

## SCREENING-LEVEL HAZARD CHARACTERIZATION

### **1,5-Cyclooctadiene (CASRN 111-78-4)**

The High Production Volume (HPV) Challenge Program<sup>1</sup> 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<sup>1,2</sup>) 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<sup>2,3</sup> 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.


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

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

<sup>3</sup> 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.

<b>Chemical Abstract Service Registry Number (CASRN)</b>	<b>111-78-4</b>
<b>Chemical Abstract Index Name</b>	<b>1,5-Cyclooctadiene</b>
<b>Structural Formula</b>	
<p><b>Summary</b></p> <p>CASRN 111-78-4 is a colorless liquid with high vapor pressure and moderate water solubility. It is expected to have moderate mobility in soil. Volatilization is considered high based on the estimated Henry's Law constant. The rate of hydrolysis is considered negligible. The rate of atmospheric photooxidation is considered rapid. CASRN 111-78-4 is expected to have moderate persistence (P2) and low bioaccumulation potential (B1).</p> <p>The acute oral and dermal toxicity of CASRN 111-78-4 in rats is low and the acute inhalation toxicity in rats is moderate. In an oral (via gavage) combined repeated-dose/reproductive/developmental toxicity screening test in rats, CASRN 111-78-4 showed reductions in body weight gain, increase in clinical signs (males and females), and histopathological findings in the liver and thyroid at 600 mg/kg/day; the NOAEL for systemic toxicity is 175 mg/kg/day. Local effects (pathological effects in the esophagus of females only) were seen at 175 mg/kg/day, resulting in a NOAEL for local effects of 50 mg/kg/day. In this same study, there were no effects on any reproductive parameters evaluated; the NOAEL for reproductive toxicity is 600 mg/kg/day (highest dose tested). The developmental toxicity portion of the combined study showed a decrease in pup body weight at 600 mg/kg/day; the NOAEL for developmental toxicity is 175 mg/kg/day. Based on the systemic effects described above, the NOAEL for maternal toxicity is 175 mg/kg/day. CASRN 111-78-4 was not mutagenic in bacterial cells and did not induce chromosomal aberrations in mammalian cells <i>in vitro</i>. CASRN 111-78-4 did not increase the number of micronucleated cells in rats <i>in vivo</i>, following inhalation exposure. CASRN 111-78-4 was a skin and eye irritant in various animal species tested and was also a dermal sensitizer in guinea pigs. CASRN 111-78-4 induced narcosis when tested for neurotoxicity.</p> <p>The 96-h LC<sub>50</sub> value of CASRN 111-78-4 for fish is 13 mg/L. The 48-h EC<sub>50</sub> value of CASRN 111-78-4 for aquatic invertebrates is 0.87 mg/L. The 72-h EC<sub>50</sub> values of CASRN 111-78-4 for aquatic plants are 3.4 and 6.3 mg/L, for biomass and growth rate, respectively.</p> <p>There were no data gaps identified under the HPV Challenge Program.</p>	

The sponsor, E.I. du Pont de Nemours and Company, submitted a Test Plan and Robust Summaries to EPA for 1,5-cyclooctadiene (CAS No. 111-78-4; 9<sup>th</sup> CI name: 1,5-cyclooctadiene) on December 11, 2002. EPA posted the submission on the ChemRTK HPV Challenge website on January 16, 2003 (<http://www.epa.gov/chemrtk/pubs/summaries/15cyclooc/c14134tc.htm>). EPA comments on the original submission were posted to the website on May 13, 2003. Public comments were also received and posted to the website. The sponsor submitted updated/revise documents on November 21, 2003 and August 27, 2010, which were posted to the ChemRTK website on May 4, 2004 and August 31, 2010, respectively.

## **1. Chemical Identity**

### **1.1 Identification and Purity**

When noted in the robust summaries for different tests (environmental and human health effects testing), the reported purity for CASRN 111-78-4 was either >98% or >99%.

### **1.2 Physical-Chemical Properties**

The physical-chemical properties of CASRN 111-78-4 are summarized in Table 1. CASRN 111-78-4 is a colorless liquid with high vapor pressure and moderate water solubility.

## **2. General Information on Exposure**

### **2.1 Production Volume and Use Pattern**

CASRN 111-78-4 had an aggregated production and/or import volume in the United States between 1 and 10 million pounds during calendar year 2005.

CASRN 111-78-4 is a co-product produced in the manufacture of cyclododecatriene (CASRN 27070-59-3) and is used as a chemical intermediate for the production of flame retardants, aroma chemicals, catalysts, and rubber goods. Non-confidential information in the IUR indicated that the industrial processing and uses of the chemical include other basic organic chemical manufacturing as an intermediate. No commercial and consumer uses were reported.

<b>Property</b>	<b>Value</b>
CASRN	111-78-4
Molecular Weight	108.20
Physical State	Colorless liquid
Melting Point	-70 to -69°C (measured) -56.4°C (measured) <sup>2</sup>
Boiling Point	150.8°C (measured) at 757 mm Hg
Vapor Pressure	6.8 mm Hg at 25°C (measured) 4.95 mm Hg at 25°C (measured) <sup>2</sup>
Water Solubility	196 mg/L (measured)
Dissociation Constant (pK <sub>a</sub> )	Not applicable
Henry's Law Constant	2.68×10 <sup>-2</sup> atm-m <sup>3</sup> /mole (estimated) <sup>3</sup>
Log K <sub>ow</sub>	3.16 (measured)

<sup>1</sup> INVISTA S.à.r.l. 2011. Revised Test Plan and Robust Summary for 1,5-Cyclooctadiene. Available online at <http://www.epa.gov/chemrtk/pubs/summaries/15cycloo/c14134tc.htm> as of February 3, 2011.

<sup>2</sup> SRC. 2010. The Physical Properties Database (PHYSPROP). SRC: Syracuse, NY. Available online at <http://www.srcinc.com/what-we-do/free-demos.aspx> as of February 3, 2011.

<sup>3</sup> U.S. EPA. 2010. Estimation Programs Interface Suite™ for Microsoft® Windows, v4.00. U.S. Environmental Protection Agency, Washington, DC, USA. Available online at <http://www.epa.gov/opptintr/exposure/pubs/episuitedl.htm> as of February 3, 2011.

## 2.2 Environmental Exposure and Fate

Then environmental fate properties of CASRN 111-78-4 are summarized in Table 2. CASRN 111-78-4 is expected to have moderate mobility in soil. CASRN 111-78-4 at a concentration of 1.5 mg/L achieved 8% of its theoretical biochemical oxygen demand (BOD) in a closed bottle test (OECD 301D) over a 4-week incubation period. CASRN 111-78-4 at a concentration of 100 mg/L achieved 0% of its theoretical BOD using an activated sludge inoculum at 30 mg/L and the modified MITI test (OECD 301C) over a 4-week incubation period. It achieved 6% of its theoretical BOD after 5 days using a dilution method with effluent from a waste treatment plant as inoculum. The rate of volatilization is considered high based on the estimated Henry's Law constant. The rate of hydrolysis is negligible. CASRN 111-78-4 is expected to have moderate persistence (P2) and low bioaccumulation potential (B1).

<b>Table 2. Environmental Fate Characteristics of 1,5-Cyclooctadiene<sup>1</sup></b>	
<b>Property</b>	<b>Value</b>
Photodegradation Half-life	1.1 hours (estimated) <sup>2</sup>
Hydrolysis Half-life	Stable
Biodegradation	8% after 28 days (not readily biodegradable) 6% after 5 days (not readily biodegradable) <sup>3</sup> 0% after 28 days (not readily biodegradable) <sup>4</sup>
Bioaccumulation Factor	BAF = 107 (estimated) <sup>2</sup>
Log K <sub>oc</sub>	2.69 (estimated) <sup>2</sup>
Fugacity (Level III Model) <sup>2</sup>	
Air (%)	0.6
Water (%)	63.7
Soil (%)	34.4
Sediment (%)	1.2
Persistence <sup>5</sup>	P2 (moderate)
Bioaccumulation <sup>5</sup>	B1 (low)

<sup>1</sup> INVISTA S.à.r.l.2011. Revised Test Plan and Robust Summary for 1,5-Cyclooctadiene. Available online at <http://www.epa.gov/chemrtk/pubs/summaries/15cycloo/c14134tc.htm> as of February 3, 2011.

<sup>2</sup> U.S. EPA. 2010. Estimation Programs Interface Suite™ for Microsoft® Windows, v4.00. U.S. Environmental Protection Agency, Washington, DC, USA. Available online at <http://www.epa.gov/opptintr/exposure/pubs/episuitedi.htm> as of February 3, 2011.

<sup>3</sup> Bridie AL; Wolff CJM; Winter M. 1979. BOD and COD of some petrochemicals. *Water Res* 13(7):627–630.

<sup>4</sup> National Institute of Technology and Evaluation. 2002. Biodegradation and Bioaccumulation of the Existing Chemical Substances under the Chemical Substances Control Law. Available online at [http://www.safe.nite.go.jp/english/kizon/KIZON\\_start\\_hazkizon.html](http://www.safe.nite.go.jp/english/kizon/KIZON_start_hazkizon.html) as of February 3, 2011.

<sup>5</sup> 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 111-78-4 is a colorless liquid with high vapor pressure and moderate water solubility. It is expected to have moderate mobility in soil. Volatilization is considered high based on the estimated Henry’s Law constant. The rate of hydrolysis is considered negligible. The rate of atmospheric photooxidation is considered rapid. CASRN 111-78-4 is expected to have moderate persistence (P2) and low bioaccumulation potential (B1).

### 3. Human Health Hazard

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

#### *Acute Oral Toxicity*

Rats (sex/strain/number not specified) were exposed to CASRN 111-78-4 (concentration, method not provided). No information was provided except for the LD<sub>50</sub>.

**LD<sub>50</sub> = 2381 mg/kg**

### ***Acute Inhalation Toxicity***

Male Crl:CD®(SD)BR rats (6/dose) were exposed (nose-only) for a single 4-hour period to CASRN 111-78-4 concentrations of 1400, 2700 or 4300 ppm (approximately 6.19, 11.9 or 19 mg/L) and observed for 14 days. Mortality was observed at the 2700 (1/6) and 4300 (4/6) ppm groups.

**ALC<sub>50</sub> = 11.9 mg/L**

### ***Acute Dermal Toxicity***

CD rats (2/sex/dose) were administered CASRN 111-78-4 via dermal doses of 2, 3 or 4 mL/kg (equivalent to 1760, 2640 and 3520 mg/kg) for 24 hours and observed for 9 days. The test substance was placed on clipped, intact skin and covered with an occlusive dressing. No mortalities were observed at any dose level.

**LD<sub>50</sub> > 3520 mg/kg**

### ***Repeated-Dose Toxicity***

(1) In a combined repeated-dose/reproductive/developmental toxicity screening test (OECD TG 422), Sprague-Dawley rats (10/sex/dose) were administered CASRN 111-78-4 via gavage at the following dose levels: 0 (vehicle control – dried arachis oil), 50, 175 or 600 mg/kg/day. In addition, two recovery groups (5/sex/dose) were given either the high dose or the vehicle control. Animals were treated daily for either 43 days (males) or 54 days (females); recovery animals were treated for 42 days followed by a 14-day no-treatment period. Treatment began approximately two weeks prior to mating. The parameters measured during the systemic toxicity evaluation portion of the study included: clinical signs, behavioral assessments, body weight/food consumption, hematology, blood chemistry and functional observational battery (the last on five parental males after completion of mating and five parental females on Day 4 postpartum).

One control female was killed *in extremis* during a difficult parturition and was the only mortality. Clinical signs were observed in males and females at the high dose (600 mg/kg/day): increased salivation, episodes of hunched posture, ataxia, generalized fur staining, wet fur and orange staining on cage tray liners (all consistently throughout exposure period) and occasional instances (in females only) of lethargy, tiptoe gait and increased lacrimation. The following clinical signs were seen at the mid-dose (175 mg/kg): increased salivation (males and females) and, in males only, orange staining on cage tray liners during the first two weeks and ataxia (days 39 and 40). At the low dose (50 mg/kg/day), increased salivation and red/brown stained fur were observed in males only. There were no treatment-related effects noted in the functional observation battery evaluations.

The following general effects were observed (with no indication of statistical significance): body weight gain was reduced in high dose males (weeks 1, 2, 4 and 6) and females (week 2 only); a reduction in food efficiency (high dose males – week 6 and high dose females – week 2); and increased water consumption (males and females, high dose only). There were no reported

treatment-related effects on hematology, blood chemistry or urinalysis. There were no treatment-related macroscopic findings in any organs evaluated. Liver weights (both absolute and relative) were statistically significantly increased in high dose non-recovery females. The increase (statistical significance not noted) was still present 14-days post-exposure in non-recovery animals). Histopathological results showed the following effects in high dose females: centrilobular hypertrophy in the liver (minimal severity); follicular cell hypertrophy in the thyroid; and increased incidence of mononuclear cell infiltration in the esophagus (this last effect was also seen in mid-dose females).

**LOAEL (systemic toxicity) = 600 mg/kg/day** (based on reductions in body weight gain in both sexes and histopathological findings in females only)

**NOAEL (systemic toxicity) = 175 mg/kg/day**

**LOAEL (local effects) = 175 mg/kg/day** (based on esophageal effects in females)

**NOAEL (local effects) = 50 mg/kg/day**

### ***Reproductive/Developmental Toxicity***

In the combined repeated dose/reproductive/developmental toxicity screening test described above, the following parameters were evaluated for reproductive (mating, gestation, offspring litter size and viability) and developmental (offspring growth and development and observations) toxicity. There were no treatment-related effects on mating, gestation or litter size/viability. Mean offspring body weight and litter weights were reduced in high dose (600 mg/kg/day) litters on Day 1 and Day 4 postpartum (statistical significance not noted). There were no clinically observable effects on offspring.

**NOAEL (reproductive toxicity) = 600 mg/kg/day** (highest dose tested)

**LOAEL (maternal toxicity) = 600 mg/kg/day** (based on reductions in body weight gain, clinical signs and some pathological effects in females only)

**NOAEL (maternal toxicity) = 175 mg/kg/day**

**LOAEL (developmental toxicity) = 600 mg/kg/day** (based on reduced mean offspring body weight and litter weights)

**NOAEL (developmental toxicity) = 175 mg/kg/day**

### ***Genetic Toxicity – Gene Mutation***

#### ***In vitro***

*Salmonella typhimurium* strains TA100, TA1535, TA97a and TA98 and *Escherichia coli* strain WP2uvrA (pKM101) were exposed to CASRN 111-78-4 in triplicate to doses of 0, 10, 50, 100, 500, 1000, 2500 or 5000 µg/plate with and without metabolic activation. Positive and negative controls were tested concurrently, but control responses were not provided.

**CASRN 111-78-4 was not mutagenic in this assay.**

## ***Genetic Toxicity – Chromosomal Aberrations***

### ***In vitro***

Cultured human lymphocytes were exposed to CASRN 111-78-4 at concentrations of 0, 0.1, 0.25, 0.5, 0.75 or 1.0 mg/L in the first trial with and without metabolic activation. In a second trial, cells were exposed to the same concentrations plus two higher ones (2.5 or 5.0 mg/L). A supplemental harvest 24 hours after the initial harvest was conducted with the 0.75, 1.0, 2.5 and 5.0 mg/L samples of trial 2. The cytotoxic concentration in the first trial was 0.75 mg/L without metabolic activation and 1.0 mg/L with activation. In the second trial, the cytotoxic concentration was 1.0 mg/L and 2.5 mg/L, with and without metabolic activation, respectively. In the supplemental trial there was no cytotoxicity in the without activation group, and there was cytotoxicity in the 0.75 mg/L activation group. There were no treatment-related effects on chromosomal aberration formation. Positive controls were tested concurrently and responded appropriately.

**CASRN 111-78-4 did not induce chromosomal aberrations in these assays.**

### ***In vivo***

Male Crl:CD(SD)BR rats (five controls and ten in the single treatment group) were exposed to CASRN 111-78-4 via whole-body inhalation to 0 or 1500 ppm (approximately 6.64 mg/L) 6 hours/day for two days. Animals were sacrificed 24 hours after the last exposure for harvest of bone marrow. A positive control group of five male rats was tested concurrently. Clinical signs of toxicity were observed during exposure (depression, lack of alerting response, incoordination) and after exposure (incoordination, abnormal gait, irregular respiration). Weight loss was evident in all exposed animals at the time of sacrifice. There was a statistically significant decrease in the proportion of polychromatic erythrocytes/1000 erythrocytes (indicative of bone-marrow toxicity); but there was no increase in micronuclei. The positive control responded appropriately.

**CASRN 111-78-4 did not increase the number of micronucleated cells in rat bone marrow in this assay.**

## ***Additional Information***

### ***Skin Irritation***

Occlusive study: Two New Zealand White rabbits of each sex were dosed with 1 mL of CASRN 111-78-4 for 6 hours/day for 3 days under occlusive conditions. (Normal irritation study protocol is for a maximum dose of 0.5 mL and a single four-hour exposure). The test material caused severe irritation of the skin, with gross injury and epidermal sloughing. Microscopic examination showed necrosis of the epidermis, ulceration and marked inflammation of the dermis.

**CASRN 111-78-4 was severely irritating to rabbit skin in this study.**

Non-occlusive studies: New Zealand White rabbits (1/sex), guinea pigs ("P" strain, 5/sex) and female hairless mice (CAH strain, two total) were administered dermal doses of 1 mL (rabbits) or 0.5 mL (guinea pigs) of CASRN 111-78-4 applied to clipped skin 5 days/week for 4.5 weeks; mice received an unknown dose for 12 days. (As with study #1 above, this is not a typical irritation study protocol). The treated area was kept uncovered for the duration of the study. Skin was examined daily and evaluated for histopathology one day after the 23<sup>rd</sup> application (rabbits and guinea pigs). In all species, erythema was observed after one application, followed by severe acute contact dermatitis with epidermal sloughing and suppression of hair growth (in rabbits and guinea pigs). A second group of guinea pigs was treated under the same conditions and observed for 3 weeks after the last exposure. Epidermal thickening and marked acanthosis remained even after the recovery time.

**CASRN 111-78-4 cause irritant contact dermatitis.**

### *Eye Irritation*

In a study that included no information on species, strain or sex of animal tested or other methodology information, CASRN 111-78-4 caused immediate irritation to the eyes followed by mild conjunctivitis, which diminished within 24 hours. Eyelids of exposed animals became red and swollen and a purulent discharge was observed. Recovery from these effects took several days.

**CASRN 111-78-4 was irritating to eyes in this study.**

### *Sensitization*

Ten guinea pigs per group (strain not specified) were tested either by subcutaneous injection or by application of a 0.1% w/v solution of CASRN 111-78-4 in light liquid paraffin to the shorn skin of the back, 3 days/week for 3 weeks. A rest period of 10 days was followed by a challenge with the same test solution to the right flank and a solvent challenge to the left flank on the 11<sup>th</sup> day. In the topical application test, 10/10 animals showed positive sensitization reactions at 24 and 48 hours. In the subcutaneous test, 9/10 animals showed positive sensitization reactions at 24 and 48 hours.

**CASRN 111-78-4 was a dermal sensitizer in guinea pigs in this study.**

### *Neurotoxicity*

Groups of 20 male Crl:CD BR rats were exposed via whole-body inhalation to measured concentrations of 0, 50, 150 or 500 ppm (equivalent to approximately 0.23, 0.66 and 2.21 mg/L) 6 hours/day for a total of nine exposures over a 2-week period, followed by a 2-week unexposed recovery period. Half of the rats in each group were evaluated for neurotoxicity; the remainder were subjected to standard toxicological evaluations. Rats exposed to 500 ppm lacked an alerting response near the conclusion of daily exposure periods; in addition, rats in this and the 150 ppm groups were more likely than controls to be sleeping after exposure. Taken together, this suggests a slight narcotic effect. There were no other treatment-related effects on clinical signs, motor activity or functional observational battery. Urine pH was decreased at the end of the exposure period in high concentration rats, but not after the recovery period. There were no other effects on urinalysis and no effects on hematology or serum chemistry. Degeneration and

necrosis of the nasal olfactory epithelium were observed upon histologic examination of the 500 ppm rats after the exposure period; regeneration of these cells was observed after recovery. Kidney weights were increased and hyaline droplets in the kidney were evident in the high concentration rats; these effects were reversed during the recovery period. Also, the summary stated that there was one minor neuropathological lesion in the high dose group, but there were no specifics.

**LOAEL ~ 0.66 mg/L (sleepiness/narcosis effect)**

**NOAEL ~ 0.23 mg/L**

**Conclusion:** The acute oral and dermal toxicity of CASRN 111-78-4 in rats is low and the acute inhalation toxicity in rats is moderate. In an oral (via gavage) combined repeated-dose/reproductive/developmental toxicity screening test in rats, CASRN 111-78-4 showed reductions in body weight gain, increase in clinical signs (males and females), and histopathological findings in the liver and thyroid at 600 mg/kg/day; the NOAEL for systemic toxicity is 175 mg/kg/day. Local effects (pathological effects in the esophagus of females only) were seen at 175 mg/kg/day, resulting in a NOAEL for local effects of 50 mg/kg/day. In this same study, there were no effects on any reproductive parameters evaluated; the NOAEL for reproductive toxicity is 600 mg/kg/day (highest dose tested). The developmental toxicity portion of the combined study showed a decrease in pup body weight at 600 mg/kg/day; the NOAEL for developmental toxicity is 175 mg/kg/day. Based on the systemic effects described above, the NOAEL for maternal toxicity is 175 mg/kg/day. CASRN 111-78-4 was not mutagenic in bacterial cells and did not induce chromosomal aberrations in mammalian cells *in vitro*. CASRN 111-78-4 did not increase the number of micronucleated cells in rats *in vivo*, following inhalation exposure. CASRN 111-78-4 was a skin and eye irritant in various animal species tested and was also a dermal sensitizer in guinea pigs. CASRN 111-78-4 induced narcosis when tested for neurotoxicity.

<b>Table 3: Summary of the Screening Information Data Set as Submitted under the U.S. HPV Challenge Program – Human Health Data</b>	
<b>Endpoints</b>	<b>SPONSORED CHEMICAL 1,5-Cyclooctadiene (111-78-4)</b>
<b>Acute Oral Toxicity</b> <b>LD<sub>50</sub> (mg/kg)</b>	<b>2381</b>
<b>Acute Inhalation Toxicity</b> <b>ALC<sub>50</sub> (mg/L)</b>	<b>11.9</b>
<b>Acute Dermal Toxicity</b> <b>LD<sub>50</sub> (mg/kg)</b>	<b>&gt; 3520</b>
<b>Repeated-Dose Toxicity</b> <b>NOAEL/LOAEL</b> <b>Oral (mg/kg/day)</b>	<b>NOAEL = 175</b> <b>LOAEL = 600</b>
<b>Reproductive Toxicity</b> <b>NOAEL/LOAEL</b> <b>Oral (mg/kg/day)</b>	
<b>Systemic Toxicity</b>	<b>NOAEL = 175</b> <b>LOAEL = 600</b>
<b>Reproductive Toxicity</b>	<b>NOAEL = 600</b> <b>(highest dose tested)</b>
<b>Developmental Toxicity</b> <b>NOAEL/LOAEL</b> <b>Oral (mg/kg/day)</b>	
<b>Maternal/Developmental Toxicity</b>	<b>NOAEL = 175</b> <b>LOAEL = 600</b>
<b>Genetic Toxicity – Gene Mutation</b> <i>In vitro</i>	<b>Negative</b>
<b>Genetic Toxicity – Chromosomal Aberrations</b> <i>In vitro</i>	<b>Negative</b>
<b>Genetic Toxicity – Chromosomal Aberrations</b> <i>In vivo</i>	<b>Negative</b>
<b>Additional Information</b> <b>Skin Irritation</b> <b>Eye Irritation</b> <b>Skin Sensitization</b> <b>Neurotoxicity</b>	<b>Irritating</b> <b>Irritating</b> <b>Positive</b> <b>Narcosis</b>

Measured data in bold

#### 4. Hazard to the Environment

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

##### *Acute Toxicity to Fish*

(1) Medaka (*Oryzias latipes*) were exposed to CASRN 111-78-4 at measured concentrations of 0, 3.5, 5.0, 6.9, 11 or 18 mg/L for 96 hours, in the closed system under semi-static conditions. (MOE, 2008) <http://www.env.go.jp/chemi/sesaku/02e.pdf>

**96-h LC<sub>50</sub> = 13 mg/L**

(2) Rainbow trout (*Oncorhynchus mykiss*) were exposed to CASRN 111-78-4 at concentrations of 0, 27.6, 30.0 or 38.1 mg/L for 96 hours. Acetone was used as a solvent. Mortality was observed at 30.0(1/5) and 38.1(5/5) mg/L. The study did not indicate whether the toxicity was based on nominal or measured concentrations; however the reported toxicity is supported by the above-mentioned study.

**96-h LC<sub>50</sub> = 30-38 mg/L**

##### *Acute Toxicity to Aquatic Invertebrates*

(1) *Daphnia magna* were exposed to CASRN 111-78-4 at measured concentrations of 0, 0.20, 0.37, 0.63, 1.3 or 2.6 mg/L for 48 hours under semi-static conditions (MOE, 2008) <http://www.env.go.jp/chemi/sesaku/02e.pdf>.

**48-h EC<sub>50</sub> = 0.87 mg/L**

(2) *Daphnia magna* were exposed to CASRN 111-78-4 at concentrations of 0, 0.37, 0.56, 0.85, 1.29, 1.96, 3.00 or 4.58 mg/L for 24 hours. Acetone was used as a solvent. Although the test duration is shorter than the guideline (EPA or OECD) required duration of 48 hours, the reported toxicity (24-h EC<sub>50</sub>) is supported by the above-mentioned study.

**24-h EC<sub>50</sub> = 0.9 mg/L**

##### *Toxicity to Aquatic Plants*

Green algae (*Pseudokirchneriella subcapitata*) were exposed to CASRN 111-78-4 under static conditions at nominal concentrations of 0.88, 2.8, 8.8, 28, or 88 mg/L for 72 hours. Measured concentrations ranged from 82 to 98% of nominal at the start of the test and from 71 to 86% at the end of the test. Mean measured concentrations were used for the determination of effect levels.

**72-h EC<sub>50</sub> (biomass) = 3.4 mg/L**

**72-h EC<sub>50</sub> (growth) = 6.3 mg/L**

**Conclusion:** The 96-h LC<sub>50</sub> value of CASRN 111-78-4 for fish is 13 mg/L. The 48-h EC<sub>50</sub> value of CASRN 111-78-4 for aquatic invertebrates is 0.87 mg/L. The 72-h EC<sub>50</sub> values of CASRN 111-78-4 for aquatic plants are 3.4 and 6.3 mg/L, for biomass and growth rate, respectively.

<b>Table 4. Summary of the Screening Information Data Set as Submitted under the U.S. HPV Challenge Program – Aquatic Toxicity Data</b>	
<b>Endpoints</b>	<b>1,5-Cyclooctadiene (111-78-4)</b>
<b>Fish 96-h LC<sub>50</sub> (mg/L)</b>	<b>13</b>
<b>Aquatic Invertebrates 48-h EC<sub>50</sub> (mg/L)</b>	<b>0.87</b>
<b>Aquatic Plants 72-h EC<sub>50</sub> (mg/L)</b>	
<b>Biomass</b>	<b>3.4</b>
<b>Growth</b>	<b>6.3</b>

## 5. References

MOE, Japan Ministry of the Environment in 2008. <http://www.env.go.jp/chemi/sesaku/02e.pdf>