OFFICE OF CHEMICAL SAFETY AND POLLUTION PREVENTION

WASHINGTON, D.C. 20460

March 6, 2024

MEMORANDUM

SUBJECT: IN-11409; Silane, hexadecyltrimethoxy-, hydrolysis products with silica: Human Health Risk Assessment and Ecological Effects Assessment to Support Inert Ingredient Approval for use in Pesticide Formulations

PC Code: 700782
Case No.: 00482681
Petition No.: IN-11409

CAS No.: 199876-45-4
Registration No.: N/A
Regulatory Action: Addition to inert ingredient list

FROM: Mohamed Ghorab, PhD, Toxicologist
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1. EXECUTIVE SUMMARY

In 2021, Evonik Corporation, 299 Jefferson Road, Parsippany, NJ 07054, submitted petition IN-11409 to the Environmental Protection Agency (herein referred to as EPA or the Agency). This petition requests an exemption from the requirement of a tolerance for residues of silane, hexadecyltrimethoxy-, hydrolysis products with silica (CAS Reg. No. 199876-45-4) when used as an inert ingredient [stabilizing emulsion (Pickering emulsion)] in pesticide formulations under 40 CFR 180.910 and 180.950 at no more than 0.6% by weight of the pesticide formulation. At this point, there is insufficient information to assess uses under 40 CFR 180.950 and the petitioner has since formally withdrawn this portion of the petition request. Therefore, the current document assessed uses under 40 CFR 180.910 only. The purpose of this document is to assess the risk to human health and the environment from this compound when used as an inert ingredient in pesticide products.

Silane, hexadecyltrimethoxy-, hydrolysis products with silica exhibits low levels of acute toxicity via the oral route of exposure. In the rats, the oral LD_{50} is 5000 mg/kg. It is not a skin irritant or a skin sensitizer, and it is not irritating to the eyes. Silane, hexadecyltrimethoxy-, hydrolysis products with silica is anticipated to have low dermal and inhalation toxicity based on studies on surrogate chemicals.

The repeated-dose toxicity for silane, hexadecyltrimethoxy-, hydrolysis products with silica is low. No adverse effects were observed in a 90-day oral rat study or in a developmental toxicity study in rats up to the limit dose. No oral chronic or carcinogenicity studies are available for silane, hexadecyltrimethoxy-, hydrolysis products with silica. However, there are no structural alerts for carcinogenicity for silane, hexadecyltrimethoxy-, hydrolysis products with silica and there is low concern for genotoxicity or mutagenicity, based on negative results in mammalian and bacterial genotoxicity tests.

Neurotoxicity and immunotoxicity toxicity studies are not available for review. However, no evidence of neurotoxicity or immunotoxicity was seen in the available studies.

Based on the low toxicity, no toxicological endpoints of concern were selected for silane, hexadecyltrimethoxy-, hydrolysis products with silica. Therefore, a qualitative assessment is appropriate for all pathways of human exposure (dietary, residential, and occupational) for silane, hexadecyltrimethoxy-, hydrolysis products with silica. As part of its qualitative assessment, the Agency did not use safety factors for assessing risk, and no additional safety factor is needed for assessing risk to infants and children.

Based on the ecotoxicity and environmental fate data available, silane, hexadecyltrimethoxy-, hydrolysis products with silica is not expected to be toxic to aquatic plants or animals, and it is stable and insoluble in water and not accessible to biological transformation. The chemical structure and composition of these silica particles is of inorganic rather than of organic nature and consequently no biodegradation is expected. Therefore, concern for environmental effects is low.

Taking into consideration all available information, EPA concludes that there is a reasonable certainty that no harm to any population subgroup, including infants and children, will result from aggregate exposure to silane, hexadecyltrimethoxy-, hydrolysis products with silica when considering sources of pesticide exposure for which there is reliable information. Therefore, the use of silane, hexadecyltrimethoxy-, hydrolysis products with silica as an inert ingredient in pesticide formulations at a maximum concentration of 0.6 % of the finished product can be considered assessed as safe.

2. BACKGROUND

In 2021, EPA received a petition (IN-11409) from Evonik Corporation, 299 Jefferson Road, Parsippany, NJ 07054. This petition requests an exemption from the requirement of a tolerance for residues of silane, hexadecyltrimethoxy-, hydrolysis products with silica (CAS Reg. No. 199876-45-4) when used as an inert ingredient in pesticide formulations. This exemption is for use on growing crops and raw agricultural commodities pre- and post-harvest under 40 CFR 180.910. Silane, hexadecyltrimethoxy-, hydrolysis products with silica is to be used as a stabilizing emulsion (Pickering emulsion) in pesticide formulations at a maximum concentration of 0.6% of the finished product. This document provides an assessment of the risk to human health and the environment for silane, hexadecyltrimethoxy-, hydrolysis products with silica when used as an inert ingredient in pesticide formulations. Information from the submitter's petition is referenced in this assessment.

3. INERT INGREDIENT PROFILE

Silica is ubiquitous in the environment, with over 95% of the earth's crust made of minerals containing silica (Uhrlandt 2006)[1]. Synthetic amorphous silica (SAS) compounds are used in food packaging, cosmetics (e.g., toothpaste), pharmaceutical agents, direct food and feed additives, and in beer and wine clarification (FDA 2015a, 2015b; Fruijtier-Polloth 2012, 2016) [(2)]. Silane, hexadecyltrimethoxy-, hydrolysis products with silica, a form of SAS, is currently approved by EPA as a nonfood use inert ingredient.

Some of the physical and chemical characteristics of silane, hexadecyltrimethoxy-, hydrolysis products with silica along with its structure and nomenclature, are found in Table 1.

Table 1. Structure and Physico-chemical Properties of Silane, hexadecyltrimethoxy-, hydrolysis products with silica

Parameter	Value	Source
Structure	Inorganic solid with three-dimensional randomly ordered SiO4 tetrahedrons, with each oxygen atom belonging to two tetrahedron.	PubChem

[1] Uhrlandt S. 2006. Silica. In: Kirk-Othmer encyclopedia of chemical technology. Vol. 22. John Wiley & Sons, Inc., 1-17.

		(https://pubchem.ncbi.nlm.nih.gov/#query=199876-45-4)
CAS Reg. No.	199876-45-4	Submitter correspondence (December, 05th, 2022)
Molecular formula	SiO2 (core material)	
Molecular Weight (g/mol)	ca. 60.08 g/mol (silicon dioxide, bulk phase) amorphous	
Physical State	Solid (powder)	
Vapor pressure	The study does not need to be conducted because the material decomposes above 300°C and does not melt below that temperature. SAS does not show any vapor pressure.	
Partition Coefficient (log P(o/w)	N.A. (theoretically calculated ca. -1.4)	
Density (g/mL at 20°C)	Skeletal density ca. 2.0 - 2.2 g/cm³	
Melting Point (°C)	ca. 1700 °C	
Water Solubility	193 mg/l	

4. HAZARD CHARACTERIZATION

4.1. Toxicity Studies Available for Analysis

Acute toxicity studies are available for silane, hexadecyltrimethoxy-, hydrolysis products with silica. A read-across approach using data from analogues has been used to inform the human health assessment where data gaps exist. Analogues were selected based on structural similarity, similar physical and chemical properties and toxicokinetics and the availability of relevant empirical data.

The chemical with CAS Reg. No. 199876-45-4 is a synthetic amorphous silica (SAS) and similar SAS substances have been selected as surrogates. SAS materials exist as highly pure, finely divided, white, fluffy powders. The characteristic feature of SAS is its high specific surface area, which is related to the very small size of its primary particles. Isolated primary particles do not exist as individual units but as non-dispersible aggregates or dispersible agglomerates.

Category/Analogue Rationale

The similarity in the chemical structure, composition, production and processing as well as the similarity in physicochemical properties and the available toxicological and health data, strongly suggest that the impact on the living organism and environment should not differ considerably between the category members: synthetic amorphous silica (SAS) (CAS No 7631-86-9) and synthetic amorphous silicates, Na-Al silicates (NAS) (CAS No 1344-00-9) and Ca silicates (CS) (CAS No 1344-95-2). They all form fine powders of amorphous particles between 1 and 350 µm with high surface areas.

The cluster analysis and resultant bridging/read-across analysis include an evaluation of the available studies and modeled data to address the physicochemical, mammalian metabolism, mammalian toxicological, environmental fate, and ecotoxicological endpoints.

Table 2: The physicochemical properties for silane, hexadecyltrimethoxy-, hydrolysis products with silica and its surrogates

	Target	**Source**		
Parameters	**Typical values AEROSIL® R 816**	**Typical values AEROSIL® R 972**	**Typical values AEROSIL®R 974**	**Typical values AEROSIL® R 812 S**
CAS Reg. No.	199876-45-4	68611-44-9	68611-44-9	68909-20-6
Chemical Name	Silane, hexadecyltrimethoxy-, hydrolysis products with silica	Silane, dichlorodimethyl-, reaction products with silica	Silane, dichlorodimethyl-, reaction products with silica	Silanamine,1,1,1-trimethyl-N-(trimethylsilyl)-, hydrolysis products with silica
Constituent particle (Internal structure) size - Internal structures cannot be isolated. d_{50}, TEM, number based	7.3 nm	8.9 nm	7.8 nm	6.4 nm

Agglomerate size distribution = particle size as sold to the market. d_{50}, volume based laser diffraction.	18.2 µm	9.5 µm	10.3 µm	16.9 µm
Morphology / Shape	Aggregates composed of intergrown spheroidal internal structures	Aggregates composed of intergrown spheroidal internal structures	Aggregates composed of intergrown spheroidal internal structures	Aggregates composed of intergrown spheroidal internal structures
Crystallographic structure	amorphous	amorphous	amorphous	amorphous
Specific surface area	190 m^2/g	103 m^2/g	154 m^2/g	212 m^2/g
Molecular structure	Inorganic solid with three-dimensional randomly ordered SiO_4 tetrahedrons, with each oxygen atom belonging to two tetrahedrons (silicon dioxide, bulk phase)	Inorganic solid with three-dimensional randomly ordered SiO_4 tetrahedrons, with each oxygen atom belonging to two tetrahedrons (silicon dioxide, bulk phase)	Inorganic solid with three-dimensional randomly ordered SiO_4 tetrahedrons, with each oxygen atom belonging to two tetrahedrons (silicon dioxide, bulk phase)	Inorganic solid with three-dimensional randomly ordered SiO_4 tetrahedrons, with each oxygen atom belonging to two tetrahedrons (silicon dioxide, bulk phase)
Molecular weight	ca. 60.08 g/mol (silicon dioxide, bulk phase)	ca. 60.08 g/mol (silicon dioxide, bulk phase)	ca. 60.08 g/mol (silicon dioxide, bulk phase)	ca. 60.08 g/mol (silicon dioxide, bulk phase)

Surface characteristics	Hexadecylsilyloxygroups (O_3Si-$C_{16}H_{33}$) covalently bond to the surface	(dimethylsilyl) oxygroups ($O_2Si(CH_3)_2$) covalently bond to the surface	(dimethylsilyl)oxygroups ($O_2Si(CH_3)_2$) covalently bond to the surface	(trimethylsilyl)oxygroups ($OSi(CH_3)_3$) covalently bond to the surface
Water solubility (enhanced OECD 105 with 0,5% EtOH	193 mg/l	107 – 232 mg/l	115 – 262 mg/l	134 mg/l
Logkow	A study is technically not feasible.			
Boiling point	Study not conducted because the substance is a solid which decomposes before boiling.			
Vapor pressure	Study not conducted because the material decomposes above 300°C and does not melt below that temperature.			

Acute Toxicity Studies

Acute Oral

In an acute oral toxicity study, groups of Sprague Dawley rats (3 female animals/group), approximately 6-7 weeks of age were given a single oral dose of 5000 mg/kg body weight of silane, hexadecyltrimethoxy-, hydrolysis products with silica (also known as AEROSIL® R 816)(99.9% purity) dissolved in arachidis oil (MRID No. 51067001). The animals were then observed twice a day for the following 14 days. There were no treatment-related effects on survival, clinical signs, body weight or necropsy findings in female rats. The oral LD_{50} of silane, hexadecyltrimethoxy-, hydrolysis products with silica is > 5000 mg/kg body weight in female rats.

Acute Dermal

In an acute dermal toxicity study performed according to OECD Guideline 402, groups of 10 CD Crl: (SD) rats (5/sex) with males 51 days of age and females 65 days of age were dermally exposed to 2000 mg/kg of test substance AEROSIL® R 202 (CAS Reg. No. 67762-90-7). The test substance is a surface treated SAS with polydimethylsiloxane (99.1% purity). Treatment was for 24 hours to an area of approximately 1/10 body surface (MRID No. 51067201). Following exposure, the animals were observed at least once daily for a period of 14 days. No clinical signs of toxicity or skin reactions were observed. The dermal LD_{50} is >2000 mg/kg body weight in rats.

Acute Dermal Irritation

In a primary dermal irritation study, 3 female New Zealand White Specific Pathogen Free (SPF), approximately 9 to 11 weeks old rabbits were dermally exposed to undiluted 0.5 g aliquot of silane, hexadecyltrimethoxy-, hydrolysis products with silica (99.9% purity) for 4 hours. Animals then were observed for 72 hours (MRID No. 51067201). No erythema or oedema was noted during the 1-, 24-, 48- and 72-hour observations, all irritation effects were reversible. Based on the results of this study, silane, hexadecyltrimethoxy-, hydrolysis products with silica is not a dermal irritant.

Acute Inhalation

No acute inhalation study is available for silane, hexadecyltrimethoxy-, hydrolysis products with silica. However, an acute inhalation toxicity study with the surrogate chemical silane, dichlorodimethyl-, reaction products with silica (CAS Reg. No. 68611-44-9) is available.

Groups of 10 Wistar rats (5/sex) 6-7 weeks of age were exposed (whole body) to inhalation (dust) of the test substance (also known as AEROSIL R 974) at a concentration 0.477 mg/L (477 mg/m^3) for 4 hrs. Animals were observed for a period of 14 days post-treatment. This study followed OECD Guideline 403 (1983). No lethal effects were observed [2]

Primary Eye Irritation

In an acute eye irritation study, 0.1 g (100 mg) of silane, hexadecyltrimethoxy-, hydrolysis products with silica (AEROSIL R816) (99.9% purity) was instilled into the conjunctival sac of the right eye of three female New Zealand White Specific Pathogen Free (SPF) rabbits for 72 hours (MRID No. 51067101) according to OECD guideline 405. The left eye remained untreated and served as the control. The eye was thoroughly rinsed with tepid tap water 24 hours after instillation to finish the exposure. Mild conjunctival reactions (erythema, edema, and lacrimation) were reported for a period of 72 hours after instillation. There were no lesions reported to the cornea or iris. All irritation effects reported resolved within 72 hours of exposure (slight chemosis and slight/moderate redness and discharge of the conjunctivae, reversible by 24 hours, were recorded in the animals following exposure to the test item). Based on the results of this study, silane, hexadecyltrimethoxy-, hydrolysis products with silica (AEROSIL R816) is not an eye irritant.

Dermal sensitization

The sensitizing potential of silane, hexadecyltrimethoxy-, hydrolysis products with silica (AEROSIL R816) was tested in a Magnusson and Kligman maximization method using female Pirbright white guinea pigs 4 to 5 weeks of age following OECD guideline 405. A 20% concentration of silane, hexadecyltrimethoxy-, hydrolysis products with silica (99.9% purity) dissolved in paraffin oil was found to be minimally irritating (intracutaneous and epicutaneous), while a 20 % concentration was non-irritating (epicutaneous) to the skin of the guinea pigs (MRID No. 51067301). After intracutaneous and epicutaneous (occlusive / 48 hours) induction using the minimally irritating concentrations, the challenge was performed with the maximally non-irritating concentration (occlusive/24 h). In the first challenge both the treated and the controls showed no skin reactions. After the second challenge, (test

[2] Appelman, L.M, ten Berge, W.F.,and Zwart, A. (1983). Concentration-time mortality response relationship of irritant and systemically acting vapours and gases. J. Hazard. Mater. 13: 301-309.

concentration lowered to 0.1%) both the treated and control groups showed no reaction observed at challenge. Under the conditions of this study, silane, hexadecyltrimethoxy-, hydrolysis products with silica is considered a non-sensitizer in guinea pigs.

Repeated Dose Toxicity Studies

Subchronic Oral Toxicity

The surrogate substance AEROSIL® R 972 (alkylsilylated silica) was evaluated for repeated dose oral toxicity in rats. Wistar rats (20/sex/dose) were administered doses of 0 and 500 mg/kg bw/day (corresponding to an actual dose of 491.5 mg/kg bw/day) via feed for 6 months and following GLP guidelines. During the treatment period, animals were observed for mortality, clinical signs, behavior, body weight and food consumption at defined intervals. Blood samples for clinical pathology, hematology and clinical chemistry examinations were collected every month. Gross pathological examination on all animal organs were also performed. No treatment related mortality was seen (three dead animals, two of them in the control group). No effects were observed in clinical signs, or food consumption. No effects were observed on body weight and body weight changes. There were no changes in behavior or hematological parameters in treated animals. There was no effect observed on gross pathological findings of treated animals. The NOAEL is ≥500 mg/kg/day, a LOAEL is not established (Leuschner F. 1965).

Inhalation toxicity

Although no acceptable repeated dose inhalation toxicity study is available for silane, hexadecyltrimethoxy-, hydrolysis products with silica, concern for systemic effects from inhalation exposure is low because only minor amounts (less than 1%) of the commercially available SAS types have been measured as respirable (alveolar fraction < 10 µm mass median aerodynamic diameter). Using the same measurement techniques, > 99% of the particle fraction of the commercial product is in excess of 90 µm in diameter and can only reach the upper airways (nasal passages and throat) or cannot be inhaled at all[3]. Furthermore, no effects were observed in the available acute inhalation study and the substance will be used at very low concentrations (maximum concentration of 0.6%).

Neurotoxicity and Immunotoxicity

There are no neurotoxicity or immunotoxicity studies available. However, no signs of neurotoxicity or immunotoxicity were observed in the available studies associated with SAS.

Developmental Toxicity

2 ECETOC JACC REPORT No. 51 ECETOC AISBL European Centre for Ecotoxicology and Toxicology of Chemicals Synthetic Amorphous Silica (CAS No. 7631-86-9) https://www.ecetoc.org/wp-content/uploads/2021/10/JACC-051.pdf

In a limited one-generation study, Wistar rats (males/females) were administered doses of 0 and 500 mg/kg bw/day of AEROSIL® R 972 (alkylsilylated SAS) via feed. One male was mated with five females. Animals were treated from 8- or 17-weeks premating and dosing was continued until the 4th week of lactation. The rats were observed daily for mortality, body weight changes, and clinical signs. Necropsy with gross pathological examinations were performed after sacrificing the animals. During the treatment period, animals were observed for mortality, clinical signs, and reproductive performance.

No treatment related effects were observed on mortality, clinical signs, or reproductive performance. No treatment related gross pathological or histopathological changes occurred in parental animals. There were no treatment-related effects in pups during the lactation on clinical signs, body weight and developmental or structural abnormalities. Overall, there were no effects on fertility. The parental, reproductive and offspring NOAEL is 500 mg/kg/day and a LOAEL was not established (Leuschner, 1965).

Mutagenicity

The surrogate substance AEROSIL® R 972 (alkylsilylated SAS) was extracted with toluene and evaluated for *in vitro* genotoxicity in Salmonella typhimurium TA 98, TA 100, TA 1537 and Escherichia coli WP2 uvrA with and without metabolic activation (S9-mix). The strain TA98 was tested with S9-mix in the presence of the epoxide hydrolase inhibitor and GSH depletory 1,1,1-trichloropropene-2-3-oxide to increase the sensitivity of the test. Negative (vehicle) and positive controls were included. The experiments were conducted according to the direct plate incorporation method. The maximum concentration tested (1580 µg/plate) was selected based on precipitation criteria. Toxicity was not reported and no biologically relevant increase in the number of revertant colonies was observed with any bacterial strain either with or without S9-mix. All solvent and positive controls gave numbers of revertant colonies within the expected ranges. Therefore, the experiment was considered valid. Under the experimental conditions of the study, test substance was not mutagenic in the bacterial reverse mutation test, either in the presence or absence of S9-mix (Degussa Corp., 1983). Based on these results, silane, hexadecyltrimethoxy-, hydrolysis products with silica is not anticipated to be mutagenic.

The surrogate substance AEROSIL® R 812 S (surface treated) was examined according to OECD Guideline 490 for induction of 5-trifluorothymidine resistant mutants in mouse lymphoma L5178Y cells. Two independent assays for mutation at the TK locus were performed using the dose levels of 2.34, 4.69, 9.38, 18.8, 37.5, and 150 µg/mL in the absence and presence of S9-mix, using a fluctuation method. Cytotoxicity test: Both in the absence and presence of S9-mix, the test substance was assayed at a maximum dose level of 300 µg/mL and at a wide range of lower dose levels; 150, 75.0, 37.5, 18.8, 9.38, 4.69, 2.34 and 1.17 µg/mL. Solvent, vehicle, and positive control treatments were included in each experiment. No relevant increases in mutant frequencies were observed following treatment with the test substance, in the absence or presence of S9-mix. Under the conditions of this study, the test substance did not induce mutations in mouse lymphoma L5178Y cells with or without S9-mix (Getuli, 2008).

Chronic/Carcinogenicity

The surrogate substance AEROSIL® R 972 (alkylsilyated SAS) was evaluated for potential carcinogenicity in rats. Wistar rats (20/sex/group) were administered doses of 0 or 100 mg/kg bw/day in diet for 2 years. Endpoints evaluated included mortality, clinical signs, body weights and body weight changes hematology and clinical chemistry, necropsy findings for all animals as well as organ weights and histopathology. No analysis of the dose formulations used in the study to confirm the final test substance concentrations was reported. There were no deaths and no treatment-related changes in the various parameters monitored and examinations performed including blood clinical chemistry, hematological and histopathological examinations. The study authors did not derive a NOAEL for the study. However, based on the results, the NOAEL of the test substance in male and female rats following lifetime exposure can be considered to be 100 mg/kg/day (Mosinger, 1969).

4.2. Toxicity Endpoint Selection

The available toxicity studies indicate that silane, hexadecyltrimethoxy-, hydrolysis products with silica has low overall toxicity. Silane, hexadecyltrimethoxy-, hydrolysis products with silica has low acute toxicity via the oral and dermal routes, it is not an eye or skin irritant, and it is not a skin sensitizer. No adverse effects were reported in the 90-day study in rats. No adverse developmental effects were found in the developmental toxicity study in rats. Furthermore, concern for carcinogenicity is low, based on negative results in mutagenicity studies, and the lack of adverse effects in a chronic study with an SAS surrogate. Therefore, based on the low toxicity of silane, hexadecyltrimethoxy-, hydrolysis products with silica, no endpoint of concern was identified for oral, dermal or inhalation exposure assessments, and a quantitative risk assessment is not necessary.

4.3. Special Considerations for Infants and Children

Based on the low toxicity of silane, hexadecyltrimethoxy-, hydrolysis products with silica in the available studies, EPA has concluded that there are no toxicological endpoints of concern for the U.S. population, including infants and children. As part of its qualitative assessment, the Agency did not use safety factors for assessing risk, and no additional safety factor is needed for assessing risk to infants and children.

5. EXPOSURE ASSESSMENT

Dietary Exposure: Dietary exposure to silane, hexadecyltrimethoxy-, hydrolysis products with silica may occur from eating foods treated with pesticide formulations containing this inert ingredient and drinking water containing runoff from soils containing the treated crops. However, no toxicological endpoints of concern were selected, and therefore, a quantitative dietary exposure assessment for silane, hexadecyltrimethoxy-, hydrolysis products with silica was not conducted.

Residential Exposure: The term “residential exposure” is used in this document to refer to non-occupational, non-dietary exposure (e.g., for lawn and garden pest control, indoor pest control,

termiticides, and flea and tick control on pets). Although the current and proposed uses of silane, hexadecyltrimethoxy-, hydrolysis products with silica can result in residential exposures, no toxicological endpoints were selected, and therefore, it is not necessary to conduct a quantitative assessment of residential exposures and risks.

Occupational Exposure: Although the current and proposed uses of silane, hexadecyltrimethoxy-, hydrolysis products with silica can result in occupational exposures, no toxicological endpoints were selected, and therefore, it is not necessary to conduct a quantitative assessment of occupational exposures and risks.

6. AGGREGATE/COMBINED RISK ASSESSMENT

The Federal Food, Drug, and Cosmetic Act (FFDCA) section 408 directs EPA to consider available information concerning exposure from the pesticide residue in food and other non-occupational exposures to determine that "there is a reasonable certainty that no harm will result from aggregate exposure to the pesticide chemical residue, including all anticipated dietary exposures and all other exposures for which there is reliable information".

Because no toxicological endpoints were selected, a qualitative risk assessment was conducted and subsequently, it is not necessary to aggregate dermal and inhalation residential exposures with estimated dietary exposures.

7. CUMULATIVE EXPOSURE

Section 408(b)(2)(D)(v) of FFDCA requires that, when considering whether to establish, modify, or revoke a tolerance, the Agency consider "available information" concerning the cumulative effects of a particular pesticide's residues and "other substances that have a common mechanism of toxicity."

EPA has not found silane, hexadecyltrimethoxy-, hydrolysis products with silica to share a common mechanism of toxicity with any other substances, and silane, hexadecyltrimethoxy-, hydrolysis products with silica does not appear to produce a toxic metabolite produced by other substances. For the purposes of this tolerance exemption, therefore, EPA has assumed that silane, hexadecyltrimethoxy-, hydrolysis products with silica does not have a common mechanism of toxicity with other substances. For information regarding EPA's efforts to determine which chemicals have a common mechanism of toxicity and to evaluate the cumulative effects of such chemicals, see EPA's website at https://www.epa.gov/pesticide-science-and-assessing-pesticide-risks/cumulative-assessment-risk-pesticides.

8. ECOTOXICITY AND ENVIRONMENTAL FATE

Environmental fate

SAS (CAS Reg. No. 7631-86-9 and 1344-00-9) are not volatile and have no lipophilic character. SAS will therefore settle mainly into soils/sediments and weakly into water. Silicates are found throughout the Earth's lithosphere. The ocean contains a huge reservoir of silica and silicates which are used by a variety of marine organisms (diatoms, radiolarians, sponges) to build up their skeletons. Based on the chemical nature of silica and silicates (inorganic structure and chemical stability of the compound: Si O bond is highly stable), no photo- or chemical degradation is expected (OECD, 2004). Due to its inherent physico-chemical properties, such as the absence of lipophilicity as well as the capability of organisms to eliminate absorbed SiO2 components, bioaccumulation is not to be expected.

Ecotoxicity

In the reviews by the OECD (2004) and the ECETOC (2006), no acute toxicity was reported for fish and daphnia, even after exposures to extremely high concentrations of SAS (CAS Reg. No. 7631-86-9). Aerosil R 974 was tested on Zebrafish (*Brachydanio rerio*) at rate, up to 10 000 mg/L. Physical effects on daphnia were observed in tests using unfiltered test medium. No effects were found in acute ecotoxicity studies with surface treated SAS (EPA, 2011). With regard to chronic aquatic toxicity data, the OECD (2004) concluded that although there were no chronic aquatic toxicity data for SAS, there is no evidence of harmful long-term effects due to the known inherent physicochemical properties, absence of acute toxic effects as well as the ubiquitous presence of silica and silicates in the environment.

As the surface modified amorphous silica are hydrophobic, nearly insoluble (<1 µg/L) and complicated to analyze, these substances are difficult to test according to the standard ecotoxicity guidelines. However, the substance dimethyldichlorosilane (CAS 68611-44-9; Aerosil R972, Aerosil R974 and Aerosil R976) tested at high dose rate, up to 10 000 mg/L, showed no toxicity to aquatic organisms[4].

Table 3: Summary of relevant information on acute aquatic toxicity

Method	Species	Exposure	Results[1]			Remarks	Reference
			LC_0	LC_{50}	LC_{100}		
OECD 203 (1984), GLP RI : 2	*Brachydanio rerio*	Static / 96h	>10000 mg/L	>10000 mg/L	>10000 mg/L	Substance tested: Aerosil R 974	Hooftman RN and van Drongelen-Sevenhuijsen D (1992a)
OECD 202 (1984), GLP RI : 2	*Daphnia magna*, immobilisation	Static / 48h	>10000 mg/L	>10000 mg/L	>10000 mg/L	Substance tested: Aerosil R 974	Hooftman RN and van Drongelen-Sevenhuijsen D (1992b)

[4] https://echa.europa.eu/documents/10162/312fb556-c177-3a58-bf67-9a7078aeac48

OECD 201 (1984), GLP RI : 2	*Scenedesmus subspicatus* Biomass and growth	Static / 72h	>10000 mg/L	>10000 mg/L	>10000 mg/L	24-h water extract of Aerosil R 972	Lebertz H (1999)

[1] Concerning the expression of the endpoints, normally the rule is to set the LC50 to the solubility limit. Based on the physico-chemical properties of the testsubstance which is practically insoluble in water, the result obtained for the acute toxicity tests expressed in nominal concentrations was accepted for biocides risk assessment purposes.

9. RISK CHARACTERIZATION

Based on the low toxicity of silane, hexadecyltrimethoxy-, hydrolysis products with silica in the available studies, EPA has concluded that there are no toxicological endpoints of concern for the U.S. population, including infants and children, and a qualitative assessment is appropriate for all pathways of human exposure. As part of its qualitative assessment, the Agency did not use safety factors for assessing risk, and no additional safety factor is needed for assessing risk to infants and children.

The highly hydrophobic surface modified SAS are very stable and insoluble in water and not accessible to biological transformation. The chemical structure and composition of these silica particles is of inorganic rather than of organic nature and consequently no biodegradation is expected. Therefore, there is low concern for environmental toxicity. Also, based on the available acute toxicity studies for various types of amorphous silica, silane, hexadecyltrimethoxy-, hydrolysis products with silica is anticipated to have low toxicity to aquatic organisms.

Taking into consideration all available information, EPA concludes that there is a reasonable certainty that no harm to any population subgroup will result from exposure to silane, hexadecyltrimethoxy-, hydrolysis products with silica when considering sources of pesticide exposure for which there is reliable information. Therefore, the use of silane, hexadecyltrimethoxy-, hydrolysis products with silica as an inert ingredient in food-use pesticide formulations at a maximum concentration of 0.6% of the finished product can be considered assessed as safe.

References

21 - Acute Eye Irritation Study in Rabbits_(AEROSIL R 816)_2012-0075-DGT01, Unpublished. MRID: 51067101.

Acute oral toxicity study in rats AEROSIL R 816 unpublished. MRID: 51067001.

Acute dermal irritation study in Rabbit AEROSIL R 816_2012-0077-DGT, Unpublished, MRID: 51067201.

Delayed dermal sensitization study in Guinea Pigs_AEROSIL R 816_2012-0079-DGT, Unpublished, 51067301.

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