

SCREENING-LEVEL HAZARD CHARACTERIZATION

Isocyanic Acid, *m*-phenylenediiso-propylidene (CASRN: 2778-42-9)

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 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.

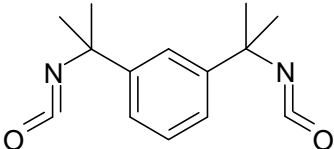
OPPT does not develop HCs for those HPV chemicals which have already been assessed internationally through the HPV program of the Organization for Economic Cooperation and Development (OECD) and for which Screening Initial Data Set (SIDS) Initial Assessment Reports (SIAR) and SIDS Initial Assessment 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)	<p style="text-align: center;">2778-42-9</p>
Chemical Abstract Index Name	<p style="text-align: center;">Benzene, 1,3-bis(1-isocyanato-1-methylethyl)-</p>
Structural Formula	 <p>The image shows the chemical structure of Benzene, 1,3-bis(1-isocyanato-1-methylethyl)-. It consists of a central benzene ring with two 1-isocyanato-1-methylethyl groups attached at the 1 and 3 positions. Each group is represented as a central carbon atom bonded to two methyl groups and one isocyanato group (-N=C=O).</p>
<p style="text-align: center;">Summary</p> <p>This chemical is a liquid that reacts slowly with water and has moderate vapor pressure. It is expected to have low mobility in soil. Volatilization of this chemical is considered slow based on its Henry's Law constant. The rate of hydrolysis is considered slow. The rate of atmospheric photooxidation is considered moderate. This chemical is expected to have low persistence (P1) and low bioaccumulation potential (B1).</p> <p>The acute toxicity of this chemical is low in rats and rabbits following oral and dermal exposures respectively, but high in rats and guinea pigs exposed via inhalation. This chemical is moderately irritating to rabbit skin and eyes and is a dermal sensitizer in guinea pigs. Repeated-dose studies in rats exposed to this chemical via vapor and aerosol showed decreased body weight gain, serum chemistry, hematology and urinalysis alterations, increased lung weights, and histopathological changes in the lungs and respiratory tract. The LOAEL for systemic toxicity was approximately 0.004 mg/L/day, and the NOAEL was not established for vapor exposure. The LOAEL for aerosol exposure was 0.0044 mg/L/day with a NOAEL of 0.0015 mg/L/day. An oral combined reproductive/developmental toxicity screening test in rats revealed significant decreases in pup weight and mean litter weights during lactation days 1 and 4. The LOAEL for developmental toxicity was 250 mg/kg-bw/day and the NOAEL was 150 mg/kg-bw/day. This chemical did not induce gene mutations or chromosomal aberrations <i>in vitro</i>.</p> <p>The acute hazard to fish, aquatic invertebrates, and aquatic plants is 0.67 mg/L, 5.2 mg/L, and 2.1 mg/L, respectively.</p> <p>No data gaps were identified under the HPV Challenge Program.</p>	

The sponsor, Cytec Industries, Inc., submitted a Test Plan and Robust Summaries to EPA for isocyanic acid, *m*-phenylenediisopropylidene [CAS No. 2778-42-9; 9th CI name: benzene, 1,3-bis(1-isocyanato-1-methylethyl)] on September 19, 2002. EPA posted the submission on the ChemRTK HPV Challenge website on October 10, 2002 (<http://www.epa.gov/hpv/pubs/summaries/isocyani/c13996tc.htm>). EPA comments on the original submission were posted to the website on February 6, 2003. Public comments were also received and posted to the website. The sponsor submitted updated/revised documents on April 9, 2003, October 3, 2003, February 8, 2004 and March 15, 2005, which were posted to the ChemRTK website on June 6, 2003, February 8, 2005, March 8, 2005 and May 10, 2005, respectively.

1. Chemical Identity

1.1 Identification and Purity

The HPV submission for this chemical did not include information on identification and purity in the Test Plan (2002).

1.2 Physical-Chemical Properties

The physical-chemical properties of isocyanic acid, *m*-phenylenediisopropylidene are summarized in Table 1.

Table 1. Physical-Chemical Properties of Isocyanic Acid, <i>m</i>-Phenylenediisopropylidene¹	
Property	Value
CASRN	2778-42-9
Molecular Weight	244.30
Physical State	Liquid
Melting Point	-10°C (measured)
Boiling Point	292°C (measured)
Vapor Pressure	3.2×10 ⁻³ mm Hg at 25°C (measured)
Water Solubility	5.83 mg/L at 25°C (estimated; reacts slowly with water)
Dissociation Constant (pK _a)	Not applicable
Henry's Law Constant	3.22×10 ⁻⁶ atm·m ³ /mole (estimated)
Log K _{ow}	4.74 (estimated)

¹Cytec Industries Inc. May 10, 2005. Revised Robust Summary and Test Plan for Isocyanic Acid, *m*-Phenylenediisopropylidene. <http://www.epa.gov/chemrtk/pubs/summaries/isocyani/c13996tc.htm>.

2. General Information on Exposure

2.1 Production Volume and Use Pattern

This chemical had an aggregated production and/or import volume in the United States of 1 to 10 million pounds during the calendar year 2005.

Non-confidential information in the IUR indicated that the industrial processing and uses of the chemical include adhesive and binding agents in the manufacturing of adhesives. Non-confidential information in the IUR indicated that the commercial and consumer products containing the chemical include adhesives, sealants, paints and coatings.

The HPV and eHPV submissions for this chemical state that it is primarily used in specialty coatings, aqueous dispersions, automotive coatings, wood coatings, inks, sealants, adhesives, thermoplastic urethanes, and lacquers. In addition, this chemical is FDA approved for use in food-packaging under specific listings in the Code of Federal Regulations (CFR) Title 21-Food and Drugs Chapter I-Food and Drug Administration, Department of Health and Human Services.

2.2 Environmental Exposure and Fate

No quantitative information is available on releases of this chemical to the environment.

The environmental fate properties are provided in Table 2. Isocyanic acid, *m*-phenylenediisopropylidene is expected to have low mobility in soil. Isocyanic acid, *m*-phenylenediisopropylidene and its hydrolysis products were not readily biodegradable using a closed bottle (OECD 301D) test. The rate of volatilization of isocyanic acid, *m*-phenylenediisopropylidene from water and moist soil is considered low based on the estimated Henry's Law constant. The rate of hydrolysis is slow [stable for 2-3 hrs at temperatures below 40 °C] under environmental conditions. Isocyanic acid, *m*-phenylenediisopropylidene is expected to have low persistence (P1) and low bioaccumulation potential (B1).

Property	Value
Photodegradation Half-life	12.7 hours (estimated)
Hydrolysis Half-life	Stable to hydrolysis for hours to days ²
Biodegradation	13.7% after 28 days (not readily biodegradable)
Bioconcentration	BCF = 900 (estimated) ³
Log K _{oc}	5.05 (estimated) ³
Fugacity (Level III Model)	Air = 0.779% Water = 18.1% Soil = 62.6% Sediment = 18.5%
Persistence ⁴	P1 (low)
Bioaccumulation ⁴	B1 (low)

¹Cytec Industries Inc. May 10, 2005. Revised Robust Summary for Isocyanic Acid, *m*-Phenylenediisopropylidene. <http://www.epa.gov/chemrtk/pubs/summaries/isocyani/c13996tc.htm>.

²<http://www.cytec.com/specialty-chemicals/pdf/UPT-797-B-TMXDI%20Dispersions.pdf> and http://www.cytec.com/specialty-chemicals/PDFs/SpecialtyUrethanes/Novel%20PUD3_07.pdf

³U.S. EPA. 2008. Estimation Programs Interface Suite™ for Microsoft® Windows, v 3.20. United States Environmental Protection Agency, Washington, DC, USA. <http://www.epa.gov/opptintr/exposure/pubs/episuite.htm>.

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

3. Human Health Hazard

Acute Oral Toxicity

(1) Sprague-Dawley rats (5/sex/dose) were administered isocyanic acid, *m*-phenylenediisopropylidene via oral gavage at 0, 2.8, 3.6, 4.5, 5.6 or 7.1 ml/kg-bw (approximately 0, 2968, 3816, 4770, 5936 or 7526 mg/kg-bw) and observed for 15 days. Mortality occurred at all exposure doses (2/10 on day 3 at 2.8; 1/10 on day 3 at 3.6; 5/10 on days 2 and 4 at 4.5; and 10/10 on days 2 and 3 at 7.1 ml/kg-bw). Treated animals gained less weight compared to controls and lost weight for 1 – 3 days post-dosing. There were no significant differences when compared to the control. Necropsy findings did not reveal any abnormalities.

LD₅₀ ~ 5300 mg/kg-bw

(2) Sprague-Dawley rats (5/sex) were administered undiluted isocyanic acid, *m*-phenylenediisopropylidene via oral gavage at 5000 mg/kg-bw and observed for 14 days. No signs of toxicity were observed on the day of dosing. Two females died on day 2. At necropsy irritation of the small intestinal mucosa was seen in three animals.

LD₅₀ > 5000 mg/kg-bw

Acute Inhalation Toxicity

(1) Sprague-Dawley rats (5/sex/concentration) were exposed (whole body) to the aerosol of isocyanic acid, *m*-phenylenediisopropylidene at mean measured concentrations of 0, 0.0200, 0.0533, 0.0935 or 0.316 mg/L for 4 hours and observed for 14 days. Mortality occurred at all exposure concentrations (10/10 at 0.316; 10/10 at 0.0935; 9/10 at 0.0533; and 3/10 at 0.02 mg/L). Clinical signs during exposure included respiratory abnormalities, whole body hypothermia, red/brown discharge from the jaws and snout, immobility, emaciation, swollen abdomen, lethargy, a dark appearance of the eyes, salivation, and wet fur around snout, matted fur and opacity of the eyes. Necropsy examinations revealed congestion and swollen lungs, a white frothy fluid in the trachea, a fluid-filled thoracic cavity, distension of the gastrointestinal tract with gas.

LC₅₀ = 0.027 mg/L

(2) English Smooth-Haired guinea pigs (5/sex/concentration) were exposed to isocyanic acid, *m*-phenylenediisopropylidene as an aerosol at concentrations of 0, 0.195, 0.233, 0.355 or 0.457 mg/L for 1 hour. Mortality occurred at all exposure concentrations (the number of deaths and the days were not specified for the study). Clinical signs included weakness, lethargy, gasping/rales and discharge from eyes, nose or mouth. Body weight losses occurred in all treatment groups. Gross pathology of the animals that died showed swollen, congested, reddened and rubbery lungs. Survivors showed swelling, reddening, collapse and foci of discoloration in lungs during the necropsy.

LC₅₀ = 0.240 mg/L

Acute Dermal Toxicity

New Zealand White rabbits (5/sex) were administered isocyanic acid, *m*-phenylenediisopropylidene dermally at 2000 mg/kg-bw on to the abraded skin under occluded conditions for 24 hours. Dermal irritation and eschar formation was seen at the application site on day 4 and was most severe 14 days after test substance application with a mean score of 3.9 out of 4. The irritation persisted until the day of scheduled sacrifice.

LD₅₀ > 2000 mg/kg-bw

Repeated-Dose Toxicity

(1) Sprague-Dawley rats (10/sex/concentration) were exposed (whole-body) to isocyanic acid, *m*-phenylenediisopropylidene vapor at nominal concentrations of 0, 0.4, 0.8 or 1.6 ppm for 6 hours/day, 5 days/week for 13 weeks. Mean analytical concentrations were 0, 0.31, 0.72 and 1.46 ppm (0, approximately 0.004, 0.008 and 0.015 mg/L, respectively). Three male rats at the high-concentration died on days 15-18. Exposure-related clinical signs included respiratory difficulties at 1.46 ppm and were present sporadically at 0.72 ppm. A significant decrease in body weight gains were seen in males and females at the highest concentration during weeks 7 and 14. Increased mean corpuscular volume (MCV), erythrocyte count; decreased albumin concentration, glucose concentration and urine volume were seen at 0.31 and 0.72 ppm. At necropsy, discolored and emphysematous lungs were observed in animals that died or were humanely killed. Increased lung weights were noted at all concentrations. Microscopic examinations revealed significant increases in rhinitis and squamous metaplasia at all exposure; nasal cavity mucus at the mid- and high doses; and olfactory epithelium degeneration at the highest dose. Histopathological examinations showed inflammatory changes and lesions in the respiratory tract, (nasal cavity, larynx and trachea) consisting of necrosis, ulceration, squamous metaplasia, congestion and hemorrhage Bronchiolar submucosal fibrosis was noted in several animals.

LOAEL ~ 0.004 mg/L/day (based on decreased body weight gains, changes in serum chemistry, hematology and urinalysis, increased lung weight and histopathological changes in the respiratory tract)

NOAEL = Not established

(2) CD-1 mice (10/sex/concentration) were exposed (whole-body) to isocyanic acid, *m*-phenylenediisopropylidene vapor at nominal concentrations of 0, 0.4, 0.8 or 1.6 ppm for 6 hours/day, 5 days/week for 13 weeks. Mean analytical concentrations were 0, 0.31, 0.72 and 1.46 ppm (0, approximately 0.004, 0.008 and 0.015 mg/L, respectively). Mortalities for male mice were 1/10 at 0.4 on day 18, 2/10 at 0.8 on days 25-66, and 7/10 at 1.6 ppm on days 6-24. Mortalities for female mice were 2/10 at 0.8 on days 18-27, and 9/10 at 1.6 ppm on days 7-38. A Decreased body weight gain was significantly different in mice at 1.46 ppm of weeks 7 and 8 in both males and females. Exposure-related clinical signs included respiratory difficulties (e.g., gasping, audible respiration) at 1.46 ppm and were observed sporadically at 0.72 ppm. Involuntary sporadic contraction of the eyes and alopecia were also observed at 0.72 and 1.46 ppm. At necropsy, discoloration and emphysematous lungs were observed in animals that died or were humanely killed. For mice that died, pulmonary congestion and alopecia were observed. Microscopic evaluations showed rhinitis and accumulated nasal mucus at all doses; acidophilic

droplets at the low to mid-doses; Increased lungs weights were noted at all concentrations. Histopathological examination revealed inflammatory changes and lesions in the respiratory tract included lesions in the nasal cavity, larynx, trachea (consisting of necrosis, ulceration, squamous metaplasia, congestion and hemorrhage). Bronchiolar submucosal fibrosis was noted in several animals.

LOAEL ~ 0.004 mg/L/day (based on mortality, decreased body weight gains, increased lungs weight and histopathological changes in respiratory tract)

NOAEL = Not established

(3) Sprague-Dawley rats (5/sex/concentration) were exposed (whole-body) to aerosols of isocyanic acid, *m*-phenylenediiso-propylidene at nominal concentrations of 0, 0.0005, 0.0015 or 0.005 mg/L for 6 hours/day, 5 days/week for 4 weeks. The mean analytical exposure concentrations were 0, 0.00038, 0.0015 and 0.0044 mg/L. All animals survived the duration of the study at all concentrations tested. Body weights were significantly decreased in males and females at the high concentration on days 5-8. Serum calcium and phosphorous levels of high-concentration males were significantly increased and females showed a similar trend, but were not significantly different. High-concentration females had a significant increase in relative lung weights, but not in absolute lung weights. Gross postmortem evaluations showed evidence of discolored lungs in one of five males exposed to the low concentration, one male and one female exposed to the mid-dose and four of five males at the high-concentration. Microscopic findings at high concentration included subacute/chronic inflammations of the lungs only in some animals and the appearance of hyperplastic and metaplastic changes in the bronchi of several animals. These changes were not seen in animals from the control or the two lower exposure levels.

LOAEL = 0.0044 mg/L/day (based on decreased body weight, serum chemistry alterations, histopathological changes in the lungs)

NOAEL = 0.0015 mg/L/day

Reproductive/Developmental Toxicity

In a combined reproductive/developmental toxicity screening test, Sprague-Dawley rats (10/sex/dose) were administered isocyanic acid, *m*-phenylenediiso-propylidene via oral gavage at 0, 15, 150 or 250 mg/kg-bw/day. Males were exposed for 19 days and females for 40 – 41 days. Mortality was observed at all doses (four low-dose, five mid-dose and four high-dose animals) but was attributed to the mal-administration of isocyanic acid, *m*-phenylenediiso-propylidene. Body weight gain was decreased in females at the high dose throughout gestation and day 1 – 4 post-partum, but was not significantly different. There was no effect of treatment on fertility or mating performance. Male and female fertility indices were 100% at the low- and mid-doses and 90% at the high-dose. One high-dose and one control pair failed to mate. There was no effect of treatment on pre-coital interval or gestation or parturition length. There were no effects of treatment on live birth or viability index, litter size, pinna unfolding, surface righting reflex or sex ratio. There were no treatment-related gross abnormalities in offspring at termination. The mean pup weight was significantly decreased on days 1 and 4 of lactation at the high dose that led to a decrease in the total mean litter weight compared to controls. Offspring weights of high-dose animals were lower than historical controls.

LOAEL = 250 mg/kg-bw/day (based on decreased pup weight and decreased litter weight during lactation days 1 and 4)

NOAEL = 150 mg/kg-bw/day

Genetic Toxicity – Gene Mutation

In vitro

Salmonella typhimurium strains TA98, TA100, TA1535, TA1537 and TA1538 were exposed to isocyanic acid, *m*-phenylenediiso-propylidene at concentrations of 0.1, 1, 10 or 100 µg/plate in the presence and absence of metabolic activation. The cytotoxic concentration was 100 – 10,000 µg/plate. Positive and vehicle controls were tested concurrently and responded appropriately. **Isocyanic acid, *m*-phenylenediiso-propylidene was not mutagenic in this assay.**

Genetic Toxicity – Chromosomal Aberrations

In vitro

Chinese hamster ovary (CHO) cells were exposed to isocyanic acid, *m*-phenylenediiso-propylidene at concentrations of 0 – 40 µg/mL in the absence of metabolic activation, and 0 – 40 or 0 – 20 µg/mL in the presence of metabolic activation. The cytotoxic concentration was ≥ 20 µg/mL. Positive and vehicle controls were tested concurrently and responded appropriately. **Isocyanic acid, *m*-phenylenediiso-propylidene did not induce chromosomal aberrations in this assay.**

Additional Information

Skin Irritation

Rabbits (6 males) were administered 0.5 mL of isocyanic acid, *m*-phenylenediiso-propylidene dermally onto two intact and two abraded skin sites under occluded conditions for 24 hours and were monitored for 13 days. Erythema ranged from mild to severe for intact sites and severe for abraded sites. Mild edema was observed for both skin types. **Isocyanic acid, *m*-phenylenediiso-propylidene was moderately irritating to rabbit skin in this assay.**

Eye Irritation

Rabbits (9 females) were administered 0.1 mL of undiluted isocyanic acid, *m*-phenylenediiso-propylidene into the conjunctival sac of the right eye of each rabbit; the left eye was untreated and served as a control. Six rabbits received no further treatment. Three rabbits had their eyes rinsed for 60 seconds, 30 seconds after the test substance instillation. All rabbits survived and gained weight. Ocular exposure produced no corneal damage at any time. All treated eyes responded to light; however, discharge, chemosis, inflammation and opacity was also observed. **Isocyanic acid, *m*-phenylenediiso-propylidene was mildly irritating to rabbit eyes in this assay.**

Sensitization

(1) Guinea pigs (10) were administered 25 μ L a single epicutaneous application of a 0.36 molar solution of isocyanic acid, *m*-phenylenediiso-propylidene. Five days after the single induction application, each animal was exposed to the same concentration and amount of test substance to a previously untreated site. No patch was applied to the induction site or challenge sites. Nine days after the initial challenge, the animals were subjected to a re-challenge at sites that had not been previously exposed. Animals were observed twice per day for clinical signs. Skin condition was evaluated at 24 and 48 hours after each application. Contact sensitization was evident for the test substance at the initial (5 days post-induction) challenge. Evidence of sensitization was negligible upon re-challenge (14 days post-induction).

Isocyanic acid, *m*-phenylenediiso-propylidene was sensitizing in this assay.

(2) Guinea pigs (12/dose) were exposed whole-body to isocyanic acid, *m*-phenylenediiso-propylidene at a nominal aerosol concentration 36 μ g/L (26.7 μ g/L measured concentration) for 3 hours a day for 5 days. A negative control group was also tested. On challenge days 22, 23 and 26, animals were exposed nose-only to a nominal aerosol concentration of 0.015 – 0.020 mg/L for a 20-minute period. On study day 24, the animals were challenged for skin sensitization potential by intradermal dosing with 100 μ L of 0.0333% isocyanic acid, *m*-phenylenediiso-propylidene and control substance at different sites. Lethargy and nasal and oral discharge were observed in both groups. None of the animals showed an increase in respiratory rate equal to or greater than the value of 36% used as a threshold value of a positive response. There was no evidence of respiratory sensitization and there were no treatment-related effects on lung weights. There was no evidence of skin sensitization as there was an absence of scores ≥ 2 for erythema.

Isocyanic acid, *m*-phenylenediiso-propylidene was not a dermal or respiratory sensitizer in this assay.

Conclusion: The acute toxicity of this chemical is low in rats and rabbits following oral and dermal exposures respectively, but high in rats and guinea pigs exposed via inhalation. This chemical is moderately irritating to rabbit skin and eyes and is a dermal sensitizer in guinea pigs. Repeated-dose studies in rats exposed to this chemical via vapor and aerosol showed decreased body weight gain, serum chemistry, hematology and urinalysis alterations, increased lung weights, and histopathological changes in the lungs and respiratory tract. The LOAEL for systemic toxicity was approximately 0.004 mg/L/day, and the NOAEL was not established for vapor exposure. The LOAEL for aerosol exposure was 0.0044 mg/L/day and the NOAEL was 0.0015 mg/L/day. An oral combined reproductive/developmental toxicity screening test in rats revealed significant decreases in pup weight and mean litter weights during lactation days 1 and 4. The developmental toxicity LOAEL was 250 mg/kg-bw/day with a NOAEL of 150 mg/kg-bw/day. This chemical did not induce gene mutations or chromosomal aberrations *in vitro*.

4. Hazard to the Environment

Acute Toxicity to Fish

Fathead minnows (*Pimephales promelas*, 10/concentration) were exposed to isocyanic acid, *m*-phenylenediiso-propylidene (in acetone) at nominal concentrations of 0, 0.10, 0.18, 0.32, 0.56 or 1.0 mg/L under static conditions for 96 hours. Measured exposure concentrations were not provided. No effects were noted at ≤ 0.32 mg/L. At 0.56 and 1.0 mg/L, mortality, surfacing, loss of equilibrium and quiescence were noted.

96-h LC₅₀ = 0.67 mg/L

Acute Toxicity to Aquatic Invertebrates

Water fleas (*Daphnia magna*, 10/replicate) were exposed to isocyanic acid, *m*-phenylenediiso-propylidene (in acetone) at nominal concentrations of 0, 0 (solvent), 1.0, 1.8, 3.2, 5.6 and 10 mg/L under static conditions for 48 hours. Measured exposure concentrations were not provided. Abnormal effects including mortality, quiescence, surfacing and daphnia lying on the bottom were observed in all test concentrations.

48-h EC₅₀ = 5.2 mg/L

Toxicity to Aquatic Plants

Green algae (*Pseudokirchneriella subcapitata*) were exposed to isocyanic acid, *m*-phenylenediiso-propylidene (in acetone) at nominal concentrations of 0, 0 (solvent), 0.32, 1.0, 3.2, 10.0 and 32 mg/L under static conditions for 96 hours. Measured exposure concentrations were not provided. Cell growth was insufficient at 24 and 48 hours to establish concentration-effect relationships for all concentrations and the blank control. The median effects could not be calculated for these time periods. The rate of cell growth was satisfactory (> 16 in 72 hours) in controls.

96-h EC₅₀ (growth) = 2.1 mg/L

Conclusion: The acute hazard to fish, aquatic invertebrates, and aquatic plants is 0.67 mg/L, 5.2 mg/L, and 2.1 mg/L, respectively.

Table 2

Summary Table of the Screening Information Data Set as Submitted under the U.S. HPV Challenge Program	
Endpoints	SPONSORED CHEMICAL Isocyanic acid, m-phenylenediiso-propylidene (2778-42-9)
Summary of Human Health Data	
Acute Oral Toxicity LD ₅₀ (mg/kg-bw)	> 5000
Acute Inhalation Toxicity LC ₅₀ (mg/L)	0.027
Acute Dermal Toxicity LD ₅₀ (mg/kg-bw)	> 2000
Repeated-Dose Toxicity LOAEL/NOAEL Inhalation (mg/L/day) Rats and Mice (vapor) Rats (aerosol)	LOAEL ~ 0.004 NOAEL = Not established LOAEL= 0.0044 NOAEL= 0.0015
Reproductive/Developmental Toxicity LOAEL/NOAEL Oral (mg/kg-bw/day) Reproductive/Developmental Toxicity	LOAEL = 250 NOAEL = 150
Genetic Toxicity – Gene Mutation <i>In vitro</i>	Negative
Genetic Toxicity – Chromosomal Aberrations <i>In vitro</i>	Negative
Additional Information Skin Irritation Eye Irritation Skin Sensitization Respiratory Sensitization	Moderate Mild Positive Negative
Summary of Environmental Effects – Aquatic Toxicity Data	
Fish 96-h LC ₅₀ (mg/L)	0.67
Aquatic Invertebrates 48-h EC ₅₀ (mg/L)	5.2

Summary Table of the Screening Information Data Set as Submitted under the U.S. HPV Challenge Program	
Endpoints	SPONSORED CHEMICAL Isocyanic acid, m-phenylenediiso-propylidene (2778-42-9)
Aquatic Plants 72-h EC₅₀ (mg/L) (growth) (biomass)	2.1 (96-h) -