

SCREENING-LEVEL HAZARD CHARACTERIZATION

(1-Methylethenyl)benzene (CASRN 98-83-9)

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 or OECD HPV 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

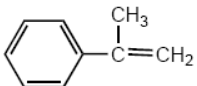
¹ U.S. EPA. High Production Volume (HPV) Challenge Program; <http://www.epa.gov/chemrtk/index.htm>.

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>.

authorities around the world. OPPT is an active participant in these meetings and accepts these documents as reliable screening-level hazard assessments.

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.

<p>Chemical Abstract Service Registry Number (CASRN)</p>	<p>98-83-9</p>
<p>Chemical Abstract Index Name</p>	<p>Benzene, (1-methylethenyl)-</p>
<p>Structural Formula</p>	
<p style="text-align: center;">Summary</p> <p>CASRN 98-83-9 is a liquid with moderate water solubility and high vapor pressure. It is expected to have moderate mobility in soil. CASRN 98-83-9 is not considered readily biodegradable. The rate of volatilization is considered moderate. The rate of hydrolysis is considered negligible. The rate of atmospheric photooxidation is moderate. Bioconcentration is low. CASRN 98-83-9 is expected to have low persistence (P1) and low bioaccumulation potential (B1).</p> <p>The acute toxicity of CASRN 98-83-9 is low in rats by the oral route and low in rabbits by the dermal route. CASRN 98-83-9 is irritating to rabbit skin and eyes. In repeated whole-body inhalation exposures in rats, effects on liver and kidney weights are observed at 2.92 mg/L, the major effect in male rats being an exposure-related increase in alpha-2μ-globulin consistent with hyaline droplet formation that cannot be entirely attributed to alpha-2μ-globulin nephropathy. The NOAEC for systemic toxicity is 1.46 mg/L. Repeated whole-body inhalation exposures to mice show liver effects (centrilobular hypertrophy) at 2.92 mg/L in both sexes with respiratory effects (hyaline degeneration) in female mice occurring at 0.73 mg/L and above. The NOAEC for systemic toxicity is 0.36 mg/L (females) and 1.46 mg/L (males). In a combined repeated-dose/reproductive/developmental toxicity study in rats via oral gavage, treatment-related effects on kidneys, liver and thymus (females) are observed at 1000 mg/kg-day. Similar histopathological changes are found in the liver and kidney of both sexes, and the thymus of female rats at 200 mg/kg-day. The NOAEL for systemic toxicity is 40 mg/kg-day. No effects on reproductive parameters are observed. However, based on two dams not nursing their litters at 1000 mg/kg-day, the NOAEL for reproductive toxicity is 200 mg/kg-day. No abnormal findings are observed on developmental parameters at the highest dose tested. The NOAEL for developmental toxicity is 1000 mg/kg-day. CASRN 98-83-9 does not induce gene mutations or chromosomal aberrations <i>in vitro</i> or <i>in vivo</i>. Sister chromatid exchange is observed in the presence of metabolic activation. CASRN 98-83-9 shows evidence of carcinogenicity in male rats and female mice, equivocal evidence in male mice and no evidence of carcinogenicity in female rats.</p> <p>Since this is a volatile chemical and testing performed with nominal concentrations underestimates its toxicity, estimated ecotoxicity values are more appropriate to address the toxicity of this chemical. Estimated toxicity values indicate that the 96-hour LC₅₀ to fish is 4.9 mg/L, the 48-hour EC₅₀ to aquatic invertebrates is 3.4 mg/L and the 72-hour EC₅₀ to aquatic</p>	

plants is 3.0 mg/L. The estimated chronic toxicity value for aquatic invertebrates is 0.498 mg/L.

No data gaps were identified for SIDS endpoints.

The Sponsor country, Japan, presented the SIDS documents at the OECD SIAM 7 during March 25-27, 1998. The SIAR, SIAP and Dossier were finalized by OECD and published by UNEP in June 2002 (<http://www.chem.unep.ch/irptc/sids/OECDSIDS/98839.pdf>). This hazard characterization includes EPA review of the SIDS documents and any relevant studies obtained through literature search.

1. Chemical Identity

1.1 Identification and Purity

CASRN 98-83-9 is an organic liquid with a purity of 99.6%. See identification and purity information at: <http://www.chem.unep.ch/irptc/sids/OECDSIDS/sidspub.html>.

1.2 Physical-Chemical Properties

See physical-chemical properties at:
<http://www.chem.unep.ch/irptc/sids/OECDSIDS/sidspub.html>.

2. General Information on Exposure

2.1 Production Volume and Use Pattern

CASRN 98-83-9 had an aggregated production and/or import volume in the United States between 100 and 500 million pounds during calendar year 2005.

Non-confidential information in the IUR indicated that the industrial processing and uses of the chemical include intermediates and processing aid, not otherwise listed. Non-confidential commercial and consumer uses of this chemical include rubber and plastic products.

2.2 Environmental Exposure and Fate

See environmental exposure and fate data at:
<http://www.chem.unep.ch/irptc/sids/OECDSIDS/sidspub.html>.

3. Human Health Hazard

See human health hazard data at:
<http://www.chem.unep.ch/irptc/sids/OECDSIDS/sidspub.html>. Additional information published since the OECD SIDS documents is provided below.

Acute Oral Toxicity

Wistar rats (5 males/dose) were administered undiluted CASRN 98-83-9 via gavage at 4.0, 8.0 or 16.0 mL/kg (approximately 3.5, 7 or 14 g/kg) and observed for 14 days. All animals at the high dose died and four of the animals exposed to 8.0 mL/kg died. Clinical signs of toxicity included sluggishness, prostration and an unsteady gait. Gross necropsy revealed petechial hemorrhage of

the lungs; mottled livers and spleens, stomachs distended by liquid or gas, gas- and liquid-filled yellow and transparent intestines, congested kidneys and full bladders.

<http://www.syrres.com/esc/tscats.htm>

LD₅₀ ~ 5.9 g/kg-bw

Repeated-Dose Toxicity

(1) In a three month National Toxicology Program (NTP) study, F344 rats (10/sex/concentration) were exposed by whole-body inhalation to CASRN 98-83-9 at 0, 75, 150, 300, 600 or 1000 ppm (approximately 0, 0.36, 0.73, 1.46, 2.92 or 4.88 mg/L, respectively) for 6 h/day 5 days/week for 14 weeks. There were no mortalities or differences in mean body weights. No exposure-related gross lesions were observed. Kidney weights (absolute and relative) were significantly increased in males at 1000 ppm and females at 600 ppm and 1000 ppm. Statistically significant increases in liver weights (absolute and relative) were observed in males at 150 ppm or greater and at 600 ppm and 1000 ppm in females. Hyaline droplet formation in males was greater than controls at 600 ppm and 1000 ppm. Consistent with the hyaline droplet formation, an exposure-related increase in alpha-2μ-globulin was detected in the kidneys of males exposed to CASRN 98-83-9. However, increased kidney weights and increased urine markers were also observed in female rats, which are not susceptible to developing alpha-2μ-globulin nephropathy. Therefore, mechanisms independent of alpha-2μ-globulin-mediated nephropathy may contribute to the observed effects in the kidney. No morphologic changes in the liver were detected.

LOAEC ~ 2.92 mg/L (based on kidney effects)

NOAEC ~ 1.46 mg/L

http://ntp-apps.niehs.nih.gov/ntp_tox/index.cfm?searchterm=98-83-9&fuseaction=ntpsearch.searchresults

(2) In a three month NTP study, B6C3F1 mice (10/sex/concentration) were exposed by whole-body inhalation to CASRN 98-83-9 at 0, 75, 150, 300, 600 or 1000 ppm (approximately 0, 0.36, 0.73, 1.46, 2.92 or 4.88 mg/L, respectively) for 6 h/day 5 days/week, for 14 weeks. Two females died at 1000 ppm. Mean body weights of males at 600 ppm and 1000 ppm, and females at 75, 300, and 600 ppm were significantly decreased when compared to controls. Moderate to severe sedation (males only) and ataxia were observed at 1000 ppm. The absolute liver weights of females at 600 ppm and 1000 ppm and relative liver weights at 300, 600 and 1000 ppm (both sexes) were significantly increased. Centrilobular hypertrophy of the liver (minimal to mild) was observed in both sexes at 600 ppm and 1000 ppm. All exposed animals showed exposure-related nasal lesions: atrophy and hyperplasia of Bowman's glands and atrophy and metaplasia of the olfactory epithelium. The incidences of hyaline degeneration, characterized by the accumulation of eosinophilic globules in the cytoplasm of the respiratory epithelium, were significantly increased in females exposed to 150 ppm or greater.

LOAEC (female) ~ 0.73 mg/L (based on respiratory effects)

NOAEC (female) ~ 0.36 mg/L

LOAEC (male) ~ 2.92 mg/L (based on liver effects)

NOAEC (male) ~ 1.46 mg/L

http://ntp-apps.niehs.nih.gov/ntp_tox/index.cfm?searchterm=98-83-9&fuseaction=ntpsearch.searchresults

Reproductive Toxicity

(1) In the three month repeated-dose inhalation studies in rats described above, no adverse effects were observed on measured reproductive parameters (organ weights, sperm motility or concentration and estrus cycle).

(2) In the three month repeated-dose inhalation studies in mice described above, no adverse effects were observed on measured male reproductive parameters (organ weights, sperm motility or concentration). The estrus cycle lengths of 600 ppm and 1000 ppm female mice were significantly longer than controls.

Genetic Toxicity

In vitro

(1) Chinese Hamster Ovary (CHO) cells were exposed for 5 hours to concentrations ranging from 0 (DMSO solvent control) to 0.15 $\mu\text{L}/\text{mL}/\text{plate}$ CASRN 98-83-9 with or without metabolic activation. The concentrations were chosen from levels in a cytotoxicity study that were associated with cloning efficiencies of 108 to 0% of solvent control. No significant substance-related mutagenicity related to control was observed with or without metabolic activation.

<http://www.syrres.com/esc/tscats.htm>

CASRN 98-83-9 was not mutagenic in this assay.

(2) CASRN 98-83-9 did not induce chromosomal aberrations in cultured CHO cells with or without metabolic activation. http://ntp-apps.niehs.nih.gov/ntp_tox/index.cfm?searchterm=98-83-9&fuseaction=ntpsearch.searchresults

CASRN 98-83-9 did not induce chromosomal aberrations in this assay.

(3) CASRN 98-83-9 significantly increased the frequency of sister chromatid exchanges in cultured CHO cells with metabolic activation. http://ntp-apps.niehs.nih.gov/ntp_tox/index.cfm?searchterm=98-83-9&fuseaction=ntpsearch.searchresults

CASRN 98-83-9 induced sister chromatid exchange in this assay.

In vivo

CASRN 98-83-9 was negative in male mice and positive in female mice in a mouse micronucleus study. http://ntp-apps.niehs.nih.gov/ntp_tox/index.cfm?searchterm=98-83-9&fuseaction=ntpsearch.searchresults

CASRN 98-83-9 did not increase the frequency of micronucleated erythrocytes in this assay.

Additional Information

Carcinogenicity

(1) In a two year NTP study, F344 rats (50/sex/concentration) were exposed whole body by inhalation to 0, 100, 300 or 1000 ppm (approximately 0, 0.49, 1.46 or 4.88 mg/L, respectively) CASRN 98-83-9 for 6 h/day, 5 days/week (except holidays) for 105 weeks. Survival rates of exposed animals were similar to controls. The mean body weights at 1000 ppm (both sexes) were

less than controls (significance not stated). Two 1000 ppm males and one 300 ppm male had a renal tubule adenoma. Because of the neoplasms observed and the finding of increased alpha-2 μ -globulin accumulation in the kidneys in the three month study, additional kidney sections were prepared. In the 1000 ppm males, the incidences of renal tubule adenoma and carcinoma (combined), mineralization of the renal papilla and mononuclear cell leukemia were significantly increased when compared to controls. In the nose, the incidences of basal cell hyperplasia were significantly increased in all exposed animals and the incidences of degeneration of the olfactory epithelium were increased in 1000 ppm males and 300 ppm females. http://ntp-apps.niehs.nih.gov/ntp_tox/index.cfm?searchterm=98-83-9&fuseaction=ntpsearch.searchresults
CASRN 98-83-9 showed evidence of carcinogenicity in male rats but not female rats in this study.

(2) In a two year NTP study, B6C3F1 mice (50/sex/concentration) were exposed whole body by inhalation to 0, 100, 300 or 600 ppm (approximately 0, 0.49, 1.46 or 2.92 mg/L, respectively) CASRN 98-83-9 for 6 h/day, 5 days/week (except holidays) for 105 weeks. Survival rates of exposed animals were similar to controls. The mean body weights at 600 ppm (both sexes) were less than controls (significance not stated). The incidences of hepatocellular adenoma or carcinoma (combined) were significantly increased in the 100 and 600 ppm males and in all exposed females; the incidences in all exposed animals exceeded the historical range for controls. In exposed animals, the incidences of olfactory epithelial metaplasia and hyperplasia of the glands overlying the olfactory epithelium were significantly increased. Atrophy of the olfactory epithelium was significantly increased in 300 ppm and 600 ppm males. The incidence and severity of nephropathy was also increased in 600 ppm females. Epithelial hyperplasia of the forestomach also was present in male mice. http://ntp-apps.niehs.nih.gov/ntp_tox/index.cfm?searchterm=98-83-9&fuseaction=ntpsearch.searchresults
CASRN 98-83-9 showed equivocal evidence of carcinogenicity in male mice but clear evidence of carcinogenicity in female mice in this study.

4. Hazard to the Environment

See environmental hazard data at:

<http://www.chem.unep.ch/irptc/sids/OECD/SIDS/sidspub.html>. Since this is a volatile chemical and testing performed with nominal concentrations underestimates its toxicity, estimated ecotoxicity values are more appropriate to address the toxicity of this chemical. Therefore, additional estimated aquatic toxicity values are provided below.

Acute Toxicity to Fish

A 96-hour LC₅₀ for fish estimated by ECOSAR v1.00a was used to evaluate the acute toxicity of CASRN 98-83-9.

96-hr LC₅₀ = 4.902 mg/L (estimated)

Acute Toxicity to Aquatic Invertebrates

A 48-hour EC₅₀ for Daphnia estimated by ECOSAR v1.00a was used to evaluate the acute toxicity of CASRN 98-83-9.

48-hr EC₅₀ = 3.421 mg/L (estimated)

Toxicity to Aquatic Plants

A 96-hour EC₅₀ for algae estimated by ECOSAR v1.00a was used to evaluate the acute toxicity of CASRN 98-83-9.

96-hr EC₅₀ = 3.038 mg/L (estimated)

Chronic Toxicity to Aquatic Invertebrates

A chronic toxicity value for Daphnia estimated by ECOSAR v1.00a was used to evaluate the acute toxicity of CASRN 98-83-9.

ChV = 0.498 mg/L (estimated)