at 20°C	ECHA 2015
Partition coefficient	Not identified	
Particle size	D50 = Less than 1.8 µm	ECHA 2015
Structure	Crystalline	HSDB 2014
Bioavailability	Usually ~10% via the GI tract but can vary depending on amount of gastric acid and the presence of other anions such as sulfates, phytates, and oxalates	HSDB 2014

Hazard Classification Summary Section:

Group I Human Health Effects (Group I Human)

Carcinogenicity (C) Score (H, M, or L): L

Calcium carbonate was assigned a score of Low for carcinogenicity based on ToxServices not classifying it as a carcinogen under GHS criteria. GreenScreen® criteria classify chemicals as a Low hazard for carcinogenicity when negative data, no structural alerts, and no GHS classification are available (CPA 2012b).

- Authoritative and Screening Lists
  - *Authoritative:* Not listed on any authoritative lists for this endpoint.
  - *Screening:* Not listed on any screening lists for this endpoint.
- Quillot et al. 1999
  - Female Wistar rats were randomly assigned to one of four groups and maintained on an 8% lipid diet for an adaptation period of four weeks. All groups were then fed a 24% lipid diet (sunflower oil), with (Groups 2 and 4) or without (Groups 1 and 3) a 1.5% calcium carbonate supplement. They were intra-rectally instilled with saline (Groups 1 and 2) or nitrosomethylurea (NMU) (Groups 3 and 4). Fecal sterol output and pH were analyzed for one week each month. Histological analysis was done at the end of the 32-week experiment. No tumors were found in the non-NMU-treated animals. The NMU-treated rats had tumors: 31% in Group 3 and 30% in Group 4. The calcium carbonate supplement had no effect on the incidence of tumors.
- Ehrnström et al. 2006
  - Wistar rats, 92 with gastric resections (surgical removal of part of the stomach; performed to induce spontaneous gastric cancer) and 60 without resections (controls), were used to assess the carcinogenic potential of different ion supplements in food. Among the resected rats, tumors were observed in 3/18 (17%, not significant (NS)) administered sodium chloride, but in 11/18 (61%, $p < 0.01$) exposed to calcium carbonate. No tumors were observed in the un-resected (un-operated) animals. These findings were further analyzed by separately investigating the effects of calcium and carbonate ions on tumorigenesis in the gastric stump model. Cancer developed in 1/26 (4%) resected animals given a diet supplemented with CaHPO4, which was lower than the rate observed in the resected control group fed a normal diet, although this difference was not statistically significant. However, the tumor incidence increased significantly in the resected animals provided diets supplemented with NaHCO3 (tumors in 13/24 rats, 54%; $p < 0.01$). These results identified a significant role for carbonate in the induction of gastric carcinoma in the rat. The relevance of this finding is supported by the fact that carbonate is a major constituent of intestinal reflux into the stomach, which is considered to be one of the major causes of gastric cancer.
- Pence et al. 1995
  - In a 49 week tumor inhibition study using male F344 rats, the incidence and multiplicity of colon adenomas was evaluated. Azoxymethane, a known carcinogen, was injected subcutaneously at a dose of 12 mg/kg for two doses. Cholic acid was administered orally as a promoter at a concentration of 5% in the diet, beginning one week following the last carcinogen dose and lasting for the duration of the study. Limestone (calcium carbonate) was administered at a concentration of 0% and 2% in the diet for 13 weeks, beginning 36 weeks after the last carcinogen dose. Although not significant, limestone caused a

decrease in the incidence of colon adenomas from 89% to 81%. However, the multiplicity of tumors decreased significantly (p-value <0.05) from 2.6 to 1.5

- Komatsu et al. 1991
    - Male Wistar rats were provided drinking water containing N-methyl-N'-nitro-N-nitrosoguanidine (MNNG) at 100 mg/L and a diet containing no additional treatment (basal diet), 10% sodium chloride, 10% sodium chloride and 2.5% calcium carbonate, 10% sodium chloride and 7.5% calcium carbonate, or 7.5% calcium carbonate for 20 weeks. No differences in the incidence of glandular stomach tumors were observed between the groups administered the basal diet and the 7.5% calcium carbonate diet at the 40th week of the study. The study authors concluded that calcium carbonate did not exhibit anti-carcinogenic effects on gastroduodenal carcinogenesis.
- In summary, three of the four studies summarized above did not identify an increase in tumor incidence following oral exposure to calcium carbonate. In the final study, dietary calcium carbonate exposure led to an increase in the incidence of gastric cancers in resected rats but not in un-resected rats. As gastric resection is a drastic surgical procedure, ToxServices concluded that calcium carbonate is not likely to be carcinogenic in normal, healthy animals. Therefore, ToxServices did not classify calcium carbonate as a carcinogen under GHS criteria (UN 2013).

Mutagenicity/Genotoxicity (M) Score (H, M, or L): L

Calcium carbonate was assigned a score of Low for mutagenicity/genotoxicity based on negative results for mutagenicity and clastogenicity in *in vitro* tests. GreenScreen® criteria classify chemicals as a Low hazard for mutagenicity/genotoxicity when negative data for mutagenicity and clastogenicity, no structural alerts, and no GHS classification are available (CPA 2012b).

- Authoritative and Screening Lists
    - *Authoritative:* Not listed on any authoritative lists for this endpoint.
    - *Screening:* Not listed on any screening lists for this endpoint.
- ECHA 2015
    - *In vitro* – Negative results for clastogenicity were obtained in a GLP-compliant mammalian chromosome aberration test conducted according to OECD 473. Human lymphocytes were exposed to calcium carbonate (98.5% purity) at 31.25-1,000 µg/mL, with and without metabolic activation. No treatment-related increase in the incidence of chromosome aberrations was observed in the presence or absence of metabolic activation.
    - *In vitro* – Negative results for mutagenicity were obtained in a GLP-compliant bacterial reverse mutation assay conducted according to OECD 471. *Salmonella typhimurium* test strains TA 98, TA 100, TA 1535, and TA 1537 and *Escherichia coli* WP2 uvr A were exposed to calcium carbonate (98.5% purity) at 50-5,000 µg/plate, with and without metabolic activation. No increase in mutation frequency was observed with treatment in the presence or absence of metabolic activation.
    - *In vitro* – Negative results for mutagenicity were obtained in a GLP-compliant mammalian cell gene mutation test conducted according to OECD 476. Mouse lymphoma L5178Y cells were exposed to calcium carbonate (98.5% purity) at 7.81-250 µg/mL, with and without metabolic activation. Mutation frequency was not increased with treatment in the presence or absence of metabolic activation.

Reproductive Toxicity (R) Score (H, M, or L): L

Calcium carbonate was assigned a score of Low for reproductive toxicity based on the lack of effects observed on reproduction in animals administered oral doses of calcium carbonate. GreenScreen®

criteria classify chemicals as a Low hazard for reproductive toxicity when negative data, no structural alerts, and no GHS classification are available (CPA 2012b).

- Authoritative and Screening Lists
  - *Authoritative:* Not listed on any authoritative lists for this endpoint.
  - *Screening:* Not listed on any screening lists for this endpoint.
- HSDB 2014
  - Rats fed up to 1.25% dietary calcium carbonate for 6 weeks prior to mating and during gestation and found no adverse effects. No further details for this study were provided.
- ECHA 2015
  - A GLP-compliant combined repeated dose toxicity study with reproduction/developmental toxicity screening test conducted according to OECD 422 was performed with Wistar rats (10/sex/dose group) administered oral doses of calcium carbonate (98.5% purity) at 0, 100, 300, or 1,000 mg/kg/day in water via gavage for up to 48 consecutive days consisting of a two-week maturation phase, pairing, gestation, and early lactation for females. The reproductive endpoints evaluated as part of the study included fertility index, mating index, gestation length, parturition index, offspring viability index, implantation losses, sex ratio, live birth index, and sex organ weights. No treatment-related effects were observed on any of these parameters and the study authors identified a reproductive NOAEL of 1,000 mg/kg/day.

Developmental Toxicity incl. Developmental Neurotoxicity (D) Score (H, M, or L): L
Calcium carbonate was assigned a score of Low for developmental toxicity based on negative results for teratogenicity and embryotoxicity identified in developmental toxicity tests. GreenScreen® criteria classify chemicals as a Low hazard for developmental toxicity when negative data, no structural alerts, and no GHS classification are available (CPA 2012b).

- Authoritative and Screening Lists
  - *Authoritative:* Not listed on any authoritative lists for this endpoint.
  - *Screening:* Not listed on any screening lists for this endpoint.
- ECHA 2015
  - A prenatal developmental toxicity study conducted according to OECD 414 with minor deviations was performed with female CD/VAF Charles River rats (45-48 pregnant rats) administered oral doses of calcium carbonate (98.62% purity) via diets containing 0.50 (control), 0.75, 1.00, or 1.25% calcium for 6 weeks prior to mating, through mating, and until gestational day 20. On gestational day 20, the animals were sacrificed and the ovaries and uterine content were examined and the fetuses evaluated for the incidence of abnormalities. No maternal toxicity or developmental toxicity was observed during the study. The study authors identified a NOAEL of 1.25% calcium in the diet based on the lack of developmental toxicity observed in this study.
  - A GLP-compliant combined repeated dose toxicity study with reproduction/developmental toxicity screening test conducted according to OECD 422 was performed with Wistar rats (10/sex/dose group) administered oral doses of calcium carbonate (98.5% purity) at 0, 100, 300, or 1,000 mg/kg/day in water via gavage for up to 48 consecutive days consisting of a two-week maturation phase, pairing, gestation, and early lactation for females. Developmental endpoints evaluated included examination of the number or corpora lutea and implantations following sacrifice of the maternal rats and evaluation of the pup body weight, litter size, and the pup surface righting reflex. No treatment-related effects were observed on any of the developmental parameters and the study authors identified a developmental NOAEL of 1,000 mg/kg/day.

Endocrine Activity (E) Score (H, M, or L): DG
Calcium carbonate was assigned a score of Data Gap for endocrine activity based on the lack of data identified for this endpoint.

- Authoritative and Screening Lists
  - *Authoritative:* Not listed on any authoritative lists for this endpoint.
  - *Screening:* Not listed on any screening lists for this endpoint.
- Not listed as a potential endocrine disruptor on the EU Priority List of Suspected Endocrine Disruptors.
- Not listed as a potential endocrine disruptor on the OSPAR List of Chemicals of Possible Concern.
- No data were identified for this endpoint.

Group II and II* Human Health Effects (Group II and II* Human)
Note: Group II and Group II* endpoints are distinguished in the v 1.2 Benchmark system. For Systemic Toxicity and Neurotoxicity, Group II and II* are considered sub-endpoints and test data for single or repeated exposures may be used. If data exist for single OR repeated exposures, then the endpoint is not considered a data gap. If data are available for both single and repeated exposures, then the more conservative value is used.

Acute Mammalian Toxicity (AT) Group II Score (vH, H, M, or L): L
Calcium carbonate was assigned a score of Low for acute toxicity based on oral and dermal LD_{50} values greater than 2,000 mg/kg and a 4-hour LC_{50} value greater than the air saturation concentration. GreenScreen® criteria classify chemicals as a Low hazard for acute toxicity when oral and dermal LD_{50} values are greater than 2,000 mg/kg and inhalation LC_{50} values are greater than the air saturation concentration (CPA 2012b).

- Authoritative and Screening Lists
  - *Authoritative:* Not listed on any authoritative lists for this endpoint.
  - *Screening:* Not listed on any screening lists for this endpoint.
- EC 2000
  - *Oral*: LD_{50} (rat) = 6,450 mg/kg
  - *Oral*: LD_{50} (mouse) = 6,450 mg/kg
  - *Inhalation*: An LC_0 of 0.0812 mg/L was determined in male rats after 90 minutes. There was no effect on lung weight, macrophage concentration, or histopathology; however, a marginal increase in phospholipids in lung lavage was seen after 21 hours.
- ECHA 2015
  - *Oral*: LD_{50} (female Sprague-Dawley rats) = greater than 2,000 mg/kg (GLP-compliant, OECD 420)
  - *Dermal*: LD_{50} (Wistar rats) = greater than 2,000 mg/kg (GLP-compliant, OECD 402)
  - *Inhalation*: 4-hour aerosol LC_{50} (Wistar rats) = greater than 3.0 mg/L (97.9% purity; GLP-compliant, OECD 403). The target aerosol concentration was 5 mg/L, which could not be technically achieved.

Systemic Toxicity/Organ Effects incl. Immunotoxicity (ST)
***Group II Score (single dose)* (vH, H, M, or L):** *M*
Calcium carbonate was assigned a score of Moderate for systemic toxicity (single dose) based on the lack of systemic toxicity observed in the acute toxicity tests and limited evidence indicating respiratory irritation. GreenScreen® criteria classify chemicals as a Moderate hazard for systemic toxicity (single dose) when they can be classified to GHS category 3 (respiratory irritation) (CPA

2012b). The confidence in the score was adjusted due to lack of sufficient data on respiratory irritation effects.

- Authoritative and Screening Lists
  - *Authoritative:* Not listed on any authoritative lists for this endpoint.
  - *Screening:* Not listed on any screening lists for this endpoint.
- ECHA 2015
  - *Oral*: In the acute toxicity study resulting in an LD_{50} value greater than 2,000 mg/kg, no clinical signs of toxicity, changes in body weight, or abnormalities at necropsy were observed.
  - *Dermal*: In the acute dermal study that identified a dermal LD_{50} value of greater than 2,000 mg/kg, no clinical signs of toxicity, dermal irritation, or abnormalities at necropsy were observed. Expected body weight gains were observed but were not of toxicological significance.
  - *Inhalation*: In the acute inhalation toxicity study that identified a 4-hour LC_{50} value greater than 3.0 mg/L, clinical signs of toxicity were limited to ruffled fur for all animals beginning at one hour following exposure but the animals recovered by day 5 of the observation period.
- HSDB 2014
  - Acute exposure to calcium carbonate can cause irritation to the eyes and the respiratory tract.

Group II* Score (repeated dose) **(H, M, or L): L**

Calcium carbonate was assigned a score of Low for systemic toxicity (repeated dose) based on ToxServices not classifying it as a repeated dose toxicant under GHS criteria. GreenScreen® criteria classify chemicals as a Low hazard for systemic toxicity (repeated dose) when negative data, no structural alerts, and no GHS classification are available (CPA 2012b).

- Authoritative and Screening Lists
  - *Authoritative:* Not listed on any authoritative lists for this endpoint.
  - *Screening:* Not listed on any screening lists for this endpoint.
- ECHA 2015
  - *Oral*: A GLP-compliant combined repeated dose toxicity study with reproduction/developmental toxicity screening test conducted according to OECD 422 was performed with Wistar rats (10/sex/dose group) administered oral doses of calcium carbonate (98.5% purity) at 0, 100, 300, or 1,000 mg/kg/day in water via gavage for up to 48 consecutive days consisting of a two-week maturation phase, pairing, gestation, and early lactation for females. The rats were evaluated for clinical signs of toxicity, food and water consumption, hematology, clinical chemistry, neurobehavior, organ weights, gross pathology, and histopathology. No treatment-related effects were observed on any of these parameters and the study authors identified a NOAEL of 1,000 mg/kg/day.
    - Based on a study duration of up to 48 days, ToxServices adjusted the guidance values of 10 and 100 mg/kg/day by a factor of 2 (48 days is approximately half of 90 days) to 20 and 200 mg/kg/day, respectively (UN 2013). As the NOAEL of 1,000 mg/kg/day is greater than the adjusted guidance value of 200 mg/kg/day, ToxServices did not classify calcium carbonate as a repeated dose toxicant under GHS criteria.
  - *Oral*: A 28-day oral repeat dose study conducted according to OECD 407 was performed with ICR mice (8/sex/dose group) administered oral doses of calcium carbonate at 0, 13, 130, or 1,300 mg/kg/day in water via gavage for 28 days. The mice were evaluated for

clinical signs of toxicity, body weight, and gross pathology. No treatment-related effects were observed on these three parameters and the study authors identified a NOAEL of 1,300 mg/kg/day.
    - Based on a study duration of 28 days, ToxServices adjusted the guidance values of 10 and 100 mg/kg/day by a factor of 3 (28 days is approximately one-third of 90 days) to 30 and 300 mg/kg/day, respectively (UN 2013). As the NOAEL of 1,300 mg/kg/day is greater than the adjusted guidance value of 300 mg/kg/day, ToxServices did not classify calcium carbonate as a repeated dose toxicant under GHS criteria.
  - *Oral*: A GLP-compliant 14-day repeat dose study was performed with Wistar rats (3/sex/dose group) administered oral doses of calcium carbonate (98.5% purity) at 0, 250, 500, or 1,000 mg/kg/day in water via gavage for 14 days. The rats were evaluated for clinical signs of toxicity, body weight, body weight gain, food and water consumption, and gross pathology. No treatment-related effects were observed on these parameters and the study authors identified a NOAEL of 1,000 mg/kg/day.
- In summary, ToxServices did not classify calcium carbonate as a repeated dose toxicant under GHS criteria based on the results of the 28-day study or the combined repeated dose toxicity study with reproduction/developmental toxicity screening test. ToxServices did not evaluate the results of the 14-day study in relation to the GHS criteria due to its short duration but included the results here for dataset completeness.

Neurotoxicity (N)

***Group II Score (single dose)* (vH, H, M, or L): L**

Calcium carbonate was assigned a score of Low for neurotoxicity (single dose) based on the lack of behavioral changes observed in acute toxicity studies. GreenScreen® criteria classify chemicals as a Low hazard for neurotoxicity (single dose) when negative data, no structural alerts, and no GHS classification are available (CPA 2012b).

- Authoritative and Screening Lists
  - *Authoritative:* Not listed on any authoritative lists for this endpoint.
  - *Screening:* Not listed on any screening lists for this endpoint.
- Not classified as a developmental neurotoxicant (Grandjean and Landrigan 2006).
- ECHA 2015
  - *Oral*: In the acute toxicity study resulting in an LD_{50} value greater than 2,000 mg/kg, no clinical signs of toxicity, no behavioral changes were observed with treatment.
  - *Dermal*: In the acute dermal study that identified a dermal LD_{50} value of greater than 2,000 mg/kg, no behavioral changes were observed with treatment.
  - *Inhalation*: In the acute inhalation toxicity study that identified a 4-hour LC_{50} value greater than 3.0 mg/L, no behavioral changes were observed with treatment.

***Group II* Score (repeated dose)* (H, M, or L): L**

Calcium carbonate was assigned a score of Low for neurotoxicity (repeated dose) based on the lack of neurotoxicity observed in a combined repeated dose toxicity study with reproduction/developmental toxicity screening test. GreenScreen® criteria classify chemicals as a Low hazard for neurotoxicity (repeated dose) when negative data, no structural alerts, and no GHS classification are available (CPA 2012a).

- Authoritative and Screening Lists
  - *Authoritative:* Not listed on any authoritative lists for this endpoint.
  - *Screening:* Not listed on any screening lists for this endpoint.

- Not classified as a developmental neurotoxicant (Grandjean and Landrigan 2006, 2014).
- ECHA 2015
    - In the GLP-compliant combined repeated dose toxicity study with reproduction/developmental toxicity screening test conducted according to OECD 422 summarized in the oral toxicity section, Wistar rats (10/sex/dose group) administered oral doses of calcium carbonate (98.5% purity) at 0, 100, 300, or 1,000 mg/kg/day in water via gavage for up to 48 consecutive days. The rats were evaluated for neurobehavioral effects using functional performance tests evaluating sensory reactivity (grasp response, touch escape, vocalization, pupil reflex, toe pinch, blink reflex, tail pinch, startle reflex, finger approach) grip strength, and motor activity. No treatment-related effects were observed in the functional performance tests. ToxServices identified a neurobehavioral NOAEL of 1,000 mg/kg/day based on the negative neurobehavioral data.
        - Based on a study duration of up to 48 days, ToxServices adjusted the guidance values of 10 and 100 mg/kg/day by a factor of 2 (48 days is approximately half of 90 days) to 20 and 200 mg/kg/day, respectively (UN 2013). As the NOAEL of 1,000 mg/kg/day is greater than the adjusted guidance value of 200 mg/kg/day, ToxServices did not classify calcium carbonate as a repeated dose toxicant under GHS criteria.

Skin Sensitization (SnS) Group II* Score (H, M, or L): L
Calcium carbonate was assigned a score of Low for skin sensitization based on negative results in a mouse local lymph node assay. GreenScreen® criteria classify chemicals as a Low hazard for skin sensitization when negative data, no structural alerts, and no GHS classification are available (CPA 2012b).

- Authoritative and Screening Lists
    - *Authoritative:* Not listed on any authoritative lists for this endpoint.
    - *Screening:* Not listed on any screening lists for this endpoint.
- ECHA 2015
    - In a GLP-compliant mouse local lymph node assay conducted according to OECD 429, female CBA/Ca (CBA/CaOlaHsd) mice (4/dose group) were administered dermal exposures to nano calcium carbonate at 5, 10, or 25% w/w in dimethylformamide. The mice were administered 25 µL of the test substance to the dorsal surface of each ear for 3 consecutive days. Following the final application, the animals were sacrificed and the lymph nodes isolated to perform the proliferation assay. The stimulation indices for the 5, 10, and 25% doses were 1.74, 1.13, and 1.9, respectively. As all of the stimulation indices for the applied doses were less than 3, calcium carbonate was not sensitizing to the skin of mice in this study.

Respiratory Sensitization (SnR) Group II* Score (H, M, or L): DG
Calcium carbonate was assigned a score of Data Gap for respiratory sensitization based on the lack of data identified for this endpoint.

- Authoritative and Screening Lists
    - *Authoritative:* Not listed on any authoritative lists for this endpoint.
    - *Screening:* Not listed on any screening lists for this endpoint.
- No data were identified for this endpoint.

Skin Irritation/Corrosivity (IrS) Group II Score (vH, H, M, or L): L
Calcium carbonate was assigned a score of Low for skin irritation/corrosivity based on negative findings in a GLP-compliant skin irritation study in rabbits. GreenScreen® criteria classify chemicals as a Low hazard for skin irritation/corrosivity when adequate data are available and negative, there are no structural alerts, and they are not classified under GHS (CPA 2012b).

- Authoritative and Screening Lists
  - *Authoritative:* Not listed on any authoritative lists for this endpoint.
  - *Screening:* Not listed on any screening lists for this endpoint.
- ECHA 2015
  - A GLP-compliant acute dermal irritation test conducted according to OECD 404 was performed with male New Zealand White rabbits (3 total) administered dermal doses of calcium carbonate (greater than 98.5% purity) at 500 mg moistened with 0.5 mL of distilled water to shaved skin in a semi-occlusive fashion for 4 hours. Observations were made 1, 24, 48, and 72 hours after the exposure ended. Edema and erythema scores of 0 were obtained after 24, 48, and 72 hours. The study authors concluded that calcium carbonate was not dermally irritating.
- EC 2000
  - Application of 500 mg calcium carbonate to the skin of rabbits in a Draize test produced moderate irritation. No further details were provided.
    - The IUCLID document states that the irritation effects are believed to be due to the alkalinity of impurities or degradation products interacting with sweating skin. Calcium carbonate as a pure solid is not likely to be responsible for the irritation.
  - Calcium carbonate was corrosive to the skin of humans. No further details were provided.
- Although no signs of dermal irritation were observed in the OECD 404 study, the IUCLID document indicates that calcium carbonate was corrosive to the skin of humans without providing any additional details. As high quality reliable data indicate that calcium carbonate is not dermally irritating, ToxServices discounted the limited evidence of it being corrosive and assigned a score of Low for this endpoint.

Eye Irritation/Corrosivity (IrE) Group II Score (vH, H, M, or L): L
Calcium carbonate was assigned a score of Low for eye irritation/corrosivity based on negative findings in a GLP-compliant eye irritation study in rabbits. GreenScreen® criteria classify chemicals as a Low hazard for eye irritation/corrosivity when adequate data are available and negative, there are no structural alerts, and they are not classifiable under GHS (CPA 2012b).

- Authoritative and Screening Lists
  - *Authoritative:* Not listed on any authoritative lists for this endpoint.
  - *Screening:* GHS New Zealand Category 6.4A (GHS Category 2) – Irritating to the eye
    - Classification based on pure chemical classification and mixture rules. No further details provided.
- ECHA 2015
  - A GLP-compliant acute eye irritation test conducted according to OECD 405 was performed with male New Zealand White rabbits (3 total) administered 61 mg of calcium carbonate (>98.5% purity) to the right eye (left eye served as control) for up to 72 hours. Observations were made at 24, 48, and 72 hours following exposure initiation. The cornea, iris, and chemosis scores were 0 and the conjunctiva score was 0.67, but the

effects were fully reversible by 72 hours. The study authors concluded that calcium carbonate is not irritating to the eyes of rabbits.

- EC 2000
  - Calcium carbonate was highly irritating to the eyes of rabbits following instillation of 0.75 mg in a Draize test. No further details were provided.
    - The IUCLID document states that calcium carbonate does not produce eye irritation provided that impurities and decomposition products are not present.
  - Calcium carbonate was not irritating to highly irritating in two additional rabbit studies. No additional details were provided for these studies.
  - Calcium carbonate was slightly irritating to the eyes of humans. No further details were provided.
- HSDB 2014
  - Acute exposure to calcium carbonate can cause irritation to the eyes and the respiratory tract.
- Although calcium carbonate did not produce sufficient ocular irritation for classification under GHS criteria in an OECD 405 test, a GHS Category 2 classification has been assigned by GHS New Zealand, and the basis of which was not clearly explained. Furthermore, some studies with limited documentation identified that calcium carbonate was highly irritating to the eyes. ToxServices considered the OECD 405 study with more weight than other data with limited details reported, as it was conducted according to guidelines under GLP. Therefore, ToxServices assigned a score of Low for this endpoint.

Ecotoxicity (Ecotox)

Acute Aquatic Toxicity (AA) Score (vH, H, M, or L): L

Calcium carbonate was assigned a score of Low for acute aquatic toxicity based on no adverse effects observed at the limit of water solubility. GreenScreen® criteria classify chemicals as a Low hazard for acute aquatic toxicity when no adverse effects are observed at the limit of water solubility (CPA 2012b).

- Authoritative and Screening Lists
  - *Authoritative:* Not listed on any authoritative lists for this endpoint.
  - *Screening:* Not listed on any screening lists for this endpoint.
- HSDB 2014
  - 96-hour LC_{50} (*Gambusia affinis*, Western mosquitofish) = greater than 56,000 mg/L
- ECHA 2015
  - 96-hour LC_{50} (*Oncorhynchus mykiss*, rainbow trout) = greater than 100% v/v saturated solution (GLP-compliant, OECD 203)
  - 48-hour mobility EC_{50} (*Daphnia magna*) = greater than 100% v/v saturated solution (GLP-compliant, OECD 202)
  - 72-hour growth rate and yield EC_{50} (*Desmodesmus subspicatus*, green algae) = greater than 14 mg/L (highest attainable test concentration due to solubility) (GLP-compliant, OECD 201)

Chronic Aquatic Toxicity (CA) Score (vH, H, M, or L): L

Calcium carbonate was assigned a score of Low for chronic aquatic toxicity based on no adverse effects observed at the limit of water solubility. GreenScreen® criteria classify chemicals as a Low hazard for chronic aquatic toxicity when no adverse effects are observed at the limit of water solubility (CPA 2012b).

- Authoritative and Screening Lists
    - *Authoritative:* Not listed on any authoritative lists for this endpoint.
    - *Screening:* Not listed on any screening lists for this endpoint.
- ECHA 2015
    - 42-day survival of *Oncorhynchus mykiss* (rainbow trout) was not adversely affected by treatment with 140 mg/L calcium carbonate.
    - 72-hour growth rate and yield NOEC (*Desmodesmus subspicatus*, green algae) = 14 mg/L (highest attainable test concentration due to solubility) (GLP-compliant, OECD 201)

Environmental Fate (Fate)

Persistence (P) Score (vH, H, M, L, or vL): *vH*
Calcium carbonate was assigned a score of Very High for persistence based on screening lists. GreenScreen® criteria classify chemicals as a High to Very High hazard for persistence when they are listed as persistent in Environment Canada's Domestic Substance List (CPA 2012b). In order to be protective of human and environmental health, ToxServices assigned a Very High score for this endpoint. The confidence in the score is adjusted as it is based on a screening list.

- Authoritative and Screening Lists
    - *Authoritative:* Not listed on any authoritative lists for this endpoint.
    - *Screening:* Environment Canada's Domestic Substance List – substances that are persistent
- EC 2000
    - Calcium carbonate is an inorganic salt and will not undergo biodegradation.

Bioaccumulation (B) Score (vH, H, M, L, or vL): *L*
Calcium carbonate was assigned a score of Low for bioaccumulation based on it being an inorganic chemical that will not undergo bioaccumulation. GreenScreen® criteria classify chemicals as a Low hazard for bioaccumulation when chemicals are not expected to undergo bioaccumulation (CPA 2012b). The confidence in the score is adjusted based on the lack of measured data for sodium carbonate.

- Authoritative and Screening Lists
    - *Authoritative:* Not listed on any authoritative lists for this endpoint.
    - *Screening:* Not listed on any screening lists for this endpoint.
- EC 2000
    - Calcium carbonate is not bioaccumulative as it is an inorganic salt.

Physical Hazards (Physical)

Reactivity (Rx) Score (vH, H, M, or L): *L*
Calcium carbonate was assigned a score of Low for reactivity based on ToxServices not classifying it as a reactive chemical under GHS criteria. GreenScreen® criteria classify chemicals as a Low hazard for reactivity when they are not classified under GHS criteria (CPA 2012b). The confidence in the score is adjusted based on the lack of measured data for sodium carbonate.

- Authoritative and Screening Lists
    - *Authoritative:* Not listed on any authoritative lists for this endpoint.
    - *Screening:* Not listed on any screening lists for this endpoint.

- Sigma-Aldrich 2015
    - A material safety data sheet for calcium carbonate states that it has a reactivity rating of 0 from the NFPA ("Normally stable, even under fire exposure conditions, and is not reactive with water") and HMIS ("Materials that are normally stable, even under fire conditions, and will not react with water, polymerize, decompose, condense, or self-react. Non-explosives").
- EC 2000
    - Calcium carbonate is not explosive. No further details provided.
- Based on an MSDS stating that calcium carbonate is not reactive, ToxServices did not classify calcium carbonate as a reactive chemical under GHS criteria (UN 2013).

Flammability (F) Score (vH, H, M, or L): L

Calcium carbonate was assigned a score of Low for flammability based on ToxServices not classifying it as a flammable solid under GHS criteria. GreenScreen® criteria classify chemicals as a Low hazard for flammability when they do not have GHS classifications (CPA 2012b).

- Authoritative and Screening Lists
    - *Authoritative:* Not listed on any authoritative lists for this endpoint.
    - *Screening:* Not listed on any screening lists for this endpoint.
- ECHA 2015
    - Calcium carbonate was not flammable in a GLP-compliant flammability test conducted according to Regulation (EC) No 1272/2008, using Method N.1.
    - Calcium carbonate was not flammable in a GLP-compliant EU Method A.10 (Flammability (Solids)) test.
- Based on the negative results for flammability in guideline studies, ToxServices did not classify calcium carbonate as a flammable solid under GHS criteria (UN 2013).

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APPENDIX A: Hazard Benchmark Acronyms
(in alphabetical order)

(AA) Acute Aquatic Toxicity

(AT) Acute Mammalian Toxicity

(B) Bioaccumulation

(C) Carcinogenicity

(CA) Chronic Aquatic Toxicity

(D) Developmental Toxicity

(E) Endocrine Activity

(F) Flammability

(IrE) Eye Irritation/Corrosivity

(IrS) Skin Irritation/Corrosivity

(M) Mutagenicity and Genotoxicity

(N) Neurotoxicity

(P) Persistence

(R) Reproductive Toxicity

(Rx) Reactivity

(SnS) Sensitization- Skin

(SnR) Sensitization- Respiratory

(ST) Systemic/Organ Toxicity

APPENDIX B: Results of Automated GreenScreen® Score Calculation for Calcium Carbonate (CAS #471-34-1)

TOXSERVICES
TOXICOLOGY RISK ASSESSMENT CONSULTING

GreenScreen® Score Inspector

Table 1: Hazard Table

	Group I Human					Group II and II* Human									Ecotox		Fate		Physical	
	Carcinogenicity	Mutagenicity/Genotoxicity	Reproductive Toxicity	Developmental Toxicity	Endocrine Activity	Acute Toxicity	Systemic Toxicity		Neurotoxicity		Skin Sensitization*	Respiratory Sensitization*	Skin Irritation	Eye Irritation	Acute Aquatic Toxicity	Chronic Aquatic Toxicity	Persistence	Bioaccumulation	Reactivity	Flammability
							S	R *	S	R *	*	*								
Inorganic Chemical? / Chemical Name / CAS#	C	M	R	D	E	AT	STs	STr	Ns	Nr	SNS*	SNR*	IrS	IrE	AA	CA	P	B	Rx	F
Yes / Calcium Carbonate / 471-34-1	L	L	L	L	DG	L	*M*	L	L	L	L	DG	L	L	L	L	*vH*	*L*	*L*	L

Table 3: Hazard Summary Table

Benchmark	a	b	c	d	e	f	g
1	No	No	No	No	No		
2	No	No	No	No	No	No	No
3	No	No	Yes	No			
4	STOP						

Table 4

Chemical Name	Preliminary GreenScreen® Benchmark Score
Calcium Carbonate	3

Note: Chemical has not undergone a data gap assessment. Not a Final GreenScreen™ Score

Table 6

Chemical Name	Final GreenScreen® Benchmark Score
Calcium Carbonate	3

After Data gap Assessment
Note: No Data gap Assessment Done if Preliminary GS Benchmark Score is 1.

Table 5: Data Gap Assessment Table

Datagap Criteria	a	b	c	d	e	f	g	h	i	j	bm4	End Result
1												
2												
3	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes		3
4												

APPENDIX C: Pharos Output for Calcium Carbonate (CAS #471-34-1)

[471-34-1] CALCIUM CARBONATE

General Information | Hazards | Life Cycle Research | GreenScreen | Sources

Direct Hazards:

EYE IRRITATION	New Zealand HSNO/GHS - 6.4A - Irritating to the eye
PERSISTENT	Environment Canada - Domestic Substances List - DSL substances that are Persistent
RESTRICTED LIST	US EPA - DfE SCIL - Green Circle - Verified Low Concern
EXEMPT	German FEA - Substances Hazardous to Waters (VwVwS) - Non-Hazardous to Water (Water Hazard Class 0 NWG)

Potential Residual Hazards:

See Life Cycle Research tab for details on residuals and other substances used in manufacture.

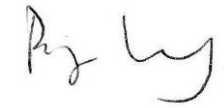
None identified

Licensed GreenScreen® Profilers

Calcium Carbonate GreenScreen® Evaluation Prepared by:

Zach Guerrette, Ph.D.
Toxicologist
ToxServices LLC

Calcium Carbonate GreenScreen® Evaluation QC'd by:



Bingxuan Wang, Ph.D.,
Toxicologist
ToxServices LLC