

SCREENING-LEVEL HAZARD CHARACTERIZATION

Silane, Dichlorodimethyl-, Reaction Product with Silica (CASRN 68611-44-9)

The High Production Volume (HPV) Challenge Program¹ was conceived as a voluntary initiative aimed at developing and making publicly available screening-level health and environmental effects information on chemicals manufactured in or imported into the United States in quantities greater than one million pounds per year. In the Challenge Program, producers and importers of HPV chemicals voluntarily sponsored chemicals; sponsorship entailed the identification and initial assessment of the adequacy of existing toxicity data/information, conducting new testing if adequate data did not exist, and making both new and existing data and information available to the public. Each complete data submission contains data on 18 internationally agreed to “SIDS” (Screening Information Data Set¹⁺²) endpoints that are screening-level indicators of potential hazards (toxicity) for humans or the environment.

The Environmental Protection Agency’s Office of Pollution Prevention and Toxics (OPPT) is evaluating the data submitted in the HPV Challenge Program on approximately 1400 sponsored chemicals by developing hazard characterizations (HCs). These HCs consist of an evaluation of the quality and completeness of the data set provided in the Challenge Program submissions. They are not intended to be definitive statements regarding the possibility of unreasonable risk of injury to health or the environment.

The evaluation is performed according to established EPA guidance^{2,3} and is based primarily on hazard data provided by sponsors; however, in preparing the hazard characterization, EPA considered its own comments and public comments on the original submission as well as the sponsor’s responses to comments and revisions made to the submission. In order to determine whether any new hazard information was developed since the time of the HPV submission, a search of the following databases was made from one year prior to the date of the HPV Challenge submission to the present: (ChemID to locate available data sources including Medline/PubMed, Toxline, HSDB, IRIS, NTP, ATSDR, IARC, EXTTOXNET, EPA SRS, etc.), STN/CAS online databases (Registry file for locators, ChemAbs for toxicology data, RTECS, Merck, etc.) and Science Direct. OPPT’s focus on these specific sources is based on their being of high quality, highly relevant to hazard characterization, and publicly available.

OPPT does not develop HCs for those HPV chemicals which have already been assessed internationally through the HPV program of the Organization for Economic Cooperation and Development (OECD) and for which Screening Initial Data Set (SIDS) Initial Assessment Reports (SIAR) and SIDS Initial Assessment Profiles (SIAP) are available. These documents are presented in an international forum that involves review and endorsement by governmental authorities around the world. OPPT is an active participant in these meetings and accepts these documents as reliable screening-level hazard assessments.

¹ U.S. EPA. High Production Volume (HPV) Challenge Program; <http://www.epa.gov/chemrtk/index.htm>.

² U.S. EPA. HPV Challenge Program – Information Sources; <http://www.epa.gov/chemrtk/pubs/general/guidocs.htm>.

³ U.S. EPA. Risk Assessment Guidelines; <http://cfpub.epa.gov/ncea/raf/rafguid.cfm>.

These hazard characterizations are technical documents intended to inform subsequent decisions and actions by OPPT. Accordingly, the documents are not written with the goal of informing the general public. However, they do provide a vehicle for public access to a concise assessment of the raw technical data on HPV chemicals and provide information previously not readily available to the public.

Chemical Abstract Service Registry Number (CASRN)	68611-44-9
Chemical Abstract Index Name	Silane, dichlorodimethyl-, reaction product with silica
Structural Formula	See Appendix
Summary	
<p>CASRN 68611-44-9 is a white, amorphous substance produced by surface modification of synthetic amorphous silica with dimethyldichlorosilane. The substance has negligible vapor pressure and negligible water solubility due to the surface hydrophobicity. Volatilization, hydrolysis, atmospheric oxidation, and biodegradation are negligible. CASRN 68611-44-9 has high persistence (P3) and low bioaccumulation potential (B1).</p> <p>CASRN 68611-44-9 showed low acute oral toxicity and high acute inhalation toxicity in rats.</p> <p>In a 6-month repeated-dose oral (dietary) toxicity study in rats, no adverse effects were seen at 500 mg/kg-bw/day, the only dose tested. In a 2-week repeated-dose inhalation toxicity study in rats, histopathological changes in the lungs were seen in both sexes at 0.031 mg/L, the lowest concentration tested. A 13-week repeated-dose inhalation toxicity study in rats showed histopathological changes in the nose and lungs, and changes in clinical chemistry, hematology and urinalysis parameters at 0.035 mg/L, the only concentration tested. In three separate repeated-dose inhalation toxicity studies in female rats, each tested at single concentrations of 0.05 or 0.08 or 0.1 mg/L for 3-12 months, histopathological findings in the lungs and lymph nodes were seen at all single individually tested concentrations. No adequate reproductive toxicity studies are available for CASRN 68611-44-9, or for the untreated synthetic amorphous silica (silica gel, CASRN 112926-00-8), supporting chemical, which is the core material of CASRN 68611-44-9. In 6-month oral and 13-week inhalation repeated-dose toxicity studies in rats with CASRN 68611-44-9 summarized above, no effects were seen on male and female reproductive organ weight or histopathology at 500 mg/kg/day (oral) or 0.035 mg/L (inhalation), the only dose/concentration tested. No adequate developmental toxicity data are available on CASRN 68611-44-9. Prenatal developmental toxicity studies by the oral route in rats, rabbits and hamsters with the untreated synthetic amorphous silica (silica gel, CASRN 112926-00-8) showed no maternal or developmental toxicity at any dose level tested; the NOAELs for both maternal and developmental toxicity are 1340, 1350, and 1600 mg/kg/day in mice, rats, and rabbits/hamsters, respectively. CASRN 68611-44-9 did not induce genetic mutations in bacteria or chromosomal aberrations in mammalian cells <i>in vitro</i>. A chronic toxicity/carcinogenicity study in rats administered CASRN 68611-44-9 in the diet for 24 months showed no evidence of carcinogenicity. CASRN 68611-44-9 was not irritating to the rabbit eye or skin.</p>	

Based on low water solubility ($< 10^{-4}$ mg/L) and other physical chemical properties of this hydrophobic amorphous silica, acute and chronic toxicity (to fish and daphnia, and toxicity to aquatic plants) will likely not be observed for CASRN 68611-44-9, which is supported by the submitted acute toxicity studies showing no effects at saturation.

No data gaps were identified under the HPV Challenge Program.

The sponsors, Cabot Corporation, Degussa AG and Wacker-Chemie GmbH, submitted a Test Plan and Robust Summaries to EPA for dichlorodimethylsilane reaction products with silica (CASRN 68611-44-9; 9th CI name: silane, dichlorodimethyl-, reaction product with silica) on October 18, 2002. EPA posted the submission on the ChemRTK HPV Challenge website on November 4, 2002 (<http://www.epa.gov/chemrtk/pubs/summaries/sIndichl/c14020tc.htm>). EPA comments on the original submission were posted to the website on March 7, 2003. Public comments were also received and posted to the website. The sponsor submitted updated/revised documents on May 1, 2003 and May 27, 2003, which were posted to the ChemRTK website on June 6, 2003 and June 26, 2003, respectively.

Synthetic amorphous silica may yield pyrogenic silica, precipitated silica, or silica gel through a variety of processes. All three types of synthetic amorphous silica, when treated with dimethyldichlorosilane, are registered under the Chemical Abstracts Service (CAS) name “Silane, dichlorodimethyl-, reaction products with silica, i.e., the HPV chemical substance.

Supporting Chemical Justification

EPA believes that the available reproductive/developmental toxicity studies on CASRN 68611-44-9 are inadequate for the purposes of the HPV Challenge Program because the studies used only one dose, a low number of animals, and an inappropriate male:female mating ratio. The sponsor proposes using existing data on untreated amorphous silica (<http://www.epa.gov/chemrtk/pubs/summaries/sIndichl/c14020rt2.pdf>), which is the core material of CASRN 68611-44-9, to read-across for these endpoints. The only available data on reproductive toxicity for the untreated synthetic amorphous silica (CASRN 112945-52-5) are inadequate for the same reasons as referred to above. However, reproductive organs of male and female rats were evaluated in two repeated-dose toxicity studies in rats with CASRN 68611-44-9 by the oral and inhalation routes. In addition, the submitted robust summaries for the untreated synthetic amorphous silica gel (CASRN 112926-00-8) appear adequate for the developmental toxicity endpoint. As a result, reproductive and developmental toxicity endpoints have been addressed for the purposes of the HPV Challenge Program.

Silica are widely used in cosmetics, foodstuffs, pharmaceutical, and dental and medical applications. Both silicon dioxide and silica gel are approved by the Food and Drug Administration (FDA) for many food applications and silica gel is considered by the FDA as a generally recognized as safe (GRAS) chemical (21 U.S. Code of Federal Regulations, Parts 172/182, Food Additives Permitted for Direct Addition to Food for Human Consumption, sections 172.480 and 182.1711).

1. Chemical Identity

1.1 Identification and Purity

According to the 2002 Test Plan, CASRN 68611-44-9 is an inorganic substance with the amorphous silicon oxide structure of sand. The starting material is pyrogenic (fumed) silica, identified by the CASRN 112945-52-5. Peripheral hydroxyl groups of silica react with dichlorodimethylsilane, C₂H₆Cl₂Si (CASRN 75-78-5), resulting in dimethylsilyl groups on the surface that make the surface hydrophobic. The product is part of the synthetic amorphous silicas family (IUPAC name: silicone dioxide, chemically prepared). The surface treatment does not change the solid properties of the inorganic substance. Test substance purity, when mentioned in the Test Plan, was > 99.8%. Particle size for the inhalation repeated-dose toxicity studies, when mentioned in the Test Plan, was < 7 µm.

1.2 Physical-Chemical Properties

The physical-chemical properties of CASRN 68611-44-9 are summarized in Table 1. In general, most physical-chemical and environmental fate properties are not applicable for these substances as they cannot be measured or estimated accurately.

CASRN 68611-44-9 is a white, amorphous substance with negligible vapor pressure that is insoluble in water owing to its surface hydrophobicity.

Table 1. Physical-Chemical Properties of Silane, dichlorodimethyl-, reaction products with silica¹	
Property	Silane, dichlorodimethyl-, reaction products with silica
CASRN	68611-44-9
Molecular Weight	Mixture
Physical State	Amorphous
Melting Point	>520°C (measured)
Boiling Point	>520°C (measured)
Vapor Pressure	Negligible
Dissociation Constant (pK _a)	Silanols on silica surfaces have an estimated pK _a range of 5–7 ²
Henry's Law Constant	Not applicable
Water Solubility	The water solubility is much lower than that of the untreated amorphous silica (<0.0001 mg/L)
Log K _{ow}	Not applicable

¹ NOTOX Safety and Environmental Research B.V. 2003. Revised Robust Summary and Test Plan for Silane, dichlorodimethyl-, reaction products with silica. Available online at <http://www.epa.gov/chemrtk/pubs/summaries/slndichl/c14020tc.htm> as of April 19, 2011.

² Kazakevich, Y; LoBrutto, R. 2007. HPLC for Pharmaceutical Scientists. Wiley Interscience, Hoboken, NJ.

2. General Information on Exposure

2.1 Production Volume and Use Pattern

CASRN 68611-44-9 had an aggregated production and/or import volume in the United States between 1 million and 10 million pounds during calendar year 2005.

Non-confidential information in the IUR indicated that the industrial processing and uses for the chemical include adhesive manufacturing, coating, engraving, heat treating and allied activities, paint and coating manufacturing, printing ink manufacturing, and resin and synthetic rubber manufacturing as viscosity adjusters. No commercial and consumer uses were reported for this chemical.

2.2 Environmental Exposure and Fate

If released to soils, CASRN 68611-44-9 will become incorporated into the soil, as it has no mobility. It is high molecular weight and hydrophobic; therefore, biodegradation, atmospheric photooxidation, and hydrolysis will be negligible. Hydrolysis does not occur in pure water, but limited breakdown may occur following wetting. Volatilization is negligible. The substance is not bioaccumulative. CASRN 68611-44-9 has high persistence (P3) and low bioaccumulation potential (B1).

The environmental fate properties are provided in Table 2.

Table 2. Environmental Fate Properties of Silane, dichlorodimethyl-, reaction products with silica^{1,2}	
Property	Silane, dichlorodimethyl-, reaction products with silica
CASRN	68611-44-9
Photodegradation Half-life	Not applicable
Hydrolysis Half-life	Stable
Biodegradation	Stable
Bioaccumulation Factor	Not applicable
Log K _{oc}	Not applicable
Fugacity (Level III Model)	Not applicable
Air (%)	
Water (%)	
Soil (%)	
Sediment (%)	
Persistence	P3 (High)
Bioaccumulation	B1 (Low)

¹ NOTOX Safety and Environmental Research B.V. 2003. Revised Robust Summary and Test Plan for Silane, dichlorodimethyl-, reaction products with silica. Available online at <http://www.epa.gov/chemrtk/pubs/summaries/slndichl/c14020tc.htm> as of April 19, 2011

² Traditional environmental fate properties cannot be measured or accurately estimated for these substances; however, it is assumed that these substances will be stable in the environment and non-bioaccumulative due to their high molecular weight and hydrophobic, inorganic nature.

Conclusion: CASRN 68611-44-9 is a white, amorphous substance produced by surface modification of synthetic amorphous silica with dimethyldichlorosilane. It has negligible vapor pressure and negligible water solubility. Volatilization, hydrolysis, atmospheric oxidation, and biodegradation are negligible. CASRN 68611-44-9 has high persistence (P3) and low bioaccumulation potential (B1).

3. Human Health Hazard

The commercially available sponsored product has a particle size in excess of 90 µm and is only capable of reaching the upper airways (nasal passages and throat) or cannot be inhaled at all. OECD guidelines for inhalation toxicity testing require exposure to respirable dusts to insure that particles reach the tracheobronchial area of the respiratory tract. In order to reach the atmospheric concentrations required by experimental design, the inhalation toxicity studies with rats submitted by the sponsor used a test substance with nearly 100% of the particle fraction below 10 µm, thereby making it capable of entering the deep lung. Therefore, the test substance had a smaller particle size than the commercially available product for the repeated-dose

inhalation toxicity endpoints. In addition, the repeated-dose inhalation toxicity studies individually are deficient largely because they are all single dose studies (and actual NOAELs/LOAELs cannot be determined). However, EPA believes that, taken together, the repeated-dose inhalation toxicity studies are adequate to address this endpoint for the purposes of the HPV Challenge Program.

A summary of the human health toxicity data submitted for SIDS endpoint is provided in Table 3.

Acute Oral Toxicity

(1) Sprague-Dawley rats (10/sex/dose) were administered CASRN 68611-44-9 via gavage at 2500 or 5000 mg/kg-bw in peanut oil and observed for 14 days. No mortality was observed.
LD₅₀ > 5000 mg/kg

(2) Sprague-Dawley rats (10/sex/dose) were administered CASRN 68611-44-9 via gavage at 5040, 6350 or 7900 mg/kg-bw in olive oil and observed for 14 days. No mortality was observed.
LD₅₀ > 7900 mg/kg

(3) Sprague-Dawley rats (10/sex) were administered CASRN 68611-44-9 via the oral route at a dietary concentration of 10% (approximately 5000 mg/kg-bw) for 19 hours and observed for 14 days. No mortality were observed.
LD₅₀ > 5000 mg/kg

Acute Inhalation Toxicity

(1) Wistar rats (5/sex/concentration) were exposed to aerosols of CASRN 68611-44-9 via whole-body inhalation at measured concentrations of 210, 540 or 2100 mg/m³ (0.21, 0.54 or 2.1 mg/L, respectively) for 4 hours and observed for 14 days. Mortality occurred within one day at 0.54 mg/L (7/10) and 2.1 mg/L (10/10).
LC₅₀ = 0.45 mg/L

(2) Crl:[WI]WU BR rats (5/sex at the low and high concentrations and 7/sex at the mid concentration) were exposed to aerosols of CASRN 68611-44-9 via nose-only inhalation at measured concentrations of 520, 1120 or 2790 mg/m³ (0.52, 1.12 or 2.79 mg/L, respectively) for 4 hours and observed for 14 days. Mortality occurred during exposure at 1.12 mg/L (14/14) and 2.79 mg/L (10/10).
LC₅₀ = 0.52 – 1.12 mg/L

(3) Wistar rats (5/sex/concentration) were administered aerosols of CASRN 68611-44-9 via whole-body inhalation at a measured concentration of 477 mg/m³ (0.477 mg/L) for 4 hours and observed for 14 days. No mortalities were observed.
LC₅₀ > 0.477 mg/L

(4) Crl:CD (SD)BR rats (5/sex/concentration) were exposed to aerosols of CASRN 68611-44-9 via whole-body inhalation at measured concentrations of 0 or 2280 mg/m³ (0 and 2.28 mg/L) for 1 hour and observed for 14 days. No mortalities were observed.

LC₅₀ > 2.8 mg/L

Repeated-Dose Toxicity

(1) Wistar rats (40/sex) were administered CASRN 68611-44-9 via the diet to either 0 or 500 mg/kg-bw/day for 6 months. Animals were examined for mortality, clinical signs of toxicity and body weight throughout the study. Blood was drawn monthly from 10 rats/sex and hematological parameters were evaluated. All rats were subject to necropsy examination and major organs (including reproductive organs) were weighed. Histopathological examination was performed on eight organs (including the reproductive organs). No treatment-related effects were observed. Slight but reversible histopathology of the adrenal cortex among females was reported.

No adverse treatment-related effects observed at 500 mg/kg-bw/day (single dose tested)

(2) Wistar rats (5/sex/dose) were administered CASRN 68611-44-9 via the diet at 0, 500, 1000, and 2000 mg/kg-bw/day for 5 weeks up to 8 weeks. After 2 weeks, the 2000 mg/kg-bw/day dose was gradually increased at 2-week intervals to 4000, 8000 and 16,000 mg/kg-bw/day. Animals were examined for mortality, clinical signs of toxicity and food consumption. Blood was collected at the end of the exposure period (5 rats/dose) and examined for hematological alterations. All rats were subject to gross necropsy and livers and kidneys underwent histopathological examination. Two males and two females died after 9 and 13 days of exposure to 16,000 mg/kg-bw/day. Apathy and decreased grooming were noted at this dose level. After 1 week of exposure to 8000 or 16,000 mg/kg-bw/day, body weight gain was severely decreased (reports on food consumption were not included in the Robust Summary for this study). Hemorrhage of the mucous membranes of the eyes and nose were seen in animals exposed to 16,000 mg/kg-bw/day. Atrophic hepatocytes with decreased appearance and decreased glycogen contents of the cytoplasm were observed in two of five females at 1000 mg/kg-bw/day and eight animals in the high-dose group (2000 to 16,000 mg/kg-bw/day combined). However, since organ weight measurements and biochemical/ urinalyses were not conducted, it is unclear if the effects observed in the liver were clearly adverse and treatment-related. Due to several limitations in the study design, a clear NOAEL/LOAEL cannot be determined.

(3) Female rats (30 animals, strain not specified) were administered CASRN 68611-44-9 via gavage to 500 or 1000 mg/kg-bw/day for 19 or 39 days (treatment was administered every other day, 10 or 20 treatments). No data were provided regarding the type and frequency of clinical observations performed. All animals were subject to macroscopic examination. A control group was not included. No treatment-related findings were reported.

NOAEL = 1000 mg/kg-bw/day (highest dose tested)

(4) Wistar rats (10/sex/group) were administered CASRN 68611-44-9 via whole-body inhalation at concentrations of 0, 31, 87 or 209 mg/m³ (0, 0.031, 0.087 and 0.209 mg/L) for 6 hours/day, 5 days/week for 2 weeks. The high-dose level was initially 420 mg/m³, but was reduced after

1 day to 260 mg/m³ and then further reduced to approximately 151 mg/m³ after an additional 3 days of exposure. The mean exposure concentration for the high exposure groups was 209 mg/m³. Animals were examined for mortality, body weight and food consumption. Blood was taken for hematological evaluation during week 2. All animals underwent necropsy and the lungs of all animals underwent microscopic examination. At 0.209 mg/L, the kidneys, liver, trachea, larynx, mediastinal lymph node and nasal cavity also underwent microscopic examination. At 0.209 mg/L, four males and two females died within 2 days. Decreased body weight gain was observed at 0.087 mg/L and 0.209 mg/L. Increased red blood cell counts, packed cell volume and hemoglobin were observed in males at 0.087 mg/L and in both sexes exposed 0.209 mg/L. Increased lung weights were observed at all concentrations. Increased kidney and liver weights were seen at the two highest concentrations. Granulomata, focal increased septal cellularity and accumulation of alveolar macrophages were seen in lungs at all treatment levels.

LOAEC = 0.031 mg/L (based on gross and histopathological findings in the lungs)

NOAEC = Not established

(5) Wistar rats (50/sex/group) were administered CASRN 68611-44-9 via whole-body inhalation at a concentration of 0 or 35 mg/m³ (0 or 0.035 mg/L) for 6 hours/day, 5 days/week for 13 weeks. Groups of 10 rats/sex were sacrificed at 13, 26, 39 and 52 weeks post exposure for observation. Animals were examined for mortality, clinical signs and body weight throughout the study. Hematological, clinical chemistry and urinalysis examinations were performed every 13 weeks during exposure. All rats were subject to necropsy examinations. At the week 13 sacrifice, a full complement of tissues underwent histopathological examination, including reproductive organs. At 13, 26 and 39 weeks, the lungs, hilus and mediastinal lymph nodes were microscopically examined. No treatment-related mortalities occurred. Decreased body weight gains were seen in males during weeks 6 through 9. At week 13, animals had clinical chemistry changes (decreased glucose and plasma sodium in males), hematological changes (increased neutrophils and decreased lymphocytes in females and increased red blood cell count, hemoglobin and prothrombin time in males) and urinalysis changes (decreased urinary volume with increased density in females). Until week 39, males and females had increased lung weights (absolute and relative) and at week 13, males had increased absolute thymus weights. At week 13, lung lesions (spongy tissue, spotted surface) were observed in both sexes, along with abnormal lung histopathology (granuloma-like lesions, interstitial fibrosis). Changes in the lung decreased in incidence and severity at 13 weeks post exposure or had completely disappeared at 52 weeks post exposure. Findings in the nose were not found as of week 13 post exposure.

Adverse treatment-related effects observed at 0.035 mg/L (based on transient effects in the nose and lungs, and changes in clinical chemistry, hematology and urinalysis parameters)

NOAEC = Not established (single concentration tested)

(6) Female Sprague-Dawley rats (80 animals used, group size not indicated) were administered CASRN 68611-44-9 via inhalation at concentrations of 0 or 50 mg/m³ (0 or 0.05 mg/L) for 5 hours/day twice weekly for 8 or 12 months. Animals were examined for silica deposition in the lungs and mediastinal lymph nodes. Other endpoints examined were not specified. Lungs and lymph nodes were examined after 8 and 12 months (15 animals each) and at 1, 3 and

5 months after exposure. After 1 – 5, 8 and 12 months of exposure, interstitial white dust deposits and slightly enlarged lymph nodes were observed. Histopathological findings in the lung included slight epithelial desquamation (present after 1 month of exposure), locally perivascular and peribronchiolar dust deposits with slight to moderate formation of fibrous tissue and thickening of the alveolar wall. Histopathological findings in the lymph nodes included increased number of granular phagocytes and local fibrosis. Signs of recovery were observed from 1-5 months.

Adverse treatment-related effects observed at 0.05 mg/L (based on histopathological findings in the lungs and lymph nodes)

NOAEC = Not established (single concentration tested)

(7) Female rats (strain not indicated; 235 animals used, group size not specified) were administered CASRN 68611-44-9 via inhalation at concentrations of 0 or 80 mg/m³ (0 or 0.080 mg/L) via inhalation for 4 hours/day for 3, 5 or 8 months. Animals were examined for mortality and silica deposition in the lungs and mediastinal lymph nodes. Other endpoints examined were not specified. No treatment-related deaths were observed. Grey-white foci under the pleura and enlarged lymph nodes were observed. Dust cell granulomata in the lungs and alveolar spaces were seen.

Adverse treatment-related effects observed at 0.080 mg/L (based on histopathological findings in the lungs and lymph nodes)

NOAEC = Not established (single concentration tested)

(8) Female rats (strain not indicated; 340 animals used, group size was not reported) were administered CASRN 68611-44-9 via inhalation at concentrations of 100 mg/m³ (0.1 mg/L) via inhalation for 5 hours/day, 5 days/week for 1 year; with a post-exposure observation period of between 3 to 6 months. A control group was not included. Animals were examined for mortality and lungs and lymph nodes were examined and silica deposition. Mortality was not reported. Gray-white dust foci were noted under the lung surface in all rats exposed. The mediastinal lymph nodes were enlarged following 3 months of exposure and had a grey-black appearance following 9 months of exposure. Increasing incidences of desquamous alveolar cells, foci of dust cells with increasing number of dust granules and cell detritus in the alveolar space were noted in the lungs at 3, 6 and 12 months. A reticulin network developed after increasing exposure times in the lungs. No signs of proliferation, fibrosis or necrosis were observed in the lungs or mediastinal lymph nodes. The mediastinal lymph nodes contained massive amounts of dust cells after 3 or 6 months.

Adverse treatment-related effects observed at 0.1 mg/L (based on histopathological findings in the lungs and lymph nodes)

NOAEC = Not established (single concentration tested)

Reproductive Toxicity

No adequate reproductive toxicity studies are available on CASRN 68611-44-9, or on the untreated amorphous silica, which is the core material of CASRN 68611-44-9. Two repeated-dose toxicity studies in rats with CASRN 68611-44-9 by the oral and inhalation routes summarized above (#1 and #5) reported no effects on male and female reproductive organ

weight or histopathology at 500 mg/kg-bw/day (oral) or 0.035 mg/L (inhalation), the only doses/concentrations tested.

Developmental Toxicity

Silica gel (CASRN 112926-00-8, supporting chemical)

In a prenatal developmental toxicity study, pregnant Wistar rats (number/dose unspecified), were administered CASRN 112926-00-8 via gavage at doses of 0, 13.5, 62.7, 292, and 1350 mg/kg-day during gestation days 6-15. Limited study parameters were reported in the robust summary. No clear treatment-related adverse effects were reported in the dams or offspring.

NOAEL (maternal/developmental toxicity) = 1350 mg/kg-day (highest dose tested)

Silica gel (CASRN 112926-00-8, supporting chemical)

In a prenatal developmental toxicity study, pregnant CD-1 mice (number/dose unspecified), were administered CASRN 112926-00-8 via gavage at doses of 0, 13.4, 62.3, 289, and 1340 mg/kg-day from gestation day 6-15. Limited study parameters were reported in the robust summary. No clearly treatment-related adverse effects were reported in the dams or offspring.

NOAEL (maternal/developmental toxicity) = 1340 mg/kg-day (highest dose tested)

Silica gel (CASRN 112926-00-8, supporting chemical)

In a prenatal developmental toxicity study, pregnant Dutch rabbits (number/dose unspecified), were administered CASRN 112926-00-8 via gavage at doses of 0, 16.0, 74.3, 345, and 1600 mg/kg-day from gestation day 6-15. Limited study parameters were reported in the robust summary. No clearly treatment-related adverse effects were reported in the dams or offspring.

NOAEL (maternal/developmental toxicity) = 1600 mg/kg-day (highest dose tested)

Silica gel (CASRN 112926-00-8, supporting chemical)

In a prenatal developmental toxicity study, pregnant Syrian hamsters (number/dose unspecified), were administered CASRN 112926-00-8 via gavage at doses of 0, 16.0, 74.3, 345, and 1600 mg/kg-day from gestation day 6-15. Limited study parameters were reported in the robust summary. No clearly treatment-related adverse effects were reported in the dams or offspring.

NOAEL (maternal/developmental toxicity) = 1600 mg/kg-day (highest dose tested)

Genetic Toxicity – Gene Mutation

In vitro

(1) *Salmonella typhimurium* strains TA98, TA100, TA1535, TA1537 and TA1538 were exposed to silane, dichlorodimethyl-, reaction products with silica at concentrations of 0, 100, 333, 1000, 3333 or 5000 µg/plate in the presence or absence of metabolic activation. Appropriate positive and negative controls were employed, but control responses were not reported. Cytotoxicity was not observed. Precipitation was observed at 3333 µg/plate.

CASRN 68611-44-9 was not mutagenic in this assay.

(2) *S. typhimurium* strains TA98, TA100 and TA1537 and *E. coli* strain WP2 uvrA were exposed to silane, dichlorodimethyl-, reaction products with silica at concentrations of 5 – 1580 µg/plate in the presence or absence of metabolic activation. Appropriate positive and negative controls were employed, but control responses were not reported. Cytotoxicity was not observed. Precipitation was observed at 1580 µg/plate.

CASRN 68611-44-9 was not mutagenic in this assay.

Genetic Toxicity – Chromosomal Aberrations

In vitro

Chinese hamster ovary (CHO) cells were exposed to silane, dichlorodimethyl-, reaction products with silica at concentrations of 63, 125, 250 and 500 µg/mL in the presence and absence of metabolic activation. The maximum soluble concentration was selected as the highest concentration. Appropriate positive and negative controls were employed and positive controls responded appropriately. Cytotoxicity was not observed.

CASRN 68611-44-9 did not induce chromosomal aberrations in this assay.

Additional Information

Eye Irritation

(1) Undiluted silane, dichlorodimethyl-, reaction products with silica (0.1 mL) was instilled in the conjunctiva of one eye of each of nine New Zealand Albino rabbits (five males and four females). Eyes of three animals were rinsed with saline 20 seconds after instillation. The rabbits were observed for 72 hours. Slight conjunctival redness (score of 0.33) was seen at 1 and 24 hours. The substance is considered not irritating.

CASRN 68611-44-9 was not irritating to the rabbit eye.

(2) Undiluted silane, dichlorodimethyl-, reaction products with silica (0.1 mL) was instilled in the conjunctiva of one eye of each of eight New Zealand Albino rabbits (sex not indicated). Eyes of five animals were rinsed with water 5 minutes after instillation and eyes of three animals were rinsed 24 hours after instillation. The rabbits were observed for 7 days. No effects were seen. The substance is considered not irritating.

CASRN 68611-44-9 was not irritating to the rabbit eye.

(3) Silane, dichlorodimethyl-, reaction products with silica (0.1 g) was instilled in the conjunctiva of one eye of each of eight New Zealand Albino rabbits (sex not indicated). Eyes of five animals were rinsed with water 5 minutes after instillation and eyes of three animals were rinsed 24 hours after instillation. The rabbits were observed for 72 hours. Conjunctival redness (score 1.0) was seen at 1, 24 and 48 hours. The substance is considered not irritating.

CASRN 68611-44-9 was not irritating to the rabbit eye.

Skin Irritation

(1) Silane, dichlorodimethyl-, reaction products with silica (0.5 g in water) was applied to intact skin of New Zealand White rabbits (3/sex) under semi-occlusive conditions for 4 hours. Animals were observed for 72 hours. No skin irritation was observed.

CASRN 68611-44-9 was not irritating to rabbit skin.

(2) Silane, dichlorodimethyl-, reaction products with silica (6% in aqueous methylhydroxyethylcellulose-gel) was applied to intact and abraded skin of New Zealand White rabbits (3/sex) under occlusive conditions for 24 hours. Animals were observed for up to 14 days. No skin irritation was observed.

CASRN 68611-44-9 was not irritating to rabbit skin.

(3) Silane, dichlorodimethyl-, reaction products with silica (50% in olive oil) was applied to intact and abraded skin of New Zealand White rabbits (3/sex) under occlusive conditions for 24 hours. Animals were observed for up to 14 days. No skin irritation was observed.

CASRN 68611-44-9 was not irritating to rabbit skin.

Chronic Toxicity/Carcinogenicity

Wistar rats (20/sex) were administered silane, dichlorodimethyl-, reaction products with silica via the diet at 100 mg/kg-bw/day for 24 months (for the control group, historical control data were considered in the study). Animals were examined for mortality, clinical signs of toxicity and body weight. At the end of the treatment period, blood was analyzed for clinical chemistry and hematology. Necropsy was conducted at the end of treatment and ~ 22 tissues (including reproductive organs) were examined histopathologically. The only reported effects were testis atrophy in one male and increased fat accumulation in three males and five females. No carcinogenic effects and no other treatment-related effects were observed.

CASRN 68611-44-9 showed no evidence of carcinogenicity in this study.

Conclusion: CASRN 68611-44-9 showed low acute oral toxicity and high acute inhalation toxicity in rats. In a 6-month repeated-dose oral toxicity study in rats, no adverse effects were seen at 500 mg/kg-bw/day, the only dose tested. In a 2-week repeated-dose inhalation toxicity study in male and female rats, histopathological changes in the lungs were seen at 0.031 mg/L, the lowest concentration tested. A repeated-dose inhalation toxicity study in male and female rats exposed for 13 weeks showed histopathological changes in the nose and lungs, and changes in clinical chemistry, hematology and urinalysis parameters at 0.035 mg/L, the only concentration tested. In three separate repeated-dose inhalation toxicity studies in female rats exposed for 3-12 months, histopathological findings in the lungs and lymph nodes were seen at all concentrations tested (0.05, 0.08, and 0.1 mg/L). No adequate reproductive toxicity studies by the oral or inhalation routes with CASRN 68611-44-9, or on the untreated synthetic amorphous silica, which is the core material of CASRN 68611-44-9 and is used as read-across for reproductive toxicity, are available. Two repeated-dose toxicity studies in rats with CASRN 68611-44-9 by the oral and inhalation routes summarized above reported no effects on male and female reproductive organ weight or histopathology at 500 mg/kg/day (oral) or

0.035 mg/L (inhalation), the only doses/concentrations tested. No adequate developmental toxicity data by the oral or inhalation routes on CASRN 68611-44-9 are available. The untreated synthetic amorphous silica, which is the core material of CASRN 68611-44-9, is used to read-across for developmental toxicity. Prenatal developmental toxicity studies by the oral route in rats, rabbits, and hamsters with the untreated synthetic amorphous silica (silica gel, CASRN 112926-00-8) showed no maternal or developmental toxicity at any dose level tested; the lowest NOAELs for both maternal and developmental toxicity are 1340, 1350, and 1600 mg/kg/day in mice, rats, and rabbits/hamsters, respectively. CASRN 68611-44-9 did not induce genetic mutations in bacterial cells or chromosomal aberrations in mammalian cells *in vitro*. A chronic toxicity/carcinogenicity study in rats administered CASRN 68611-44-9 in the diet for 24 months showed no evidence of carcinogenicity. CASRN 68611-44-9 was not irritating to the rabbit eye or skin.

Table 3. Summary Table of the Screening Information Data Set as Submitted under the U.S. HPV Challenge Program – Human Health Data		
Endpoints	SPONSORED CHEMICAL Silane, Dichlorodimethyl-, Reaction Product with Silica (68611-44-9)	SUPPORTING CHEMICAL Silica Gel (112926-00-8)
Acute Oral Toxicity LD₅₀ (mg/kg)	>5000	–
Acute Inhalation Toxicity LC₅₀ (mg/L)	0.45	–
Repeated-Dose Toxicity NOAEC/LOAEC Inhalation (mg/L/day)	0.031	–
Reproductive Toxicity NOAEC/LOAEC/NOAEL/LO AEL Inhalation (mg/L/day) Oral (mg/kg/day)	No adequate data available. The 13-week and 6-month repeated dose toxicity studies showed no effects on the male and female reproductive organs	–
Developmental Toxicity NOAEL/LOAEL Oral (mg/kg/day)	No adequate data available.	
Maternal Toxicity	1340 (mice) 1350 (rats) 1600 (rabbits)	1340 (mice) 1350 (rats) 1600 (rabbits)
Developmental Toxicity	1340 (mice) 1350 (rats) 1600 (rabbits) (RA)	1340 (mice) 1350 (rats) 1600 (rabbits)
Genetic Toxicity – Gene Mutation <i>In vitro</i>	Negative	–
Genetic Toxicity – Chromosomal Aberrations <i>In vivo</i>	Negative	–
Additional Information		
Eye Irritation	Not irritating	–
Skin Irritation	Not irritating	–
Carcinogenicity	Negative evidence	–

–data not needed

4. Hazard to the Environment

Due to low water solubility ($< 10^{-4}$ mg/L) and other physical chemical properties of this hydrophobic amorphous silica, EPA believes acute and chronic toxicity will not be observed for CASRN 68611-44-9, which is supported by the submitted acute toxicity studies below. A summary of aquatic toxicity data submitted for SIDS endpoints is provided in Table 4.

Acute Toxicity to Fish

Zebrafish (*Brachydanio rerio*) were exposed to CASRN 68611-44-9 at nominal concentrations of 1000 or 10,000 mg/L under static conditions for 96 hours. The estimated water solubility is less than 10^{-4} mg/L; therefore, tested concentrations were above the water solubility limit and un-dissolved test substance was observed in the test vessels. No mortalities occurred.

96-h LC₅₀ = No effects at saturation.

Acute Toxicity to Aquatic Invertebrates

Water fleas (*Daphnia magna*) were exposed to CASRN 68611-44-9 at nominal concentrations of 1000 or 10,000 mg/L (filtered/unfiltered) under static conditions for 24 hours. The estimated water solubility is less than 10^{-4} mg/L; therefore, tested concentrations were above the water solubility limit and un-dissolved test substance was observed in the test vessels. No immobilization was observed.

24-h EC₅₀ = No effects at saturation.

Toxicity to Aquatic Plants

Green algae (*Scenedesmus subspicatus*) were exposed to CASRN 68611-44-9 at nominal test concentrations of 0, 100.8, 1008 or 10,000 mg/L (filtered) under static conditions for 72 hours.

72-h EC₅₀ (biomass) = No effects at saturation.

72-h EC₅₀ (growth rate) = No effects at saturation.

Conclusion: Based on low water solubility ($< 10^{-4}$ mg/L) and other physical chemical properties of this hydrophobic amorphous silica, acute and chronic toxicity (to fish and daphnia, and toxicity to aquatic plants) will likely not be observed for CASRN 68611-44-9, which is supported by the submitted acute toxicity studies showing no effects at saturation.

Table 4. Summary Table of the Screening Information Data Set as Submitted under the U.S. HPV Challenge Program - Aquatic Toxicity Data	
Endpoint	Sponsored Chemical (CASRN 68611-44-9)
Fish 96-h LC₅₀ (mg/L)	NES
Aquatic Invertebrates 24-h EC₅₀ (mg/L)	NES
Aquatic Plants 72-h EC₅₀ (mg/L) (growth rate) (biomass)	NES NES

Bold=experimental data (i.e. derived from testing); NES = no effects at saturation (water solubility limit)

APPENDIX

Sponsored Chemical		
Chemical Name	CASRN	Structure¹
Silane, dichlorodimethyl-, reaction products with silica	68611-44-9	An amorphous material resulting from surface-modification of synthetic amorphous silica with dimethyldichlorosilane. It consists of amorphous silica core material, in addition to surface silanols and polydimethylsiloxane units.

¹Meaningful molecular structures cannot be drawn for these high molecular weight materials.