

SCREENING-LEVEL HAZARD CHARACTERIZATION

1,5,9-Cyclododecatriene (CASRN 4904-61-4)

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 Set^{1,2}) 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, EXTOXNET, 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.

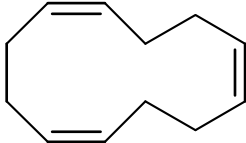
OPPT does not develop HCs for those HPV chemicals which have already been assessed internationally through the HPV program of the Organization for Economic Cooperation and Development (OECD) and for which Screening Initial Data Set (SIDS) Initial Assessment Reports (SIAR) and SIDS Initial Assessment 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)	4904-61-4
Chemical Abstract Index Name	1,5,9-Cyclododecatriene
Structural Formula	
<p style="text-align: center;">Summary</p> <p>CASRN 4094-61-4 is a liquid with moderate water solubility and moderate vapor pressure. It is expected to have moderate mobility in soil. Volatilization of CASRN 4094-61-4 is considered high based on its Henry's Law constant. The rate of hydrolysis is considered negligible. The rate of atmospheric photooxidation is considered rapid and this chemical was not readily biodegradable. CASRN 4094-61-4 is expected to have moderate persistence (P2) and high bioaccumulation potential (B3).</p> <p>The acute oral and dermal toxicity of CASRN 4904-61-4 in rats is low, and the acute inhalation toxicity in rats is moderate. In a combined repeated-dose/reproductive/developmental toxicity screening test of CASRN 4904-61-6 in rats via gavage, systemic effects (decreases in body weight and body weight gain in males and females) were seen at 100 mg/kg-day; the NOAEL for both maternal and systemic toxicity is 30 mg/kg/day. In this same study, there were no effects on the reproductive parameters evaluated at doses up to 300 mg/kg-day, the highest dose tested; the NOAEL for reproductive toxicity is 300 mg/kg/day. Signs of developmental toxicity consisted of reductions in pup body weight at 300 mg/kg/day; the NOAEL for developmental toxicity is 100 mg/kg/day. In a separate inhalation prenatal developmental toxicity study, signs of maternal toxicity included reduced body weight and body weight gain at 0.166 mg/L; the NOAEC for maternal toxicity is 0.066 mg/L. Developmental toxicity (lower mean fetal weight and increased incidence of delayed ossification) was seen at 0.445 mg/L; the NOAEC for developmental toxicity is 0.166 mg/L. CASRN 4904-41-6 did not induce gene mutation in bacteria, chromosomal aberrations in human lymphocytes <i>in vitro</i> or micronuclei in rats <i>in vivo</i>. CASRN 4904-61-4 is irritating to the rabbit skin, minimally irritating to the rabbit eye and showed skin sensitizing properties in guinea pigs.</p> <p>The acute 96-hr LC₅₀ value for CASRN 4904-61-4 for fish is 2.02 mg/L. The acute 96-hr LC₅₀ value of CASRN 4904-614 for aquatic invertebrates is 0.47 mg/L. The estimated 96-hr EC₅₀ value of CASRN 4904-61-4 for algae is 0.19 mg/L.</p> <p>A data gap for chronic aquatic invertebrate toxicity has been identified under the HPV Challenge Program.</p>	

The sponsor, E. I. du Pont de Nemours & Company, Inc. submitted a Test Plan and Robust Summaries to EPA for 1,5,9-cyclododecatriene on December 11, 2001. EPA posted the submission on the ChemRTK HPV Challenge website on January 23, 2002 (<http://www.epa.gov/HPV/pubs/summaries/cyclo/c13404tc.htm>). EPA comments on the original submission were posted to the website on October 10, 2002. Public comments were also received and posted to the website. The sponsor submitted updated/revised documents on October 17, 2003, which were posted to the ChemRTK website on December 3, 2003.

1. Chemical Identity

1.1 Identification and Purity

CASRN 4904-61-4 is a yellowish liquid with a pungent odor. The purity of the sponsored chemical was mentioned in some robust summaries; in all cases it was reported as >99%.

1.2 Physical-Chemical Properties

The physical-chemical properties of CASRN 4094-61-4 are summarized in Table 1. CASRN 4094-61-4 is liquid with moderate water solubility and moderate vapor pressure.

Property	Value
CASRN	4904-61-4
Molecular Weight	162.27
Physical State	Liquid with a yellow tint
Melting Point	-17°C (measured)
Boiling Point	237°C (measured)
Vapor Pressure	0.09 mm Hg at 20°C (extrapolated from the experimentally determined vapor pressure curve)
Water Solubility	5 mg/L at 20°C (measured)
Dissociation Constant (pK _a)	Not applicable
Henry's Law Constant	0.0281 atm·m ³ /mole (estimated) ²
Log K _{ow}	4.97 (measured)

¹E.I. DuPont de Nemours & Company. October 27, 2003. Revised Robust Summary for 1,5,9-Cyclododecatriene. Available online from:

<http://www.epa.gov/chemrtk/pubs/summaries/cyclo/c13404tc.htm> as of May 13, 2010.

²U.S. EPA. 2010. Estimation Programs Interface Suite™ for Microsoft® Windows, v4.00. U.S. Environmental Protection Agency, Washington, DC, USA. Available online from: <http://www.epa.gov/opptintr/exposure/pubs/episuitedl.htm> as of May 13, 2010.

2. General Information on Exposure

2.1 Production Volume and Use Pattern

According to the 2006 IUR submissions, CASRN 4904-61-4 had an aggregated production and/or import volume in the United States between 50 million and 100 million pounds.

Non-confidential information in the IUR indicated that the industrial processing and uses of the chemical include all other chemical product and preparation manufacturing as intermediates; and other basic organic chemical manufacturing as intermediates. No commercial and consumer uses were reported.

2.2 Environmental Exposure and Fate

The environmental fate properties of CASRN 4904-61-4 are provided in Table 2. CASRN 4094-61-4 is expected to have moderate mobility in soil. CASRN 4094-61-4 was not readily biodegradable using a closed bottle test (OECD 301D), manometric respirometry test (OECD 301F) and a modified MITI test (OECD 301C). Practically no degradation was observed in the closed bottle study and the modified MITI test; however, at 1 and 10 mg/L starting concentrations, CASRN 4094-61-4 degraded 45 and 21%, respectively in 28 days using the manometric respirometry test. At the lower concentration, nearly 100% degradation was observed after 42 days. Approximately 18% degradation was observed for CASRN 4094-61-4 using the modified Sturm test (OECD 301B) at an initial concentration of 0.2 mg/L over the course of a 28-day incubation period. The rate of hydrolysis is expected to be negligible under environmental pH and temperature. Volatility is considered high based on its Henry's Law constant. CASRN 4094-61-4 is expected to have moderate persistence (P2) and high bioaccumulation potential (B3).

Property	Value
Photodegradation Half-life	0.7 hours (estimated) ²
Hydrolysis Half-life	Stable
Biodegradation	1% biodegradation in 28 days (not readily biodegradable); 0% in 14 days (not readily biodegradable) ³ ; 45% biodegradation in 28 days (not readily biodegradable) ⁴ ; 21% biodegradation in 28 days (not readily biodegradable) ⁴ ; 18% after 28 days (not readily biodegradable) ⁴
Bioaccumulation Factor	BCF = 2,630–12,500 (measured in carp at 10 ppb) ³ ; BCF = 1,920–14,800 (measured in carp at 1 ppb) ³ ; BAF = 2.5×10^4 (estimated) ²
Log K _{oc}	3.7 (estimated) ²
Fugacity (Level III Model) ²	
Air (%)	0.1
Water (%)	24.5
Soil (%)	71.4
Sediment (%)	4.0
Persistence ⁵	P2 (moderate)
Bioaccumulation ⁵	B3 (high)

¹ E.I. DuPont de Nemours & Company. October 27, 2003. Revised Robust Summary for 1,5,9-Cyclododecatriene. Available online from:

<http://www.epa.gov/chemrtk/pubs/summaries/cyclo/c13404tc.htm> as of May 13, 2010.

² U.S. EPA. 2010. Estimation Programs Interface Suite™ for Microsoft® Windows, v4.00. U.S. Environmental Protection Agency, Washington, DC, USA. Available online from: <http://www.epa.gov/opptintr/exposure/pubs/episuitedi.htm> as of May 13, 2010.

³ National Institute of Technology and Evaluation. 2002. Biodegradation and Bioaccumulation of the Existing Chemical Substances under the Chemical Substances Control Law. Available online from: http://www.safe.nite.go.jp/english/kizon/KIZON_start_hazkizon.html as of May 17, 2010.

⁴ European Union PBT Working Group. 2008. PBT List 39. Results for the Evaluation of the PBT/VPVB Properties of Cyclododeca-1,5,9-triene. Available online from: http://ecb.jrc.ec.europa.eu/Documents/PBT_EVALUATION/PBT_sum039_CAS_4904-61-4.pdf as of May 17, 2010.

⁵ Federal Register. 1999. Category for Persistent, Bioaccumulative, and Toxic New Chemical Substances. *Federal Register* 64, Number 213 (November 4, 1999) pp. 60194–60204.

Conclusion: CASRN 4094-61-4 is a liquid with moderate water solubility and moderate vapor pressure. It is expected to have moderate mobility in soil. Volatilization of CASRN 4094-61-4 is considered high based on its Henry's Law constant. The rate of hydrolysis is considered negligible. The rate of atmospheric photooxidation is considered rapid and this chemical was not readily biodegradable. CASRN 4094-61-4 is expected to have moderate persistence (P2) and high bioaccumulation potential (B3).

3. Human Health Effects

A summary of health effects data submitted for SIDS endpoints is provided in Table 3.

Acute Oral Toxicity

Sprague-Dawley rats (5/sex/dose) were administered single doses of 1,5,9-cyclododecatriene by gavage (vehicle not specified) at 1, 2, 3, 4 or 5 mL/kg (equivalent to 891, 1782, 2673, 3564 or 4455 mg/kg) and were observed for up to 14 days following dosing. Mortalities were 20%, 20%, 60%, 80% and 100% at the 1, 2, 3, 4, and 5 mL/kg-bw dose levels, respectively.

LD₅₀ (combined) = 2500 mg/kg

Acute Inhalation Toxicity

(1) Male Crl:CD rats (10 or 20/exposure level) were exposed whole-body to an aerosol of 1,5,9-cyclododecatriene for 6 hours at mean nominal concentrations of 5.0, 6.0, 7.0, 8.0, 8.5, 9.0 or 10.0 mg/L (groups of 20 animals were used for the 8 and 10 mg/L concentrations and 10 animals were used for all others) and were observed for up to 14 days following exposure. Mortalities occurred at all but the lowest concentration: 1/10, 5/10, 5/20, 4/10, 3/10, and 18/20 at the 6.0, 7.0, 8.0, 8.5, 9.0, and 10 mg/L concentrations, respectively. Most deaths (92%) occurred during the exposure period.

LC₅₀ = 8.2 mg/L

(2) Male Crl:CD rats (6/exposure level) were exposed nose-only to an aerosol/vapor of 1,5,9-cyclododecatriene for 4 hours at measured concentrations of 6.1 or 8.1 mg/L and were observed for up to 14 days following exposure. One rat died during the 8.1 mg/L exposure. No other mortalities were observed during the study.

LC₅₀ > 8.1 mg/L

Acute Dermal Toxicity

CD rats (two/sex/dose) were exposed to 1,5,9-cyclododecatriene via dermal administration (the test substance was placed on the shaved backs of the animals) under occluded conditions for a 24-hour period at 2, 3, or 4 mL/kg (equivalent to 1782, 2673 or 3564 mg/kg). After the 24-hour period, the occluded dressing was removed and the animals were observed for nine days. There were no mortalities.

LD₅₀ > 3520 mg/kg

Repeated-Dose Toxicity

A combined repeated-dose/reproductive/developmental toxicity study was conducted with 1,5,9-cyclododecatriene. Crl:CD rats (10/sex/dose) were administered daily doses of 0, 30, 100 or 300 mg/kg-day 1,5,9-cyclododecatriene by gavage. Dosing covered pre-mating (four weeks), mating (one to two weeks), gestation (approximately three weeks), and approximately four days of lactation. Males were dosed for a total of up to 55 days. Systemic endpoints evaluated on a weekly basis included clinical signs, body weight and food consumption. Hematology, clinical

chemistry tests and urinalysis were conducted after 4 weeks of dosing. Functional observation battery and motor activity tests were performed on all rats prior to dosing and after 4 weeks of dosing. Males were sacrificed approximately 3 weeks post-mating; females and offspring were sacrificed on lactation day 4. Selected parental organs were examined for gross lesions and preserved for microscopic examination. The only parental effects were statistically significant decreases in weight gain and increase in food utilization in high-dose males and statistically significant decreases in both body weight and body weight gain in mid- and high-dose females during gestation. There were no adverse neurobehavioral effects.

LOAEL (systemic toxicity) = 100 mg/kg-day (based on reduced body weight and body weight gain in females)

NOAEL (systemic toxicity) = 30 mg/kg-day

Reproductive Toxicity

A combined repeated-dose/reproductive/developmental toxicity study, described previously, was conducted with 1,5,9-cyclododecatriene. Crl:CD rats (10/sex/dose level) were administered daily doses of 0, 30, 100 or 300 mg/kg-day 1,5,9-cyclododecatriene by gavage. Dosing covered pre-mating (four weeks), mating (one to two weeks), gestation (approximately three weeks), and up through approximately four days of lactation. Reproductive parameters examined included gestation length, mating index, gestation index, fecundity index, implantation site numbers, implantation efficiency, sex ratio, pups born alive and viability index. There were no adverse reproductive effects.

NOAEL (reproductive toxicity) = 300 mg/kg-day (highest dose tested)

Developmental Toxicity

(1) A combined repeated-dose/reproductive/developmental toxicity study was conducted with 1,5,9-cyclododecatriene. Crl:CD rats (10/sex/dose level) were administered daily doses of 0, 30, 100 or 300 mg/kg-day 1,5,9-cyclododecatriene by gavage. Dosing covered pre-mating (four weeks), mating, (one to two weeks), gestation (approximately three weeks), and approximately four days of lactation. Offspring were evaluated for body weight and clinical abnormalities. Effects in pups were limited to the high-dose (300 mg/kg-day) group and consisted of significantly decreased body weight on lactation days 0 and 4 (magnitude not provided).

LOAEL (maternal toxicity) = 100 mg/kg-day (based on reduced body weight and body weight gain)

NOAEL (maternal toxicity) = 30 mg/kg-day

LOAEL (developmental toxicity) = 300 mg/kg-day (based on reduced pup weight on lactation day 0 and 4)

NOAEL (developmental toxicity) = 100 mg/kg-day

(2) Crl:CD time-mated female rats (22/exposure concentration) were exposed whole-body to atmospheres of 1,5,9-cyclododecatriene at nominal concentrations of 0, 10, 25 or 67 ppm (0, 0.066, 0.166 or 0.445 mg/L-day) for 6 hours/day on gestation days 6 – 20. Analytical measurements throughout the experiment confirmed the nominal concentrations. The high concentration (67 ppm) chamber contained a mixture of aerosol and vapor components, while the low (10 ppm) and intermediate (25 ppm) concentration chambers contained primarily vapor. Dams were sacrificed on gestation day 21. Maternal endpoints evaluated were morbidity and

mortality, clinical signs and body weight. Maternal organs of the thoracic and abdominal cavities were subjected to a gross examination. Developmental endpoints examined included number of corpora lutea, live and dead fetuses and resorptions. Fetuses were examined for external alterations as well as visceral and skeletal alterations. Maternal effects consisted of significant reductions in body weight gain, body weight, and food consumption (magnitude not provided) and clinical signs observed included stained fur; all in the mid and high-dose groups. Developmental effects included significant reductions in mean fetal weight and increased incidence of delayed skeletal ossification (magnitudes not provided) at 67 ppm.

LOAEC (maternal toxicity) = 0.166 mg/L-day (based on reduced body weight, weight gain and clinical signs)

NOAEC (maternal toxicity) = 0.066 mg/L-day

LOAEC (developmental toxicity) = 0.445 mg/L-day (based on reduced fetal weight and delayed ossification)

NOAEC (developmental toxicity) = 0.166 mg/L-day

Genetic Toxicity – Gene Mutation

In vitro

Bacteria reverse mutation tests were conducted in cultures of *Salmonella typhimurium* strains TA97a, TA98, TA100 and TA1535 and *Escherichia coli* WP2 *uvrA* incubated with 1,5,9-cyclododecatriene in DMSO at 0, 10, 50, 100, 500, 1000, 2500 or 5000 µg/plate for about 48 hours in the presence or absence of metabolic activation. Solvent and positive controls were used. No evidence of mutagenicity was detected with or without metabolic activation. No information was provided regarding the results obtained with the positive controls.

1,5,9-Cyclododecatriene was not mutagenic in these assays.

Genetic Toxicity – Chromosomal Effects

In vitro

Human lymphocytes were incubated with 1,5,9-cyclododecatriene at 0.25 – 2.5 mg/mL (trial 1) or 0.5 – 5.0 mg/mL (trial 2) in acetone in the presence or absence of metabolic activation. Cells were harvested approximately 19-21 hours after the end of for the 3 hours incubation in trial 1 and 43-45 hours after the 3 hours incubation in trial 2 to determine chromosomal damage. For each trial, 100 cells (50 from each replicate; 50 from male and 50 from female) were analyzed for aberrations. Solvent and positive controls were used. Cytotoxicity was seen at 2.5 mg/mL in trial 1 and at 5 mg/mL in trial 2. No statistically significant increases in percent cells with structural chromosomal aberrations were observed at any concentration tested. No information was provided regarding the results obtained with the positive controls.

1,5,9-Cyclododecatriene was negative for clastogenicity in this assay.

In vivo

Sprague-Dawley male rats (10 test animals and 5 negative controls) were exposed nose-only to target concentrations of 0 or 500 ppm (3.3 mg/L) of an aerosol/vapor of 1,5,9-cyclododecatriene 6 hours/day for 2 consecutive days. The mean analytically measured concentration of 1,5,9-cyclododecatriene was 3.2 mg/L. Cyclophosphamide was used as positive control. Micronuclei were evaluated in polychromatic erythrocytes from bone marrow from the femur immediately after sacrifice. Rats exposed to 1,5,9-cyclododecatriene exhibited weight loss and reduced

response to an alerting stimulus during exposure. After exposure, rats showed lethargy and/or irregular respiration. Exposure to 1,5,9-cyclododecatriene did not increase the incidence of micronuclei relative to negative controls. The positive control responded appropriately.

1,5,9-Cyclododecatriene did not induce micronuclei in this assay.

Additional Information

Skin Irritation

Six New Zealand White rabbits were dermally administered an unspecified amount of undiluted 1,5,9-cyclododecatriene to the shaved back (abraded and intact areas used in each animal) under occluded conditions. Observations were made at various unspecified time points. 1,5,9-Cyclododecatriene produced minimal erythema in all rabbits and minimal edema of the abraded skin in two rabbits. Subsequent observations revealed a gradual return to normal (complete after 1 week).

1,5,9-Cyclododecatriene was slightly irritating in this assay.

Eye Irritation

Undiluted 1,5,9-cyclododecatriene (0.1 mL) was instilled into the conjunctival sac of the right eye of rabbits (strain and number not provided). Observations of the rabbits occurred at 1, 24, 48 and 72 hours and one week following treatment. 1,5,9-Cyclododecatriene produced erythema of the palpebral conjunctiva, swelling of the lids and nictitating membrane and lacrimation within one hour. Improvement was seen within 24 hours and a return to normal within one week following treatment. Average score, the end of 1, 24, 48, 72 hours, and 1 week, were 6.6, 2.3, 1.0, 1.0, and 0, respectively, with 110.0 the maximum score attainable.

1,5,9-Cyclododecatriene was minimally irritating in this assay.

Dermal Sensitization

(1) A skin sensitization test was carried out in 10 guinea pigs (strain or sex not specified) by injecting or applying 0.1% w/v 1,5,9-cyclododecatriene in light liquid paraffin to the clipped skin on their backs on 3 days in each of 3 successive weeks. After a 10-day period of no exposure, the same concentration was applied on the right flank (with a solvent control on the left flank) on the 11th day. Following the challenge, the guinea pigs were examined at 1, 24 and 48 hours for signs of a sensitization-type reaction. Results showed all guinea pigs (10/10) had a positive sensitizer reaction at 24 and 48 hours (for both the topical and intradermal tests).

1,5,9-Cyclododecatriene was a dermal sensitizer in this assay.

(2) Dermal sensitization was evaluated in 12 male Albino guinea pigs exposed to undiluted 1,5,9-cyclododecatrieneone (one drop, ca. 0.05mL) and various (unspecified) solutions in 1:1 acetone-dioxane containing 13% guinea pig fat (f.a.d.) to shaved, intact skin. Then the animals received a series of exposures over a three week period in one of two ways: (1) six with the application of nine doses of 1,5,9-cyclododecatriene (one dose of 10%, two doses of 25%, one dose of 50%, and five doses of 25%; all as solutions in guinea pig fat) and (2) six others receiving four intradermal injections (0.1 mL of a 1% solution in dimethyl phthalate). In both cases, following a two week rest period, a challenge test on both intact and abraded skin was done (with 12 previously unexposed guinea pigs similarly treated and serving as challenge controls. This chemical was not a dermal sensitizer in under the conditions of this experiment. 1,5,9-Cyclododecatriene was a strong irritant. On intact skin, undiluted 1,5,9-cyclododecatriene produced generally strong erythema with edema through 2 days. On abraded skin, a 50% solution caused strong irritation at 10 minutes, which generally developed into partial necrosis at day 1. It is not clear whether the irritation was due to the carrier/vehicle since eye and skin irritation studies summarized above show the sponsored chemical to be only slightly irritating to the skin.

1,5,9-Cyclododecatriene was not a dermal sensitizer in this assay.

Conclusion: The acute oral and dermal toxicity of CASRN 4904-61-4 in rats is low, and the acute inhalation toxicity in rats is moderate. In a combined repeated-dose/reproductive/developmental toxicity screening test of CASRN 4904-61-6 in rats via gavage, systemic effects (decreases in body weight and body weight gain in males and females) were seen at 100 mg/kg-day; the NOAEL for both maternal and systemic toxicity is 30 mg/kg/day. In this same study, there were no effects on the reproductive parameters evaluated at doses up to 300 mg/kg-day, the highest dose tested; the NOAEL for reproductive toxicity is 300 mg/kg/day. Signs of developmental toxicity consisted of reductions in pup body weight at 300 mg/kg/day; the NOAEL for developmental toxicity is 100 mg/kg/day. In a separate inhalation prenatal developmental toxicity study, signs of maternal toxicity included reduced body weight and body weight gain at 0.166 mg/L; the NOAEC for maternal toxicity is 0.066 mg/L. Developmental toxicity (lower mean fetal weight and increased incidence of delayed ossification) was seen at 0.445 mg/L; the NOAEC for developmental toxicity is 0.166 mg/L. CASRN 4904-41-6 did not induce gene mutation in bacteria, chromosomal aberrations in human lymphocytes *in vitro* or micronuclei in rats *in vivo*. CASRN 4904-61-4 is irritating to the rabbit skin, minimally irritating to the rabbit eye and showed skin sensitizing properties in guinea pigs.

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 1,5,9-Cyclododecatriene (4904-61-4)
Acute Oral Toxicity LD₅₀ (mg/kg)	2500
Acute Dermal Toxicity LD₅₀ (mg/kg)	>3520
Acute Inhalation Toxicity LC₅₀ (mg/L)	8.2
Repeated-Dose Toxicity NOAEL/LOAEL Oral (gavage) (mg/kg-day)	NOAEL = 30 LOAEL = 100
Reproductive Toxicity NOAEL/LOAEL Oral (gavage) (mg/kg-day) Reproductive Toxicity	 NOAEL = 300 (highest dose tested)
Developmental Toxicity NOAEL/LOAEL Oral (gavage) (mg/kg-day) Maternal toxicity Developmental toxicity	 NOAEL = 30 LOAEL = 100 NOAEL = 100 LOAEL = 300
Developmental Toxicity NOAEC/LOAEC Inhalation (mg/L-day) Maternal toxicity Developmental toxicity	 NOAEC = 0.066 LOAEC = 0.166 NOAEC = 0.166 LOAEC = 0.445
Genetic Toxicity – Gene Mutation <i>In vitro</i>	Negative
Genetic Toxicity – Chromosomal effects <i>In vitro and in vivo</i>	Negative
Additional Information Skin irritation Eye irritation Dermal Sensitization	Slightly irritating Minimally irritating Positive

4. Hazard to the Environment

A summary of aquatic toxicity data submitted for SIDS endpoints is provided in Table 4.

Acute Toxicity to Fish

Sheephead minnow (*Cyprinodon variegates*) were exposed to CASRN 4904-61-4 at nominal concentrations of 0.313, 0.625, 1.25, 2.5, or 5.0 mg/L under static conditions for 96 hours. The test substance purity was reported at 100%.

96-hr EC₅₀ = 2.02 mg/Lw

Acute Toxicity to Aquatic Invertebrates

Mysid shrimp (*Mysidopsis bahia*) were exposed to CASRN 4904-61-4 at nominal concentrations of 0.0625, 0.125, 0.25, 0.5, or 1.0 mg/L under static conditions for 96 hours. The test substance purity was reported at 100%.

96-hr LC₅₀ = 0.47 mg/L

A 48-hour EC₅₀ for Daphnia estimated by ECOSAR v1.00a was used to evaluate the acute toxicity of CASRN 4904-61-4.

48-hr EC₅₀ = 0.256 mg/L (estimated)

Toxicity to Aquatic Plants

A 96-hour LC₅₀ for algae estimated by ECOSAR v1.00a was used to evaluate the acute toxicity of CASRN 4904-61-4.

96-hr EC₅₀ = 0.19 mg/L (estimated)

Conclusion: The acute 96-hr LC₅₀ value of CASRN 4904-61-4 for fish is 2.02 mg/L. The acute 96-hr LC₅₀ value of CASRN 4904-614 for aquatic invertebrates is 0.47 mg/L. The estimated 96-hr EC₅₀ value of CASRN 4904-61-4 for algae is 0.19 mg/L.

Since this is a volatile chemical and testing performed with nominal concentrations may underestimate its toxicity, the estimated ecotoxicity values are used in support of this chemical's experimental results.

Table 4. Summary of the Screening Information Data Set as Submitted under the U.S. HPV Challenge Program	
Endpoints	SPONSORED CHEMICAL 1,5,9-Cyclododecatriene (4904-61-4)
Summary of Environmental Effects – Aquatic Toxicity Data	
Fish 96-h LC₅₀ (mg/L)	2.02¹ 0.194 (e)
Aquatic Invertebrates 96-h LC₅₀ (mg/L) 48-h EC₅₀ (mg/L)	0.47¹ 0.256 (e)
Aquatic Plants 96-h EC₅₀ (mg/L)	0.190 (e)
Chronic Aquatic Toxicity	No Data

¹Nominal concentration; (e) = estimated value using ECOSAR (v1.00a)