GR

ORIGINAL SUBMISSION

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RECEIVED
JUL 13 2009
BY: (b)(6)

Date: June 11, 2009

Office of Food Additive Safety
Center for Food Additive Safety and Applied Nutrition
Food & Drug Administration
5100 Paint Branch Parkway
College Park, MD 20740

Re: Notification of the GRAS Determination of Silicon Dioxide When Added Directly or Indirectly to Human Food

Dear Sir or Madam:

We wish to notify you that Lewis & Harrison on behalf of Cabot Corporation has determined that silicon dioxide used in all of its forms and added to food either directly or indirectly is exempt from the premarket approval requirements of the Federal Food Drug and Cosmetic Act.

We are submitting the attached summary of information upon which Lewis & Harrison relied in making its GRAS determination.

Name and Address of Notifier:

Mr. Eliot Harrison
Lewis & Harrison, Agent for Cabot Corporation
122 C Street, N.W. Suite 740
Washington, D.C. 20001
Telephone: (202) 393-3903 Ext 14
Facsimile: (202) 393-3906
e-mail: eharrison@lewisharrison.com

Names and Identities of GRAS Substances:

The substance is silicon dioxide. Silicon dioxide includes both naturally occurring and synthetic silicas. All silicas are silicon dioxide.

Naturally occurring silicon dioxide has a crystalline structure whereas synthetic amorphous silica (SAS) is non-crystalline.

Synthetic amorphous silica (SAS) is another form of silica also known as untreated synthetic silica.

Synthetic amorphous silica (SAS) may be produced by a thermal route yielding pryogenic silica or by a wet route yielding either precipitated silica or silica gel.

Precipitated silicas and silica gel (also known as aerogel silica) are powders obtained by polymerization and precipitation of silica particles from an aqueous medium under the influence of high salt concentrations or other coagulants.

Silica sols are colloidal silica. Colloidal silica is a stable aqueous dispersion or sol of discrete amorphous silica particles having diameters of 1 to 100 nm.

Silicon dioxide and synthetic amorphous silica are chemically identical.

Applicable Conditions of Use:

Cabot Corporation intends to use silicon dioxide in all of its forms for both direct and indirect uses.

As a direct use, it can be added directly to food and is currently regulated under several 21 CFR Regulations.

As an indirect use, silicon dioxide can be used in the manufacture of adhesives, coatings, defoaming agents, greases and lubricants, paper and paperboard and polymers that are then used as components of food-packaging materials. There are many FDA clearances for the indirect use of silicon dioxide under 21 CFR 175, 176, 177 and 178.

Basis for GRAS determination:

The basis for Lewis & Harrison's GRAS determination for silicon dioxide is through scientific procedures and on scientific reviews of this chemical by two separate scientific groups. This dossier includes a comprehensive discussion of, and citations to, references to background scientific information and to the FDA clearances for silica and fumed silica in the 21 CFR and EPA clearances for silicon dioxide under 40 CFR 180.

Silicon dioxide and silicates have a long history of use in food without detrimental effects. They have been reviewed by two scientific groups. The U.S. EPA has also reassessed silicon dioxide for food safety.

The 1979 report by the Select Committee on GRAS Substances (SCOGS) concluded that there is no scientific evidence that there is any available information on aluminum calcium silicate, calcium silicate, magnesium silicate, potassium silicate, sodium silicate, sodium aluminosilicate, sodium calcium aluminosilicate, tricalcium silicate, silica aerogel and talc that demonstrates or suggests reasonable grounds to suspect a hazard to the public when they are used at levels that are now current or might reasonably be expected in the future.

In 2005, a comprehensive review of the safety data base for amorphous silica and silicates was conducted by industry and government scientists pursuant to OECD's Screening Information Data Sets or SIDS) program. The OECD document confirms the opinion of the SCOGS group regarding the safety of the silicates and provides further support that silicon dioxide is GRAS when added either directly or indirectly to food. Both documents include an extensive list of references of the scientific studies used in support of the safety determinations for the chemical.

Silica gel (aerogel) consists of 97% silicon dioxide and 3% water and is very chemically similar to other silicon products. Fumed silica has been cleared by the Food & Drug Administration. Synthetic amorphous silica is prepared by a high temperature combustion process which creates silicon dioxide molecules which condense to form particles or can be prepared by a wet route. It differs from natural silicon dioxide in that the synthetic amorphous silica does not have the crystalline lattice structure that natural silicon dioxide possesses. It is comprised of small silicon dioxide particles. It has increased flowability and thickening characteristics compared to natural silicon dioxide. It is also a very high purity silicon dioxide (>99.8%). Pyrogenic silica is a fluffy form of silica that is of higher purity than are silicas precipitated from water. Precipitated silicon dioxide is a particulate silica composed of aggregates (or secondary particles) of primary particles of colloidal-size silica that have not become linked as a massive gel network during the preparation process. Silica sol is colloidal silica, usually in water.

The chemical properties of these silicas do not differ significantly from those of natural silica.

GRAS Exemption Claim:

Employing scientific procedures established under 21 CFR § 170.30 (b) and on scientific data contained in and reviewed by the SCOGS group and the OECD committee, Lewis & Harrison have determined that silicon dioxide when either directly or indirectly is GRAS.

The attached GRAS Determination Dossier provides detailed information about the identities of the notified substance, including, chemical name, Chemical Abstracts Service Registry Numbers, empirical formulas, quantitative composition, method of

Employing scientific procedures established under 21 CFR § 170.30 (b) and on scientific data contained in and reviewed by the SCOGS group and the OECD committee, Lewis & Harrison have determined that silicon dioxide when either directly or indirectly is GRAS.

The attached GRAS Determination Dossier provides detailed information about the identities of the notified substance, including, chemical name, Chemical Abstracts Service Registry Numbers, empirical formulas, quantitative composition, method of manufacture and characteristic properties. The attached GRAS dossier also contains information on the levels of use and a detailed summary of the basis for Lewis & Harrison's determination that its particular uses of the notified substance is exempt from the premarket approval requirements of the Food & Drug Act because the use is GRAS.

Availability of Information:

The data and information that are the basis for Cabot's GRAS determination are available for FDA to review and copy at reasonable times at the offices of Eliot Harrison, Lewis & Harrison, 122 C St., NW, Suite 740, Washington, D.C. 20001; telephone: (202) 393-3903, ext. 14.

Sincerely yours,

(b)(6)

Eliot Harrison
Lewis & Harrison
Agent for Cabot

RECEIVED
JUN 1 2 2009
Division of
Biotechnology and
GRAS Notice Review

GENERALLY RECOGNIZED AS SAFE DETERMINATION FOR SILICON DIOXIDE WHEN ADDED DIRECTLY AND/OR INDIRECTLY TO HUMAN FOOD

Silicon Dioxide GRAS Notification

Prepared for:

Cabot Corporation
Boston, Massachusetts

Prepared by:

Lewis & Harrison, LLC
Washington, D.C.

June 11, 2009

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8. Attachments:

Attachment 1: Select Committee on GRAS Substances (SCOGS). *Evaluation of the Health Aspects of Certain Silicates as Food Ingredients* (1979).

Attachment 2: OECD SIDS – *Synthetic Amorphous Silica*, UNEP Publications (2004)

Attachment 3: ECETOC JACC Report No. 51 – *Synthetic Amorphous Silica* (2006).

Attachment 4: Food Chemicals Codex Monograph for Silicon Dioxide, 4th Edition (1996).

Attachment 5: EPA Tolerance Exemptions for Various Silica Compounds (40 CFR §180.950).

Attachment 6: EPA Reregistration Eligibility Document (RED) for Silicon Dioxide and Silica Gel (1991).

Attachment 7: KIRK-OTHMER Encyclopedia of Chemical Technology, Volume 21, Fourth Edition, John Wiley & Sons. Silica (Introduction).

Attachment 8: KIRK-OTHMER Encyclopedia of Chemical Technology, Volume 21, Fourth Edition, John Wiley & Sons. Silica (Amorphous).

GRAS EXEMPTION CLAIM

1. Lewis & Harrison, LLC on behalf of Cabot Corporation is filing this GRAS Notification to:

Office of Food Additive Safety (HFS-255)
Center for Food Safety and Applied Nutrition
Food & Drug Administration
5100 Paint Branch Parkway
College Park, MD 20740

The use of silicon dioxide, when added to food directly or indirectly, is exempt from the premarket approval requirements of the Federal Food, Drug, and Cosmetic Act because the notifier has determined that such use is GRAS.

(i) Notifier:

Lewis & Harrison, LLC
On behalf of Cabot Corporation
122 C Street, N.W., Suite 740
Washington, D.C. 20001

(ii) Name of GRAS Substance:

Silicon Dioxide (CAS# 7631-86-9)

The term "silica" refers to the compound, silicon dioxide. All silicas are silicon dioxide. Silicon dioxide forms have been evaluated by the ECETOC JACC REPORT NO. 51, SCOGS, Food Chemicals Codex Monograph for Silicon Dioxide and by OECD/SIDS.

Synthetic amorphous silica (SAS) is also known as untreated fumed silica. The IUPAC name for this substance is silicon dioxide, chemically prepared. Silicon dioxide and synthetic amorphous silica are chemically identical.

Synthetic amorphous silica (SAS) may be produced by a thermal route yielding pryogenic silica or by a wet route yielding either precipitated silica or silica gel. Precipitated silicas and silica gel (also known as aerogel silica) are powders obtained by polymerization and precipitation of silica particles from an aqueous medium under the influence of high salt concentrations or other coagulants.

Silica sols are colloidal silica. Colloidal silica is a stable aqueous dispersion or sol of discrete amorphous silica particles having diameters of 1 to 100 nm.

Another form of silica is naturally occurring silicon dioxide. Natural silicon dioxide has a crystalline structure whereas SAS is non-crystalline.

iii) <u>Conditions of Use:</u>

DIRECT USES
Silicon dioxide in its forms can be used as a direct ingredient in food and as a component of food-packaging materials, at levels in accordance with good manufacturing practices. When directly added to food, silicon dioxide has the following uses:

- Anticaking agent
- Defoaming agent
- Stabilizer
- Adsorbent
- Carrier
- Conditioning agent
- Chillproofing agent
- Filter aid
- Emulsifying agent
- Viscosity control agent
- Anti-settling agent

INDIRECT USES
As an indirect additive, silicon dioxide is used in the manufacture of adhesives, coatings, defoaming agents, greases and lubricants, paper and paperboard and polymers that are then used as components of food-packaging materials.

All segments of the population may be exposed to dietary intake of synthetic amorphous silica from its direct use in food and/or by migration from impregnated food-packaging materials into food.

(iv) (v) <u>Basis for GRAS Determination:</u>

The GRAS determination for silicon dioxide is based on the following:

1) The current GRAS listing for silica aerogel or hydrated silica as multiple purpose GRAS Food Substance used in Human Consumption Food 21CFR§182.1711 - Silica aerogel.

(a) Product. Silica aerogel as a finely powdered microcellular silica foam having a minimum silica content of 89.5 percent.

(b) [Reserved] (c) Limitations, restrictions, or explanation. This substance is generally recognized as safe when used as a component of an anti-foaming agent in accordance with good manufacturing practice.

2) The US Food and Drug Administration has affirmed in a letter to the Silica Trade Association that the use of silica gel in dietary supplements is generally recognized as safe (1993 Food Chemical News Guide, page 407). Both silica aerogel and SAS are silicon dioxide.

3) Technical reviews by three expert scientific groups on the safety of the silicates and SAS.

- The Select Committee on GRAS Substances (*SCOGS*) addressed the safety of dietary exposure to the silicates, including silicon dioxide, in the document entitled, "Evaluation Of The Health Aspects of Certain Silicates As Food Ingredients", which was published in 1979. The SCOGS report concluded that there is no evidence in the available literature that demonstrates or suggests reasonable grounds to suspect a hazard to the public when the various silicates (including silicon dioxide) are used at levels that are now current or that might reasonably be expected in the future. The *SCOGS* document is included with this submission (see Attachment 1).

- A government-industry group established by the Organization of Economic Cooperation and Development (OECD) issued a "Screening Information Data Set" or "SIDS" document for silicon dioxide (see Attachment 2). The OECD SIDS document was issued in 2004 so studies conducted subsequent to the SCOGS report were evaluated. The OECD SIDS document confirmed the overall safety assessment of the SCOGS report.

- In 2006, the European Centre for Ecotoxicology and Toxicology of Chemicals (ECETOC) issued a comprehensive report, which is a critical evaluation of the physic-chemical properties, toxicology, ecotoxicology and environmental fate of SAS.

A significant human exposure route to silica is through the diet, as silicas, in general, are widely used in foodstuffs, pharmaceuticals, and a wide variety of medical and dental applications. Various forms of silica are used as direct and indirect food ingredients, as shown below in Table 1, numerous clearances under 21 CFR for direct use in food and food-packaging. Both silicon dioxide and silica gel have been cleared by the United States Food and Drug Administration (FDA) for many food applications, as both a direct food additive at levels up to 2 percent by weight, and as a substance allowed in the manufacture of materials that come in direct contact with food in various producing, manufacturing, packing, preparing, transporting and holding operations. [Ref. FDA letter to the Silica trade association – May 23rd, 2007- Additional discussion of toxicity issues for silane, dichloromethyl-, reaction products with silica (201-14501A)].

Table 1:Current Approvals for Silicon Dioxide used as Direct and Indirect Food Additive

asp	1393	Direct Food additive		21 CFR reference	
		Silicon dioxide	7631-86-9	133.146(b)	Anti-caking in grated cheese
				160.05(a) (d)	Anti-caking in dried eggs
				160.185	Anti-caking in dried eggs yolks
				172.230(a)	Microencapsulation of flavoring oils
				172.480	Principal section, free-flow and anti-caking in foods
				173.340(a)	Defoamer agents
				182.1711	Dietary supplements
				73.1	Diluents in color additive mixtures for food use exempt from certification (not more than 2% of the ink solids)
				73.575(a)(2)	Titanium dioxide color additive mixtures; SiO_2 as a dispersing aid (not more than 2% total)
		Indirect Food Additive		21 CFR reference	
		Silicon dioxide	7631-86-9	175.105	Adhesives
				175.300	Resinous and polymeric coatings
				175.320	Resinous and polymeric coatings for polyolefin films
				175.350	Vinyl acetate/crotonic acid copolymer
				175.380	Xylem-formaldehyde resins
				175.390	Zinc-silicon dioxide matrix coatings
				176.170	Components of paper and paperboard on contact with aqueous and fatty foods
				176.180	Components of paper and paperboard on contact with dry foods
				176.200	Defoaming agents in coatings
				176.210	Defoaming agents used in manufacture of paper and paperboard
				177.1200	Cellophane
				177.1210	Closure with sealing gaskets for food containers
				177.1350	Ethylene-vinyl acetate copolymers
				177.1400	Hydroxyethyl cellulose film, water-insoluble
				177.1460	Melamine-formaldehyde resins in molded articles
				177.2250	Filters, microporous polymeric
				177.2420	Polyester resins, cross-linked
				177.2600	Rubber articles intended for repeated use
				178.3297	Colorants for polymers
				178.3570	Lubricants with incidental food contact
				182.90	Substances migrating to food from paper and paperboard products

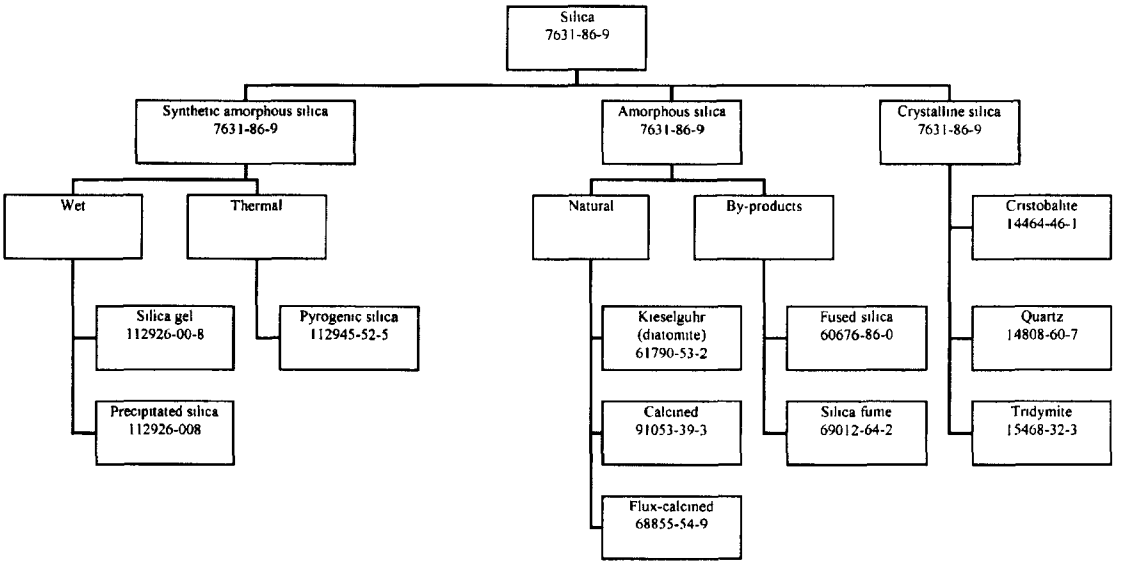
SAS, *per se,* has a direct food additive clearance under 21 CFR 172.480 (a) when used as an anti-caking agent, (b) as a stabilizer in the production of beer and (c) as an adsorbent for *dl* – α – tocopheryl acetate and pantothenyl alcohol in tableted foods for special dietary needs.

2. Detailed Information

Silicon Dioxide Identity:

Silica denotes the compound silicon dioxide, SiO2, and includes both naturally occurring and synthetic silicas. Silica has the structural formula: O=Si=O. Silica is present in its natural state in the crystalline form and is commonly found as quartz. The physical forms of silica can be grouped as crystalline, amorphous, and synthetic amorphous. Figure 1 categorizes the many forms of silica with their respective Chemical Abstract Numbers.

Figure 1:



Production of Synthetic Amorphous Silicas

Synthetic amorphous silica (SAS) may be produced by a thermal route yielding pryogenic silica or by a wet route yielding either precipitated silica or silica gel. The information provided below refers only to SAS and does not include crystalline or other amorphous silicas.

- Thermal Route: Pyrogenic silica, also known as fumed silica in English speaking countries, is produced by the vapor-phase hydrolysis of chlorosilanes in an oxygen/hydrogen flame at temperatures of approximately 1000C. The relatively high temperature yields a SAS powder that has low water content and is amorphous.

- Wet Route: Precipitated silica and silica gel (also known as silica aerogel are produced by controlled polymerization and precipitation of SAS from a solution of sodium silicate. SAS powders produced from the wet route contain large amounts of bound water. They also have an amorphous structure.

- Silica Sols: Silica Sols, also know as colloidal silicas, are stable dispersions of SAS particles in a liquid, typically water. Sols may be directly produced by hydrolysis of silicon tetrachloride in aqueous solution or polymerization of a solution of sodium silicate. Sols may also be indirectly produced by re-dispersion of SAS particles into a liquid.

References: Kirk-Othmer and JACC 51

Physical and Chemical Properties of Synthetic Amorphous Silica

Property	*Pyrogenic*	*Precipitated*	*Gel*	*Sol*	***Unit***
Purity, SiO2	>99.8	>95	>95	15-50	% by weight
Color	White	White	White	White, milky	
BET Surface Area	50 – 400	30 – 500	250 – 1000	50 – 400	m2/g
Mean Pore Size	None	>0.03	0.0001 – 1	NA	µm
Pore Size Distribution	NA	Very wide	Narrow	Wide	
Loss on drying	<2.5	5 – 7	2 – 6	50 – 85	% by weight
pH	3.6 – 4.5	5 – 9	3 – 8	3 – 5 8 - 11	
Bulk density	30 – 250	30 – 500	500 – 1000	NA	g/l
Loss on ignition	<2	3 – 14	2 – 15	50 – 90	% by weight

Reference pg 12 JACC No. 51

Impurities of Synthetic Amorphous Silica

SAS is a highly pure substance. SAS meet the 5 mg/kg maximum Lead content specified in the Monograph "Silicon Dioxide" in the Food Chemical Codex 5th Edition (2003). Heavy metals content of SAS is <0.1%.

Silicon Dioxide Conclusions

Both the wet and thermal routes produce synthetic amorphous silica; however, the physical properties of the particles produced by these processes vary significant. It is these properties that dictate usage. For example, the extremely high internal surface area and high porosity of silica gels make these powders ideally suited for use as a carrier of flavors or filtering aid for clarification of beverages.

3. Self-Limiting Levels of Use: There is no self-limiting factor for the use of silicon dioxide in food or food-packaging materials. Silica will be used in an amount that is reasonably needed to produce the intended effect. Therefore, silicon dioxide will be used in accordance with good manufacturing practices.

4. Basis for the Notifiers Determination That the Use of the Notified Substances are Exempt from the Pre-Market Approval Requirements of the Act Because the Use is GRAS:

As noted above, the bases for the silicon dioxide GRAS determination are: (i) scientific review by expert groups that concluded that the silicates, silicon dioxide and SAS are safe when ingested; (ii) the current GRAS listing for silica aerogel; (iii) the common use in food of silicon dioxide.

5. EPA Clearances for Silica in Food

USEPA has established a tolerance exemption for silicon compounds when used in pesticide chemicals either post-harvest on food crops or on growing food crops. The tolerance exemption is codified in 40 CFR §180.950 (see Attachment 5), as is referred to as a list of minimal risk active and inert ingredients. Accordingly, the 40 CFR §180.950 list can be considered equivalent to a GRAS list.

The list of silica substances in 40 CFR §180.950 are as follows:

Silica, amorphous, fumed (crystalline free)	CAS# 112945-52-5
Silica, amorphous, precipitated and gel	CAS# 7699-41-4
Silica gel	CAS# 63231-67-4
Silica gel, precipitated, crystalline free	CAS# 112926-00-8
Silica, hydrate	CAS# 10279-57-9

The EPA has also evaluated silicon dioxide and silica gel and found them to be of moderate to low toxicity. Consequently, residues have been exempted from the requirement of a tolerance when applied to growing crops or raw agricultural commodities after harvest [40 CFR, § 180.1001(c)], to growing crops only [40 CFR, § 180.1001(d) or in pesticide formulations applied to animals [40 CFR, § 180.1001(e)]. Likewise silica, this High Production Volume chemical substance, has also been exempted from the requirement of tolerance limit when applied to growing crops or raw agricultural commodities after harvest or in pesticide formulations applied to animals [40 CFR, § 180.1001(c) and (e)]. These clearances, all of which lead to human exposure to silica through the diet, support the view that the several uses of silicas as direct and indirect food ingredients are GRAS. (Lewinson, J., Mayr, W., Wagner, H.: Characterisation and Toxicological Behaviour of Synthetic Amorphous Hydrophobic Silica. Regul. Toxicol. Pharmacol., 20, 37-57, 1994) (ref. FDA letter to the Silica trade association – May 23rd, 2007- Additional discussion of toxicity issues for silane, dichloromethyl-, reaction products with silica (201-14501A)).

In 1991, the USEPA conducted a comprehensive safety assessment of silicon dioxide and silica gel pursuant to its "Reregistration Eligibility Document" or "RED" for these substances (see Attachment 6). Regarding dietary exposure to silicon dioxide, EPA concluded that "because of their negligible toxicity when ingested, silicon dioxide and silica gel have received exemptions from tolerances and clearances for certain use patterns associated with food commodities".

6. GRAS Exemption Claim

Employing scientific procedures established under 21 CFR § 170.30 (b), this document affirms that SAS is generally recognized as safe (GRAS). This opinion is based on the fact that both silicon dioxide and silica gel are cleared by the United States Food and Drug Administration (FDA) for many food applications; the pertinent sections of the regulations can be found in Section 21 of the U.S. Code of Federal Regulations, Part 172 Food Additives Permitted for Direct Addition to Food for Human Consumption (21 CFR § 172.480). In addition, the FDA has affirmed that the use of silica gel in dietary supplements is Generally Recognized As Safe (GRAS) (21 CFR § 182.1711) and the use of silicon dioxide in paper and paperboard is Generally Recognized As Safe (GRAS) (21 CFR § 182.90), and is consistent with, the determination made by the SCOGS report on the silicates.

The SCOGS report notes that silicon dioxide is present throughout the environment in natural waters, animals and plants and is also part of the normal human diet. The report also states that silicon compounds added to food contribute only a minor portion of the total dietary silicon intake. Further, it indicates that "silicon compounds that are GRAS for use as a direct food ingredient, except potassium and sodium silicates, are insoluble or slightly soluble in water and appear to be biologically inert" and that no significant tissue accumulation, pathology, or toxicity has been reported from the ingestion of those compounds based on the available data.

The OECD SIDS and ECETOC documents are a comprehensive evaluation of the toxicology for multiple forms of silicon dioxide (ECETOC, JACC No. 51, Synthetic Amorphous Silica, September, 2006; OECD High Production Volume Chemicals Programme, SIDS Dossier, Silicon dioxide, October 2004). . While many of the studies reviewed in the OECD SIDS and ECETOC reports concern inhalation exposure, studies that address the safety of ingested silicon dioxide were also evaluated.

In multiple acute oral studies conducted in rats, no deaths and no significant toxicity occurred at doses of up to 5000 mg/kg silica. In addition, a number of repeated oral toxicity studies for hydrophilic silicas were conducted in rats and mice. In subchronic studies, silica was administered to rats for 2 weeks to 6 months at doses of up to 8% of silica in the diet. In a chronic toxicity study, silica gel was administered orally to rats and mice for up to 24 months at doses up to 5% of the diet. The authors of these studies concluded that were no signs of carcinogenicity and no other significant treatment-related adverse effects. Finally, there were no signs of reproductive or developmental toxicity in studies in mice, hamsters, rats and rabbits administered silica orally during gestation.

In summary, the OECD SIDS and ECETOC documents confirm the conclusion of the *SCOGS* group regarding the safety and GRAS status of silicon dioxide and provides further support that silicon dioxide is GRAS when added directly or indirectly to food.

7. Environmental Assessment:

Claim of categorical exclusion for the use of silicon dioxide in polymers under 21 § CFR 25.32.

This Regulation states that, " The classes of actions listed in this section are categorically excluded and, therefore, ordinarily do not require the preparation of an EI or an EIS:.....(r) Approval of a food additive petition, color additive, GRAS affirmation petition, or allowing a notification submitted under 21 U.S.C. 348 (h) to become effective for a substance that occurs naturally in the environment, when the action does not alter significantly the concentration or distribution of the substance, its metabolites or degradation products in the environment".

Silicon dioxide occurs naturally in the environment and meets these criteria. As stated above, synthetic amorphous silica is chemically identical to silicon dioxide.

The OECD SIDS Report review of environmental data, pages 194-196 did not raise any environmental issues regarding either certain silicate salts or silicon dioxide. The OECD SIDS review includes synthetic amorphous silica.

Attachment 1

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ATTACHMENT 1

NTIS
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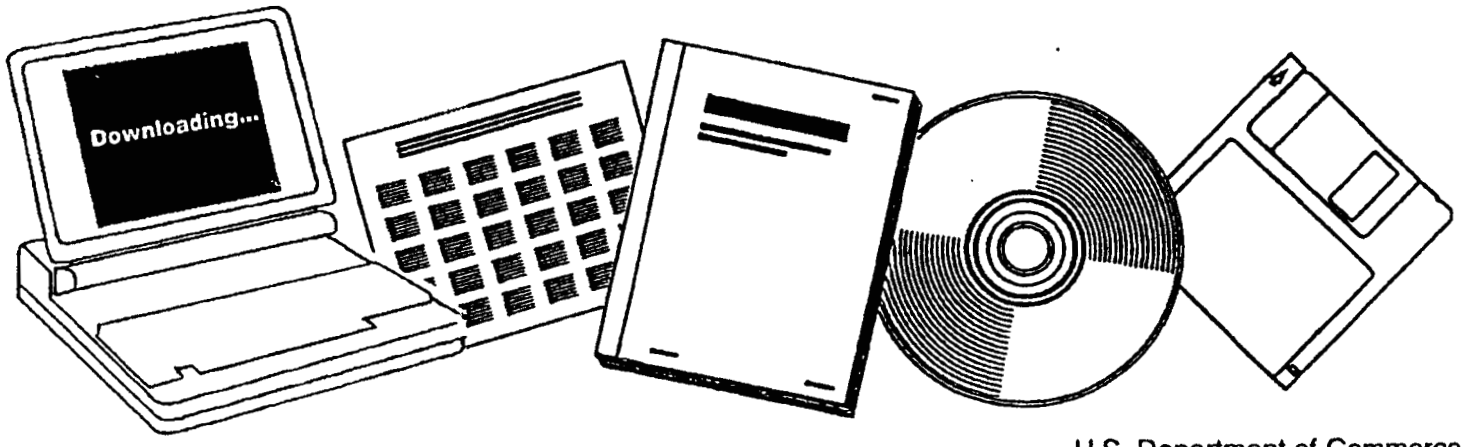
EVALUATION OF THE HEALTH ASPECTS OF CERTAIN SILICATES AS FOOD INGREDIENTS

FEDERATION OF AMERICAN SOCIETIES FOR EXPERIMENTAL BIOLOGY, BETHESDA, MD. LIFE SCIENCES RESEARCH OFFICE

1979



U.S. Department of Commerce
National Technical Information Service

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Attachment 2

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ATTACHMENT 2

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Attachment 3

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ATTACHMENT 3

Pages 000311 - 000547 have been removed in accordance with copyright laws. Please see appended bibliography list of the references that have been removed from this request.

Attachment 4

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ATTACHMENT 4

Pages 000549 - 000550 have been removed in accordance with copyright laws. Please see appended bibliography list of the references that have been removed from this request.

Attachment 5

000550.001

ATTACHMENT 5

[69 FR 23136, Apr. 28, 2004]

§ 180.950 Tolerance exemptions for minimal risk active and inert ingredients.

Unless specifically excluded, residues resulting from the use of the following substances as either an inert or an active ingredient in a pesticide chemical formulation, including antimicrobial pesticide chemicals, are exempted from the requirement of a tolerance under FFDCA section 408, if such use is in accordance with good agricultural or manufacturing practices.

(a) *Commonly consumed food commodities.* Commonly consumed food commodities means foods that are commonly consumed for their nutrient properties. The term commonly consumed food commodities shall only apply to food commodities (whether a raw agricultural commodity or a processed commodity) in the form the commodity is sold or distributed to the public for consumption.

(1) Included within the term commonly consumed food commodities are:

(i) Sugars such as sucrose, lactose, dextrose and fructose, and invert sugar and syrup.

(ii) Spices such as cinnamon, cloves, and red pepper.

(iii) Herbs such as basil, anise, or fenugreek.

(2) Excluded from the term commonly consumed food commodities are:

(i) Any food commodity that is adulterated under 21 U.S.C. 342.

(ii) Both the raw and processed forms of peanuts, tree nuts, milk, soybeans, eggs, fish, crustacea, and wheat.

(iii) Alcoholic beverages.

(iv) Dietary supplements.

(b) *Animal feed items.* Animal feed items means meat meal and all items derived from field crops that are fed to livestock excluding both the raw and processed forms of peanuts, tree nuts, milk, soybeans, eggs, fish, crustacea, and wheat. Meat meal is an animal feed composed of dried animal fat and protein that has been sterilized. Other than meat meal, the term animal feed item does not extend to any item designed to be fed to animals that contains, to any extent, components of animals Included within the term animal feed items are:

(1) The hulls and shells of the commodities specified in paragraph (a)(2)(ii) of this section, and cocoa bean.

(2) Bird feed such as canary seed.

(3) Any feed component of a medicated feed meeting the definition of an animal feed item.

(c) *Edible fats and oils.* Edible fats and oils means all edible (food or feed) fats and oils, derived from either plants or animals, whether or not commonly consumed, including products derived from hydrogenating (food or feed) oils, or liquefying (food or feed) fats.

(1) Included within the term edible fats and oils are oils (such as soybean oil) that are derived from the commodities specified in paragraph (a)(2)(ii) of this section when such oils are highly refined via a solvent extraction procedure.

(2) Excluded from the term edible fats and oils are plant oils used in the pesticide chemical formulation specifically to impart their characteristic fragrance and/or flavoring.

(d) [Reserved]

(e) *Specific chemical substances.* Residues resulting from the use of the following substances as either an inert or an active ingredient in a pesticide chemical formulation, including antimicrobial pesticide chemicals, are exempted from the requirement of a tolerance under FFDCA section 408, if such use is in accordance with good agricultural or manufacturing practices.

Chemical	CAS No
Acetic acid, sodium salt	127-09-3
Animal glue	None
Carob gum (locust bean gum)	9000-40-2
Castor oil	8001-79-4
Castor oil, hydrogenated	8001-78-3
Cellulose	9004-34-6
Cellulose acetate	9004-35-7
Cellulose, carboxy methyl ether, sodium salt	9004-32-4
Cellulose, 2-hydroxyethyl ether	9004-62-0
Cellulose, 2-hydroxypropyl ether	9004-64-2
Cellulose, 2-hydroxypropyl methyl ether	9004-65-3
Cellulose, methyl ether	9004-67-5
Cellulose, mixture with cellulose carboxymethyl ether, sodium salt	51395-75-6
Cellulose, pulp	65996-61-4
Cellulose, regenerated	68442-85-3
Citric acid	77-92-9
Citric acid, 2-(acetyloxy)-, tributyl ester	77-90-7
Citric acid, calcium salt	7693-13-2
Citric acid, calcium salt (2 3)	813-94-5
Citric acid, dipotassium salt	3609-96-9
Citric acid, disodium salt	144-33-2
Citric acid, monohydrate	5949-29-1
Citric acid, monopotassium salt	866-83-1
Citric acid, monosodium salt	18996-35-5

Chemical	CAS No
Citric acid, potassium salt	7778–49–6
Citric acid, triethyl ester	77–93–0
Citric acid, tripotassium salt	866–84–2
Citric acid, tripotassium salt, monohydrate	6100–05–6
Citric acid, sodium salt	994–36–5
Citric acid, trisodium salt	68–04–2
Citric acid, trisodium salt, dihydrate	6132–04–3
Citric acid, trisodium salt, pentahydrate	6858–44–2
Coffee grounds	68916–18–7
Dextrins	9004–53–9
1,3-Dioxolan-2-one, 4-methyl-(propylene carbonate)	108–32–7
Fumaric acid	110–17–8
Gellan gum	71010–52–1
Guar gum	9000–30–0
Humic acid	1413–93–6
Humic acid, potassium salt	68514–28–3
Humic acid, sodium salt	68131–04–4
Lactic acid, n-butyl ester	138–22–7
Lactic acid, n-butyl ester, (S)	34451–19–9
Lactic acid, ethyl ester	97–64–3
Lactic acid, ethyl ester,(S)	687–47–8
Lanolin	8006–54–0
Lecithins	8002–43–5
Lecithins, soya	8030–76–0
Liconce Extract	68916–91–6
Maltodextrin	9050–36–6
Paper	None
Potassium chloride	7447–40–7
Red cabbage color, expressed from edible red cabbage heads via a pressing process using only acidified water	None
Silica, amorphous, fumed (crystalline free)	112945–52–5
Silica, amorphous, precipitated and gel	7699–41–4
Silica gel	63231–67–4
Silica gel, precipitated, crystalline-free	112926–00–8
Silica, hydrate	10279–57–9
Silica, vitreous	60676–86–0
Soapbark (Quillaja saponin)	1393–03–9
Sodium alginate	9005–38–3
Sodium chloride	7647–14–5
Syrups, hydrolyzed starch, hydrogenated	68425–17–2
Ultramarine blue (C.I. Pigment Blue 29)	57455–37–5
Urea	57–13–6
Xanthan gum	11138–66–2

[67 FR 36537, May 24, 2002, as amended at 67 FR 56229, Sept. 3, 2002; 67 FR 78718, Dec. 26, 2002; 68 FR 16437, Apr. 4, 2003; 68 FR 18552, Apr. 16, 2003; 68 FR 52700, Sept. 5, 2003; 69 FR 4077, Jan. 28, 2004; 69 FR 9963, Mar. 3, 2004; 69 FR 29894, May 26, 2004; 69 FR 33578, June 16, 2004; 69 FR 58070, Sept. 29, 2004; 70 FR 7876, Feb. 16, 2005; 70 FR 28447, May 18, 2005]

§ 180.960 Polymers; exemptions from the requirement of a tolerance.

Residues resulting from the use of the following substances, that meet the definition of a polymer and the criteria specified for defining a low-risk polymer in 40 CFR 723.250, as an inert ingredient in a pesticide chemical formulation, including antimicrobial pesticide chemical formulations, are exempted from the requirement of a tolerance under FFDCA section 408, if such use is in accordance with good agricultural or manufacturing practices.

Polymer	CAS No.
Acetic acid ethenyl ester, polymer with ethenol and (α)-2-propenyl-(ω)-hydroxypoly (oxy-1,2-ethanediyl) minimum number average molecular weight (in amu), 15,000	137091–12–4
Acrylic acid, polymerized, and its ethyl and methyl esters	None
Acrylic acid-sodium acrylate-sodium-2-methylpropanesulfonate copolymer, minimum average molecular weight (in amu), 4,500	97953–25–8
Acrylic acid-stearyl methacrylate copolymer, minimum number average molecular weight (in amu), 2,500	27756–15–6
Acrylic acid, styrene, α-methyl styrene copolymer, ammonium salt, minimum number average molecular weight (in amu), 1,250	89678–90–0
Acrylic acid terpolymer, partial sodium salt, minimum number average molecular weight (in amu), 2,400	151006–66–5
Acrylic polymers composed of one or more of the following monomers: Acrylic acid, methyl acrylate, ethyl acrylate, butyl acrylate, hydroxyethyl acrylate, hydroxypropyl acrylate, hydroxybutyl acrylate, carboxyethyl acrylate, methacrylic acid, methyl methacrylate, ethyl methacrylate, butyl methacrylate, isobutyl methacrylate, hydroxyethyl methacrylate, hydroxypropyl methacrylate, hydroxybutyl methacrylate, lauryl methacrylate, and stearyl methacrylate; with none and/or one or more of the following monomers: Acrylamide, N-methyl acrylamide, N,N-dimethyl acrylamide, N-octylacrylamide, maleic anhydride, maleic acid, monoethyl maleate, diethyl maleate, monooctyl maleate, dioctyl maleate; and their corresponding sodium, potassium, ammonium, isopropylamine, triethylamine, monoethanolamine, and/or triethanolamine salts; the resulting polymer having a minimum number average molecular weight (in amu), 1,200	None
Acrylonitrile-butadiene copolymer conforming to 21 CFR 180.22, minimum average molecular weight (in amu), 1,000	9003–18–3
Acrylonitrile-styrene-hydroxypropyl methacrylate copolymer, minimum number average molecular weight (in amu), 447,000	None
α-alkyl (C_{12}–C_{15}) - ω-hydroxypoly(oxypropylene) poly(oxyethylene)copolymers (where the poly(oxypropylene) content is 3–60 moles and the poly(oxyethylene) content is 5–80 moles), the resulting ethoxylated propoxylated (C_{12}–C_{15}) alcohols having a minimum molecular weight (in amu), 1,500	68551–13–3
Alkyl (C_{12}–C_{20}) methacrylate-methacrylic acid copolymer, minimum molecular weight (in amu), 11,900	None

GR

Attachment 6

000553.001

ATTACHMENT 6

REREGISTRATION ELIGIBILITY DOCUMENT
SILICON DIOXIDE AND SILICA GEL

LIST D

CASE 4081

SEPTEMBER 1991

ENVIRONMENTAL PROTECTION AGENCY
OFFICE OF PESTICIDE PROGRAMS
SPECIAL REVIEW AND REREGISTRATION DIVISION
WASHINGTON, D.C.

SILICON DIOXIDE AND SILICA GEL
REREGISTRATION ELIGIBILITY TEAM

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GLOSSARY OF TERMS AND ABBREVIATIONS

a.i.	Active Ingredient
CAS	Chemical Abstracts Service
CFR	Code of Federal Regulations
EPA	U. S. Environmental Protection Agency
FDA	Food and Drug Administration
FIFRA	Federal Insecticide, Fungicide, and Rodenticide Act
FFDCA	Federal Food, Drug, and Cosmetic Act
GRAS	Generally Recognized As Safe
LC50	Median lethal concentration - a statistically derived concentration of a substance that can be expected to cause death in 50% of test animals. It is usually expressed as the weight of substance per weight or volume of water or feed, e.g., mg/l or ppm.
LD50	Median lethal dose - a statistically derived single dose that can be expected to cause death in 50% of the test animals, when administered by the route indicated (oral, dermal, inhalation). It is expressed as a weight of substance per unit weight of animal, e.g., mg/kg.
MRID	Master Record Identification (number). EPA's system of recording and tracking studies submitted to the EPA.

EXECUTIVE SUMMARY

This Reregistration Eligibility Document addresses both silicon dioxide and silica gel. Silicon dioxide is essentially an inert material that contains approximately 90% silica. It is commonly used as an inert carrier in dry concentrates, dry pesticides, as an anti-caking agent, soil conditioner and turf soil supplement and occasionally used as an active ingredient. Silicon dioxide's most common insecticidal use today is for control of stored grain insects. It is also registered for use to control a variety of insects/mites in and around domestic/commercial dwellings, ornamental gardens, in kennels and on domestic pets. Silica gel is a registered insecticide and acaricide for use to control a variety of insects in and around residences/commercial dwellings, agricultural premises, institutions, warehouses, food plants, livestock, cat, dogs and in granaries. Because of their abrasive characteristics both active ingredients act on insects by removing the oily protective film covering their bodies which normally prevents the loss of water. Thus the mode of action is physical in nature causing desiccation of the insect. Both active ingredients are usually combined with other pesticides which act as a knockdown agent. All products which contain silicon dioxide and silica gel registered for these uses are eligible for reregistration.

The U. S. Environmental Protection Agency (EPA) conducted a review of the scientific data base and other relevant information supporting the reregistration of silicon dioxide and silica gel and has determined that the data base is sufficient to conduct a reasonable risk assessment. In addition, the Agency has conducted a tolerance reassessment for silicon dioxide and silica gel and its conclusions are discussed in Section IIC. The data available to the EPA support the conclusion that the currently registered uses of silicon dioxide and silica gel will not result in unreasonable public health risks or effects to the environment. No further generic data are required.

Accordingly, the EPA has determined that all products containing silicon dioxide and silica gel as the active ingredients are eligible for reregistration and will be reregistered when appropriate labeling and/or product specific data are submitted and/or cited. Before reregistering each product, the EPA is requiring product specific data to be submitted within eight months of the issuance of this document. After reviewing these data and the revised labels, the EPA will determine whether to reregister a product based on whether or not the conditions of the Federal Insecticide, Fungicide, and Rodenticide Act (FIFRA) Section 3(c)(5) have been met. End use products containing silicon dioxide and silica gel in combination with other active ingredients will not be reregistered until

those other active ingredients are determined to be eligible for reregistration. However, product specific data are being called in at this time.

I. INTRODUCTION

In 1988, FIFRA was amended to accelerate the reregistration of products with active ingredients registered prior to November 1, 1984. The amended Act provides a schedule for the reregistration process to be completed in nine years. There are five phases to the reregistration process. The first four phases of the process focus on identification of data requirements to support the reregistration of an active ingredient and the generation and submission of data to fulfill the requirements. The fifth phase is a review by EPA of all data submitted to support reregistration.

Section 4(g)(2)(A) of FIFRA states that in Phase 5 "the Administrator shall determine whether pesticides containing such active ingredient are eligible for reregistration" before calling in data on products, 4(g)(2)(B), and either reregistering products or taking "other appropriate regulatory action," sections 4(g)(2)(C) and (D). Thus, reregistration involves a thorough review of the scientific data base underlying a pesticide's registration. The purpose of the review is to reassess the potential hazards arising from the currently registered uses of the pesticide; to determine the need for additional data on health and environmental effects; and to determine whether the pesticide meets the "no unreasonable adverse effects" criterion of FIFRA, 3(c)(5).

This document presents the EPA's decision regarding the reregistration eligibility of the active ingredients silicon dioxide and silica gel. The document consists of five sections. Section I is this introduction. Section II describes silicon dioxide and silica gel, their uses and regulatory history. Section III discusses the human health and environmental assessments based on the data available to the EPA. Section IV discusses the reregistration eligibility decision for silicon dioxide and silica gel. Section V discusses product reregistration requirements. Additional details concerning the review of available data are available on request. *

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*EPA's reviews of specific reports and information on the set of registered uses considered for EPA's analyses may be obtained from: EPA, Freedom of Information, 401 M Street, S.W., Washington, D.C. 20460

II. ACTIVE INGREDIENTS COVERED BY THIS REREGISTRATION ELIGIBILITY DECISION DOCUMENT

A. IDENTIFICATION OF ACTIVE INGREDIENTS

1. Chemical Name: Silicon dioxide (diatomaceous earth)

CAS Number: 7631-86-9

Office of Pesticide Programs Chemical Code Number: 72605

Empirical Formula: SiO_2

Trade Name: Diatomite, Dicalite, DiaFil, Celatom,

Celite

Other Name: Infusorial Earth, Fossil Flour, Siliceous Earth

Basic Manufacturer: Produced by a number of manufacturers.

2. Chemical Name: Silica Gel

CAS Number: 63231-67-4

Office of Pesticide Programs Chemical Code Number: 72602

Empirical Formula: SiO_2

Trade Name: Dri-Die, Drione, Syloid

Basic Manufacturer: Fairfield American Company plus other manufacturers.

B. USE PROFILE

Type of pesticide:

Silicon Dioxide: Acaricide and/or insecticide

Silica Gel: Acaricide and/or insecticide

Registered use sites:

SILICON DIOXIDE:

Terrestrial Food/Feed Crops (including Greenhouse Crops)*:

Cranberry, pecan, peach, asparagus, broccoli, brussels sprouts, cabbage, cauliflower, celery, collards, kale, lettuce, mustard, radish, spinach, tomato, turnip, potato (Irish/white), beans, barley, corn, oats, sorghum, wheat, peanuts, peas, soybeans, and pastures

Terrestrial Non-Food Crops (including Greenhouse Crops)*:

Tobacco, ornamental herbaceous plants, ornamental woody shrubs and vines, and ornamental and/or shade trees

Outdoor Sites (including Commercial/Residential)*:

Kennels, pet sleeping quarters/veterinary and household/domestic dwelling (outdoor premises)

Indoor Food (including Commercial/Residential Sites):

Stored grains: beans, barley, grain crops, oats, rice, rye, sorghum, wheat, buckwheat, flax, corn, peas, seeds, soybeans

Grain/cereal/flour bins (empty/full), grain/cereal/flour storage areas (empty/full), food/feed storage areas (empty/full), silo, household/domestic dwelling indoor food handling areas, commercial transportation facilities, food processing plant premise/equipment, eating establishments food handling areas (food contact), eating establishment food serving areas (food contact), and food/grocery marketing/storage/distribution facility premise

Indoor Non-Food (including Commercial/Residential Sites):

Kennels, pet sleeping quarters/veterinary, cats (adult/kitten)*, dogs/canine (adult/puppies), pet living/sleeping quarters, pet bedding, domestic dwelling, household/domestic dwelling indoor premise, household/domestic dwelling content, human bedding/mattresses, refuse/solid waste containers (garbage cans)

SILICA GEL:

Aquatic Non-Food Site (Commercial):

Sewage Systems

Outdoor Sites (including Commercial/Residential):

Kennels/pet sleeping quarters/veterinary, household/domestic dwelling (outdoor), wood protection treatment to building/products (outdoor), commercial/institutional/industrial areas (outdoor)

Indoor Food (including Commercial/Agricultural/ Residential):

Grain crops, grain/cereal/flour bins (empty/full), grain/cereal/flour elevators (empty/full), food/feed storage areas (empty/full), grain/cereal/flour storage areas, dairy cattle, poultry, beef/range/feeder (cattle), hog/pig/swine, household/domestic dwelling food indoor establishment, food processing plants premise/equipment, feed mills/feed processing plants, flour mills, cereal plants, eating establishments food handling areas (contact), eating establishments food serving areas (contact), food/grocery marketing/storage distribution facility premise

Indoor Non-Food (including Commercial/Agricultural/ Residential):

Kennels/pet sleeping quarters/veterinary, horses, animals (lab/research), commercial transportation facility, eating establishments non-food areas, commercial/institutional/industrial premise/equipment (indoor), cats (adults/kittens), dogs/canines (adult/puppies), monkeys, ferrets, birds, pet living/ sleeping quarters, pet bedding, domestic dwellings, household/domestic dwellings (indoor), household/ domestic dwelling content, wood protection treatment to building (indoor), human bedding/mattresses

Indoor Medical:

Hospitals/medical institutions (human/veterinary)

Formulation Types Registered:

SILICON DIOXIDE: Silicon dioxide end-use products are formulated as dusts containing at least 80% diatomaceous earth as the sole active ingredient (and as a dust in combination with other active ingredients (pyrethrin, piperonyl butoxide). There are no technical or manufacturing use products registered.

SILICA GEL: Silica gel end use products are formulated as dusts (at 96% active ingredients); and as pressurized liquids at (4% active ingredient) with multi-active ingredients such as pyrethrin, piperonyl butoxide, carbaryl and as a manufacturing use product (40% a.i.)

*Registered on these sites only in combination with other active ingredients.

Methods of Application:

SILICON DIOXIDE: Silicon dioxide is applied by a hand held or power duster.

SILICA GEL: Silica gel is applied by hand held power duster, aerosol can or injection (i.e., crack and crevice treatment).

C. REGULATORY HISTORY

In 1960 and 1956 EPA first registered pesticide products containing silicon dioxide and silica gel, respectively, as active ingredients. Because of their negligible toxicity when ingested, silicon dioxide and silica gel (hydrated silica) have received exemptions from tolerances and clearances for certain use patterns associated with food commodities. These exemptions and clearances are:

-when applied as an inert ingredient, or occasionally as an active, to growing crops and raw agricultural commodities (40 CFR 180.1001(c) and (d));

-when applied as an inert, or occasionally as an active to livestock (40 CFR 180.1001(e));

-when applied as an active ingredient to growing crops, raw agricultural commodities after harvest and to livestock (40 CFR 180.1017).

Current exemptions from tolerances in 40 CFR 180.1017, 185.1700 and 186.1700 are limited to the naturally mined silicon dioxide-containing product diatomaceous earth.

The Agency intends to revise 40 CFR 180.1017 to specifically exempt silicon dioxide and silica gel from the requirements of a tolerance when used on raw agricultural commodities (growing crops and post-harvest uses) and animals. Similarly, EPA intends to revise the exemptions in 40 CFR 185.1700 and 186.1700 for diatomaceous earth to include silica gel used in food and feed handling establishments.

The use of silicon dioxide as a direct food additive (anti-caking agent) is described in 21 CFR 121.380. Silica gels with a minimum silica content of 89.5% are considered GRAS when used as anti-foaming agents in accordance with good manufacturing practice (21 CFR 172.11711). Silicon dioxides are considered GRAS as substances migrating from paper and paper-board products used in food packaging (40 CFR 182.90).

III. AGENCY ASSESSMENT OF ACTIVE INGREDIENT

The Agency has conducted a thorough review of the scientific data base for silicon dioxide and silica gel. Based on the evaluation of these data, the EPA has no reason to request additional data.

A. INGREDIENT DESCRIPTION

Anhydrous silicon dioxide has a molecular weight of 60.09. Silica gel and other amorphous forms of silicon dioxide will have a varying molecular weight, depending upon the extent of hydration. Datomaceous earth consists of siliceous frustules and fragments of various species of diatoms mined from the beds of former inland lakes. It is composed of approximately 85% silica, other oxides and organic materials. The natural grades are mined and then dried, ground, sifted and bagged. Both forms used as pesticidal active ingredients are generally white powders at room temperature which melt to a glassy consistency at high temperatures. Silicon dioxide is practically insoluble in water, but is soluble in hydrofluoric acid. Heating with concentrated phosphoric acid may slowly dissolve silicon dioxide as well. Amorphous forms of silica may be dissolved by hot concentrated alkaline solutions, but crystalline forms generally are not soluble. Silica is not soluble in any organic solvent. The bulk density is in the range of 10-20 lb/ft 3 and the true density is approximately 2.2 g/cm 3. The pH of an aqueous suspension of silica gel can range from 2.3-7. All product chemistry requirements have been satisfied.

B. HUMAN HEALTH ASSESSMENT

1. Toxicology

a. Acute Toxicity

Acute toxicity studies demonstrate that silicon dioxide and silica gel have moderate to low acute toxicities. An acute oral LD_{50} study (rat) with silicon dioxide resulted in an LD_{50} value of 3160 mg/g [1/]; this value is considered Toxicity Category III. In an acute dermal LD_{50} study [2/] silica gel produced moderate to low toxicity for a Toxicity Category of III. No test animals in an acute inhalation study [3/] died as a result of exposure to 40% silica gel. Likewise, eye and dermal irritation studies [4/] have suggested moderate and low toxicities, respectively.

b. **Subchronic and Chronic Toxicity**

Crystalline silicon dioxide has long been associated with silicosis, a progressive lung disease, which has been associated with the development of lung cancer in humans. Amorphous silicon dioxide has not been associated with silicosis.

1/ NIOSH (1977) Registry of Toxic Effects of Chemical Substances. U.S. Department of Health Education and Welfare, DHEW Publ. No. (NIOSH) 78-104-A. Government Printing Office, Washington, D.C.

2/ Fairfield American Corp. Acute Dermal Study No. 03240, 4/10/80. Acc. No. 242851.

3/ Fairfield American Corp. Acute Inhalation Toxicity Study,\ No. 0324E, 5/21/80, Acc. No. 242852.

4/ Fairfield American Corp. Primary Eye Irritation Study No 0324B, 4/21/80, Acc. No. 242850 and Primary Dermal Irritation Study No. 0324C, 4/17/80, Acc. No. 242849.

The International Agency for Research on Cancer (IARC) has conducted an in depth evaluation of the potential carcinogenicity of silicon dioxide. [5]/ Based on the data available, the IARC Working Group expressed its expert opinion that 1) there is sufficient evidence for the carcinogenicity of crystalline silica to experimental animals; 2) there is limited evidence for the carcinogenicity of crystalline silica to humans; 3) there is inadequate evidence for carcinogenicity of amorphous silica to experimental animals; and 4) there is inadequate evidence for the carcinogenicity of amorphous silica to humans. IARC also indicated that no adequate epidemiological data were available to evaluate the carcinogenicity of amorphous silica. EPA concurs with IARC's assessment of the available data. Some of the experimental animal studies evaluated are as follows:

a. Oral Administration

Rat: A group of 30 weanling Sprague-Dawley rats was administered 20 mg/day of diatomaceous earth in cottage cheese at a concentration of 5 mg/g cheese, in addition to a basal diet ad libitum. The rats were observed for their life span (mean survival 840 days). Five malignant tumors (1 salivary gland carcinoma, 1 skin carcinoma, 2 sarcomas of the uterus, 1 peritoneal mesothelioma) and 13 benign tumors (9 mammary fibroadenomas, 1 adrenal pheochromocytoma, 3 pancreatic adenomas) were observed in treated animals. A control group of 27 rats with mean survival of 690 days had 3 carcinomas (1 each in lung, ovary and forestomach) and 5 mammary fibroadenomas. [6]/

5/ IARC (1987) IARC Monographs on the Evaluation of Carcinogenic Risk of Chemicals to Humans, Vol. 42, Silica and Some Silicates, Lyon, France, p. 39-143.

6/ Hilding, A.C., Hilding, D.A., Larson, D.M., and Aulderheide,, A. C. (1981) Biological Effects of Ingested Amosite Asbestos, Taconite Tailings, Diatomaceous Earth and Lake Superior Water in Rats. Arch. Environ. Health 36: 298-303

b. Inhalation Exposure

Mouse: Groups of 75 mice were exposed to various particulates including 0.5 g/day precipitated silica (particle size was reported to about 5 um or less in diameter) once an hour for 6 hours on 5 days/week for 1 year and observed for their lifespan. Survival at 600 days was 12/74 in the silica treated group and 17/75 in one control group and 13/73 in the second control group. The incidence of pulmonary adenomas and adenocarcinomas in mice surviving 200 days or more was 5/63 and 5/52 in the control groups at 13/61 in the silica treated group. 7/

Rabbit: Inhalation of 40 mg/ml amorphous silica for up to to 1100 days was reported to produce "diffuse tissue reactions." 8/

2. **Occupational and Residential Exposure**

Silicon dioxide end-use products are formulated as dusts and applied by a hand held or power duster to crops, stored grains, pets, and indoors. Silica gel end-use products are formulated as dusts; and as pressurized liquids and applied by a hand held power duster, aerosol can or injection (i.e., crack and crevice treatment). Current product labels for dust formulations have requirements for use of a dust mask for prolonged periods of use. EPA believes potential inhalation and dermal exposure for the applicator may be significant. However, applications and exposures are believed to be infrequent to a few times per year.

7/ Campbell, J.A. (1940) Effects of Precipitated Silica and Iron Oxide on the Incidence of Primary Lung Tumors in Mice. Br. Med. J., ii, 275-280

8/ Gartner, H. (1952) Studies on the Action of Fine Amorphous Silica on the Lung of Rabbits (Ger.) Arch. Hyg. 136: 451-467

3. **Dietary Exposure**

Dietary exposure to silicon dioxide and silica gel may occur from their application to certain crops and in and around food handling and preparation areas. The amount of ingestion has not been quantified for this assessment because they are exempt from tolerance requirements at all levels in food. They are believed to be inconsequential because of the ubiquity of forms of silicon dioxide in the environment.

4. **Human Health Risk Assessment**

EPA has considered several factors in the risk assessment for pesticidal uses of silicon dioxide. Silicon dioxide and silica gel's acute toxicity profile can be characterized as moderate to low. Dietary exposure from the direct application to food commodities or from inadvertent residues in food handling and preparation areas are not quantified here but are believed to be insignificant from a a toxicological standpoint. Ingestion of various chemical forms of silicon dioxide occurs due to their natural occurrence in the environment. FDA has classified these chemicals as Generally Recognized as Safe and has approved their use as dietary food additives at levels up to 2% by weight in food. Applicator exposure may be significant for each application, however, EPA believes based on the use patterns, the application is infrequent and therefore exposure is acute rather than chronic. In addition, the labels caution the applicator to avoid contact with eyes and skin, avoid breathing dust, and use a dust mask for prolonged periods of of use. Given these factors and assumptions, EPA concludes the human health risk is low and not unreasonable.

C. ENVIRONMENTAL ASSESSMENT

1. Environmental Fate Assessment

Silicon dioxide (diatomaceous earth) is primarily composed of silica, the same inactive ingredient as is in quartz, sand and agate. Silica gel is an amorphous (non-crystalline) form of silicon dioxide ($SiO_2 \cdot H_2O$) made by the gelation of sodium silicate and sulfuric acid. It is unlikely that silicon dioxide or silica gel would react chemically with any natural substance(s) in the environment.

The environmental fate data requirements have been waived based on the availability of public information on these compounds.

2. Ecological Effects Assessments

Based on the Environmental Fate Assessment, that both silicon dioxide and silica gel are chemically unreactive in the environment and the fact that they are practically non-toxic to non-target organisms, there is no evidence that demonstrates or suggests any grounds to suspect a hazard to the environment or to non-target organisms when these pesticides are used at the registered levels. Therefore, ecological effects studies are waived.

3. Environmental Risk Assessment

EPA concludes that silicon dioxide and silica gel do not pose unreasonable risks to the environment, including non-target organisms, when used at their registered levels. This conclusion is based on the belief that silicon dioxide and silica gel are chemically unreactive in the environment, occur naturally in various forms and are practically non-toxic to non-target organisms.

IV. REREGISTRATION DECISION FOR ACTIVE INGREDIENT

A. DETERMINATION OF ELIGIBILITY

Section 4(g)(2)(B) of FIFRA calls for the Agency to determine, after submission of relevant data concerning an active ingredient, whether products containing the active ingredient are eligible for reregistration. The Agency has previously identified and required or waived the submission of the generic (i.e., active ingredient specific) data required to support reregistration of products containing silicon dioxide and silica gel as active ingredients. The Agency has completed its review of these generic data, and has determined that the data are sufficient to support reregistration of products containing silicon dioxide and silica gel. Appendix B identifies the generic data requirements that the EPA reviewed as part of its determination of reregistration eligibility of silicon dioxide and silica gel and lists the submitted studies that the EPA found acceptable.

The data identified in Appendix B as well as information from the open literature are sufficient to allow the Agency to conduct a reasonable risk assessment for the registered uses of silicon dioxide and silica gel. The data available to the EPA supports the conclusion that the registered uses of silicon dioxide and silica gel will not result in unreasonable adverse effects to the environment. The Agency has determined that all products containing silicon dioxide and silica gel as the active ingredients are eligible for reregistration. The reregistration of particular products is addressed in section V of this document ("Product Reregistration").

The Agency made its reregistration eligibility determination based upon the target data base required for reregistration, the current guidelines for conducting acceptable studies to generate such data, and the data identified in Appendix B. Although the EPA has found that products containing silicon dioxide and silica gel are eligible for reregistration, it should be understood that the EPA may take appropriate regulatory action, and/or

require the submission of additional data to support reregistration of products containing silicon dioxide and silica gel, if new information comes to the EPA's attention or if the data requirements for registration (or the guidelines for generating such data) change.

B. ADDITIONAL GENERIC DATA REQUIREMENTS

The generic data base supporting the reregistration of products containing silicon dioxide and silica gel has been reviewed and determined to be complete for reregistration. No further generic data are required.

C. LABELING REQUIREMENTS FOR MANUFACTURING USE PRODUCTS CONTAINING SILICON DIOXIDE AND SILICA GEL

The labels and labeling of all products must comply with EPA's current regulations and requirements. Follow the instructions in the Product Reregistration Handbook with respect to labels and labeling. Any product label which allows both manufacturing and end use must be amended to specify only manufacturing or end use. In this situation, if a registrant amends his/her label to specify manufacturing use only and wishes to retain end use registration, he/she must apply for a separate end/use product registration.

Although there are no technicals or MUP's for silicon dioxide (diatomaceous earth) there are MUP's for silica gel.

V. PRODUCT REREGISTRATION

A. DETERMINATION OF ELIGIBILITY

Based on the reviews of the generic data for the active ingredients, silicon dioxide and silica gel, the products containing these active ingredients are eligible for reregistration. Section 4(g)(2)(B) of FIFRA calls for the EPA to obtain any needed product-specific data regarding the pesticide after a determination of eligibility has been made. The EPA will review these data when they have been submitted and/or cited and determine whether to reregister individual products.

B. PRODUCT SPECIFIC DATA REQUIREMENTS

The product-specific data requirements are stated

in the attached appendices.

C. LABELING REQUIREMENTS FOR END-USE PRODUCTS CONTAINING SILICON DIOXIDE AND SILICA GEL

The labels and labeling of all products must comply with EPA's current regulations and requirements. Follow the instructions in the Product Reregistration Handbook with respect to labels and labeling. Any product label which allows both manufacturing and end use must be amended to specify only manufacturing or end use. In this situation, if a registrant amends his label to specify end-use registration and wishes to retain manufacturing use registration, he must apply for a separate manufacturing use product registration.

Product labels must specify the active ingredient concentration as a percentage by weight if solid. If the product is a liquid, the ingredients statement must have a substatement giving the pounds per gallon of the product. The application rate, maximum number of applications, and minimum interval between applications must be included. All sites where application is permitted must be specifically listed.

For end-use products containing silicon dioxide as the sole active ingredient and which are used commercially, the following statement is required:

"Wear a suitable dust mask approved by NIOSH/MSHA."

APPENDIX A

USE PATTERNS SUBJECT TO REREGISTRATION

SILICON DIOXIDE AND SILICA GEL

APPENDIX B

Generic Data Requirements for Reregistration of Silicon Dioxide and Silica Gel and Data Citations Supporting Reregistration

GUIDE TO APPENDIX B

Appendix B contains listings of data requirements which support the reregistration for the pesticide covered by this Reregistration Eligibility Document.

Appendix B contains generic data requirements that apply to the pesticide in all products, including data requirements for which a "typical formulation" is the test substance.

The data tables are generally organized according to the following format:

1. Data Requirement (Column 1). The data requirements are listed in the order in which they appear in 40 CFR Part 158. The reference numbers accompanying each test refer to the test protocols set out in the Pesticide Assessment Guidelines, which are available from the National Technical Information Service, 5285 Port Royal Road, Springfield, VA 22161.

2. Use Pattern (Column 2). This column indicates the use patterns to which the data requirement applies. The following letter designations are used for the given use patterns:

A	Terrestrial food
B	Terrestrial feed
C	Terrestrial non-food
D	Aquatic food
E	Aquatic non-food outdoor
F	Aquatic non-food industrial
G	Aquatic non-food residential
H	Greenhouse food
I	Greenhouse non-food crop
J	Forestry
K	Residential Outdoor
L	Indoor food
M	Indoor non-food
N	Indoor medical
O	Indoor residential

Any other designations will be defined in a footnote to the table.

3. Bibliographic citation (Column 3). If the EPA has acceptable data in its files, this column lists the identifying number of each study. This normally is the Master Record Identification (MRID) number, but may be a GS number if no MRID number has been assigned. Refer to the Bibliography Appendices for a complete citation of the study.

APPENDIX B

DATA SUPPORTING GUIDELINE REQUIREMENTS FOR REREGISTRATION OF SILICON DIOXIDE

GUIDELINE CITATION	TITLE OF STUDY	USE PATTERNS	BIBLIOGRAPHIC CITATION

PRODUCT CHEMISTRY

Sufficient data exists to support reregistration of this chemical.

ECOLOGICAL EFFECTS

EPA waived 40 CFR Part 158 requirements as discussed in Section III.

TOXICOLOGY

EPA waived 40 CFR Part 158 requirements as discussed in Section III.

ENVIRONMENTAL FATE

EPA waived 40 CFR Part 158 requirements as discussed in Section III.

RESIDUE CHEMISTRY

EPA waived 40 CFR Part 158 requirements as discussed in Section III.

OCCUPATIONAL AND RESIDENTIAL EXPOSURE

EPA waived 40 CFR Part 158 requirements as discussed in Section III.

APPENDIX B

DATA SUPPORTING GUIDELINE REQUIREMENTS FOR REREGISTRATION OF SILICA GEL

GUIDELINE CITATION	TITLE OF STUDY	USE PATTERNS	BIBLIOGRAPHIC CITATION

PRODUCT CHEMISTRY

Sufficient data exists to support reregistration of this chemical.

ECOLOGICAL EFFECTS

EPA waived 40 CFR Part 158 requirements as discussed in Section III.

TOXICOLOGY

EPA waived 40 CFR Part 158 requirements as discussed in Section III.

ENVIRONMENTAL FATE

EPA waived 40 CFR Part 158 requirements as discussed in Section III.

RESIDUE CHEMISTRY

EPA waived 40 CFR Part 158 requirements as discussed in Section III.

OCCUPATIONAL AND RESIDENTIAL EXPOSURE

EPA waived 40 CFR Part 158 requirements as discussed in Section III.

APPENDIX C

SILICON DIOXIDE AND SILICA GEL BIBLIOGRAPHY

Citations Considered to be Part of the
Data Base Supporting Reregistration

GUIDE TO APPENDIX C

1. CONTENT OF BIBLIOGRAPHY. This bibliography contains citations of all studies considered relevant by EPA in arriving at the positions and conclusions stated elsewhere in the Reregistration Eligibility Document. Primary sources for studies in this bibliography have been the body of data submitted to EPA and its predecessor agencies in support of past regulatory decisions. Selections from other sources including the published literature, in those instances where they have been considered, will be included.

2. UNITS OF ENTRY. The unit of entry in this bibliography is called a "study". In the case of published materials, this corresponds closely to an article. In the case of unpublished materials submitted to the EPA the EPA has sought to identify documents at a level parallel to the published article from within the typically larger volumes in which they were submitted. The resulting "studies" generally have a distinct title (or at least a single subject), can stand alone for purposes of review, and can be described with a conventional bibliographic citation. The EPA has attempted also to unite basic documents and commentaries upon them, treating them as a single study.

3. IDENTIFICATION OF ENTRIES. The entries in this bibliography are sorted numerically by Master Record Identifier, or MRID number. This number is unique to the citation, and should be used at any time specific reference is required. It is not related to the six-digit "Accession Number" which has been used to identify volumes of submitted studies; see paragraph 4(d)(4) below for further explanation. In a few cases, entries added to the bibliography late in the review may be preceded by a nine-character temporary identifier. These entries are listed after all MRID entries. This temporary identifier number is also to be used whenever specific reference is needed.

4. FORM OF ENTRY. In addition to the Master Record Identifier (MRID), each entry consists of a citation containing standard elements followed, in the case of material submitted to EPA, by a description of the earliest known submission. Bibliographic conventions used reflect the standards of the American National Standards Institute (ANSI), expanded to provide for certain special needs.

a. Author. Whenever the EPA could confidently identify one, the EPA has chosen to show a personal author. When no individual was identified, the EPA has shown an identifiable laboratory or testing facility as author. As a last resort, the EPA has shown the first submitter as author.

b. Document date. When the date appears as four digits with no question marks, the EPA took it directly from the document. When a four-digit date is followed by a question mark the bibliographer deduced the date from evidence in the document. When the date appears as (19??), the EPA was unable to determine or estimate the date of the document.

c. Title. In some cases, it has been necessary for EPA bibliographers to create or enhance a document title. Any such editorial insertions are contained between square brackets.

d. Trailing parentheses. For studies submitted to the EPA in the past, the trailing parentheses include (in addition to any self-explanatory text) the following elements describing the earliest known submission:

(1) Submission date. The date of the earliest known submission appears immediately following the word "received."

(2) Administrative number. The next element, immediately following the word "under," is the registration number, experimental use permit number, petition number, or other administrative number associated with the earliest known submission.

(3) Submitter. The third element is the submitter, following the phrase "submitted by." When authorship is defaulted to the submitter, this element is omitted.

(4) Volume Identification (Accession Numbers). The final element in the trailing parentheses identifies the EPA accession number of the volume in which the original submission of the study appears. The six-digit accession number follows the symbol "CDL," standing for "Company Data Library." This accession number is in turn followed by an alphabetic suffix which shows the relative position of the study within the volume. For example, within accession number 123456, the first study would be 123456-A; the second, 123456-B; the 26th, 123456-Z; and the 27th, 123456-AA.

OFFICE OF PESTICIDE PROGRAMS

REREGISTRATION ELIGIBILITY DOCUMENT

BIBLIOGRAPHY

-- No studies --

Attachment 7

000586.001

ATTACHMENT 7

Pages 000588 - 000617 have been removed in accordance with copyright laws. Please see appended bibliography list of the references that have been removed from this request.

Attachment 8

000617.001

ATTACHMENT 8

Pages 000619 - 000647 have been removed in accordance with copyright laws. Please see appended bibliography list of the references that have been removed from this request.

SUBMISSION END

Reference List for Industry Submission, GRN 000298

Pages	*Author*	*Title*	*Publish Date*	*Publisher*	*BIB_Info*
000015 - 000059	Life Sciences Research Office Federation of American Societies for Experimental Biology	Evaluation of the Health Aspects of Certain Silicates as Food Ingredients	1979	Life Sciences Research Office	NA
000061 - 000309	NA	Synthetic Amorphous Silica and Silicates	2004	OCED SIDS UNEP	NA
000311 - 000547	NA	Synthetic Amorphous Silica	September 2006	JACC	Number 51
000549 - 000550	NA	Silicon Dioxide	1996	Food Chemicals Codex	Fourth Edition
000588 - 000617	Kirk, Raymond E.; Othmer, Donald F.	Silica	December 1996	Encyclopedia of Chemical Technology	Fourth Edition, Volume 21
000619 - 000647	Kirk, Raymond E.; Othmer, Donald F.	Amorphous Silica	December 1996	Encyclopedia of Chemical Technology	Fourth Edition, Volume 21

NA- Not applicable

AM

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October 9, 2009

Stacey Williams
Office of Food Additive Safety
Center for Food Safety and Applied Nutrition
Office of Foods
Food and Drug Administration (FDA)
4300 River Road
College Park, MD 20740

re: GRAS Notice for Silicon Dioxide
GRAS Notice No. 298
Submitter: Cabot Corporation

Dear Stacey:

On behalf of Cabot Corporation, I am requesting that FDA withdraw GRAS Notice No. 298. As we discussed, Cabot intends to resubmit the notice shortly in accordance with FDA's comments on the July 14, 2009 submission.

If you have questions about this correspondence, please contact me at (202) 393-3903, ext. 14.

Sincerely,
(b) (6)

Eliot Harrison
Agent for Cabot

000650