

SCREENING-LEVEL HAZARD CHARACTERIZATION

SPONSORED CHEMICAL

Vinyl toluene (CASRN 25013-15-4)

SUPPORTING CHEMICAL

***p*-Methylstyrene (CASRN 622-97-9)**

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

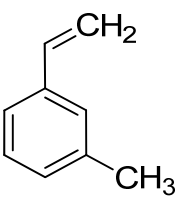
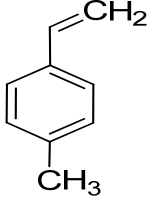
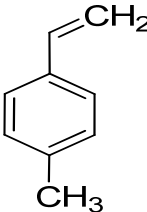
¹ U.S. EPA. High Production Volume (HPV) Challenge Program; <http://www.epa.gov/chemrtk/index.htm>.

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>.

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.

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.

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| <p>Chemical Abstract Service Registry Number (CASRN)</p> | <p><u>Sponsored Chemical</u> 25013-15-4</p> <p><u>Supporting Chemical</u> 622-97-9</p> |
| <p>Chemical Abstract Index Name</p> | <p><u>Sponsored Chemical</u> Benzene, ethenylmethyl-</p> <p><u>Supporting Chemical</u> Benzene, 1-ethenyl-4-methyl-</p> |
| <p>Structural Formula</p> | <p><u>Sponsored Chemical</u></p> <div style="display: flex; justify-content: space-around; align-items: center;"> <div style="text-align: center;">  <p>Meta isomer (~ 60%)</p> </div> <div style="text-align: center;">  <p>Para isomer (~ 40%)</p> </div> </div> <p><u>Supporting Chemical</u></p> <div style="text-align: center;">  </div> |
| <p>Summary</p> <p>CASRN 25013-15-4 is a colorless liquid with moderate water solubility and high vapor pressure. The commercial substance is a mixture known as vinyl toluene and consists of approximately 60% of the <i>meta</i>- and 40% of the <i>para</i>- constitutional isomers. It is expected to have moderate mobility in soil. Volatilization is considered moderate based on its Henry's Law constant. The rate of hydrolysis is considered negligible under environmental pH and temperature. The rate of atmospheric photooxidation is considered moderate. CASRN 25013-15-4 is expected to have low persistence (P1) and low bioaccumulation potential (B1).</p> <p>Acute oral toxicity of CASRN 25013-15-4 to male rats is low. Following repeated inhalation exposures of CASRN 25013-15-4 for 13 weeks, rats exhibited mild nephropathy at ~0.78 mg/L/day and higher; the NOAEC for systemic toxicity is ~0.28 mg/L/day. In another 13-</p> | |

week repeated-dose study, mice exhibited decreased body weights at ~0.12 mg/L/day and higher; the NOAEC for systemic toxicity is ~0.05 mg/L/day. The LOAEC for local effects from this study is ~0.05 mg/L/day based on nasal lesions. Following repeated inhalation exposures of CASRN 25013-15-4 for 139 days in several species, growth depression and liver effects were reported in rats and guinea pigs at ~5.51 mg/L/day and higher, with NOAECs of ~2.83 mg/L/day for both species; liver effects were observed in rabbits at ~6.58 mg/L/day (NOAEC of ~5.51 mg/L/day); and no adverse effects were reported in monkeys up to ~6.58 mg/L/day (highest concentration tested). No specific reproductive toxicity studies are available; however, no histopathological changes were observed in 90-day and 13-week repeated-dose studies described above. Three prenatal developmental toxicity studies in rats and rabbits were conducted via gavage with the supporting chemical, CASRN 622-97-9. In one of the rat prenatal studies, dams and fetuses exhibited decreased body weights at all doses resulting in a maternal/developmental LOAEL of 50 mg/kg/day (lowest dose tested); the NOAEL was not established. No effects were seen in the other two studies, resulting in a maternal/developmental toxicity NOAEL in rats of 600 mg/kg/day and a maternal/developmental NOAEL in rabbits of 150 mg/kg/day (highest doses tested). CASRN 25013-15-4 was mutagenic in mammalian cells but not bacteria *in vitro*. CASRN 25013-15-4 did not induce chromosomal aberrations or sister chromatid exchange in mammalian cells *in vitro* but induced mouse micronuclei *in vivo*. CASRN 25013-15-4 is irritating to rabbit skin and rabbit eyes. CASRN 25013-15-4 showed neurotoxicity in male rats. No evidence of carcinogenicity was observed in rats or mice following inhalation exposure to CASRN 25013-15-4 for 103 weeks.

No data are available for CASRN 25013-15-4 for ecotoxicity. The acute 96-hr LC₅₀ value for fish for the supporting chemical, CASRN 622-97-9, is 2.8 mg/L. The acute 48-hr EC₅₀ value for aquatic invertebrates for the supporting chemical, CASRN 622-97-9, is 1.3 mg/L. The 72-hr EC₅₀ values for aquatic plants for the supporting chemical, CASRN 622-97-9, on growth rate and biomass are 2.3 and 4.3 mg/L, respectively.

The biodegradation endpoint was identified as a data gap under the HPV Challenge Program.

The sponsor, Deltech Corporation, submitted a Test Plan and Robust Summaries to EPA for CASRN 25013-15-4 (CA name: benzene, ethenylmethyl-) on June 28, 2002. EPA posted the submission on the ChemRTK HPV Challenge website on July 24, 2002 (<http://www.epa.gov/chemrtk/pubs/summaries/vinyltol/c13843tc.htm>). EPA comments on the original submission were posted to the website on December 2, 2002. Public comments were also received and posted to the website. The sponsor submitted updated/revised documents on February 24, 2003, which were posted to the ChemRTK website on March 14, 2003.

Justification for Supporting Chemical

The industry sponsor submitted data for the supporting chemical CASRN 622-97-9 (*p*-methylstyrene) in their revised test plan, which represents approximately 40% of CASRN 25013-15-4. Because it is one of the two components of the mixture, which are both structurally similar, CASRN 622-97-9 is an appropriate supporting chemical.

Although the industry sponsor suggested that styrene (CASRN 100-42-5) would be an acceptable supporting chemical, no robust summaries were provided. However, CASRN 100-42-5 has previously been assessed at SIAM 4 (1996) in the OECD HPV program and the data can be viewed at: <http://webnet.oecd.org/hpv/UI/Search.aspx> and <http://ecb.jrc.ec.europa.eu/esis/>. CASRN 622-97-9 was evaluated separately in the HPV Challenge Program. A Test Plan and Robust Summaries were submitted in 2001 (<http://www.epa.gov/chemrtk/pubs/summaries/pmstyrn/c13044tc.htm>).

EPA has determined that data for CASRN 622-97-9 are appropriate to address SIDS endpoints for human health and ecotoxicity.

1. Chemical Identity

1.1 Identification and Purity

The submitter's test plan notes that the composition of CASRN 25013-15-4 is presumed to be an approximately 60/40 ratio of *meta*- and *para*-isomers. The sponsor also submitted information from the National Toxicology Program's (NTP's) technical report number 375 stating that the composition consists of 65-71% of the *meta*-isomer and 32-35% of the *para*-isomer.

1.2. Physical-Chemical Properties

CASRN 25013-15-4 is a colorless liquid mixture with moderate water solubility and high vapor pressure. The physical-chemical properties of this chemical are summarized in Table 1.

| Property | Value |
|--|--|
| CASRN | 25013-15-4 |
| Molecular Weight | 118.18 |
| Physical State | Liquid, colorless |
| Melting Point | -76.67°C (mixture, measured) -86.3°C (meta, measured) ² -34.1°C (para, measured) ³ |
| Boiling Point | 170–171°C (mixture, measured) 164°C (meta, measured) ² 172.8°C (para, measured) ² |
| Vapor Pressure | 1.5 mm Hg at 20°C (mixture, measured) 1.1 mm Hg at 20°C (mixture, measured) ⁴ 1.7 mm Hg (meta, measured) ⁵ 1.81 mm Hg at 25°C (para, measured) ⁵ |
| Water Solubility | 89 mg/L at 25°C (mixture, measured) 150.8 mg/L at 25°C (meta and para, estimated) ⁶ |
| Dissociation Constant (pK _a) | Not applicable |
| Henry's Law Constant | 3.0×10 ⁻³ atm·m ³ /mole (meta, estimated) ⁶ 3.2×10 ⁻³ atm·m ³ /mole (para, estimated) ⁶ |
| Log K _{ow} | 3.35 (meta, measured) ⁷ 3.35 (para, measured) ⁷ |

¹ Deltech Corporation. 2003. Revised Robust Summary and Test Plan for Benzene, ethenylmethyl- Available online at <http://www.epa.gov/chemrtk/pubs/summaries/vinyltol/c13843tc.htm>. as of June 10, 2010.

² Lide, DR. 2007. CRC Handbook of Chemistry and Physics 88th Edition 2007-2008. Boca Raton, FL: CRC Press, Taylor & Francis, pp. 3–376.

³ Deltech Corporation. 2001. Robust Summary and Test Plan for *p*-Methylstyrene. Available online at <http://www.epa.gov/chemrtk/pubs/summaries/pmstyrn/c13044tc.htm>

⁴ Chen, S; Kirk-Othmer Encyclopedia of Chemical Technology. 2006. New York, NY: John Wiley & Sons; Styrene. Available online at <http://mrw.interscience.wiley.com/emrw/9780471238966/home/> as of June 10, 2010.

⁵ Boublik, T; Fried, V; Hala, E. 1984. The Vapor Pressures Of Pure Substances: Selected Values Of The Temperature Dependence Of The Vapor Pressures Of Some Pure Substances In The Normal And Low Pressure Region. Vol. 17. Amsterdam, Netherlands: Elsevier Sci Publ.

⁶ 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/episuite.html> as of June 10, 2010.

⁷ Ogata, M; Fujisawa, K; Ogino, Y; Mano, E. 1984. Partition coefficients as a measure of bioconcentration potential of crude oil compounds in fish and shellfish. Bull Environ Contam Toxicol 33:561–567.

2. General Information on Exposure

2.1. Production Volume and Use Pattern

During the calendar year 2005, CASRN 25013-15-4 had an aggregated production and/or import volume in the United States between 10 and 50 million pounds.

Non-confidential information in the IUR indicated that the industrial processing and associated uses of the chemical include (1) adhesive manufacturing as adhesives and binding agents; (2) resin and synthetic rubber manufacturing as intermediates and “other”; (3) synthetic dye and

pigment manufacturing as coloring agents, dyes; (4) fuel dealers as fuels; and (5) other basic organic chemical manufacturing as “other”. No commercial and consumer uses were reported.

2.2. Environmental Exposure and Fate

CASRN 25013-15-4 is expected to have moderate mobility in soil. CASRN 25013-15-4 was not tested for biodegradation as a mixture; however, data are available for one of the two components. A component of the mixture, CASRN 622-97-9, achieved 95% biodegradation in 19 days using an activated sludge acclimated for 14 days prior to inoculation of ¹⁴C-radiolabeled compound at concentrations of 10–50 mg/L and 20–100 mg/L. Extremely rapid loss rates of ¹⁴C-radiolabeled compound suggested that volatility of the compound had influenced the result. Another biodegradation study in a closed system indicated that CASRN 622-97-9 biodegraded 32% in 20 days with a half-life of approximately 36 days. Although this result indicates that the compound was not readily biodegradable, both studies suggest that substantial biodegradation of the sponsored substance (CASRN 25013-15-4) is likely to occur. The rate of hydrolysis of CASRN 25013-15-4 is expected to be negligible since this substance does not possess functional groups that hydrolyze under environmental conditions. The rate of volatilization is considered moderate based on its Henry’s Law constant. CASRN 25013-15-4 is expected to have low persistence (P1) and low bioaccumulation potential (B1).

Conclusion: CASRN 25013-15-4 is colorless liquid with moderate water solubility and high vapor pressure. The commercial substance is a mixture known as vinyl toluene and consists of approximately 60% of the meta- and 40% of the para- constitutional isomers. It is expected to have moderate mobility in soil. Volatilization is considered moderate based on its Henry’s Law constant. The rate of hydrolysis is considered negligible under environmental pH and temperature. The rate of atmospheric photooxidation is considered moderate. CASRN 25013-15-4 is expected to have low persistence (P1) and low bioaccumulation potential (B1).

| Property | Value | |
|--|---|------|
| Photodegradation Half-life | 4.1 hours at 25°C (meta and para, estimated) ² | |
| Hydrolysis Half-life | Stable | |
| Biodegradation | 95% biodegradation in 19 days (para) ³ 32% biodegradation in 20 days, half-life = 36 days (para) ³ | |
| Bioaccumulation Factor | BAF = 35 measured in goldfish (meta) ³ BAF = 176 (meta and para, estimated) ² BCF = 32 measured in goldfish (para) ³ BCF = 110 measured in bluegill sunfish (para) BCF = 4.0, 4.9, and 9.2 measured in channel catfish (para) ⁴ | |
| Log K _{oc} | 2.9 (meta and para, estimated) ² | |
| Fugacity (Level III Model) ² | meta | para |
| Air (%) | 1.61 | 1.61 |
| Water (%) | 24.2 | 24.2 |
| Soil (%) | 73.5 | 73.5 |
| Sediment (%) | 0.64 | 0.64 |
| Persistence ⁵ | P1 (low) | |
| Bioaccumulation ⁵ | B1 (low) | |

¹ Deltech Corporation. 2003. Revised Robust Summary and Test Plan for Benzene, ethenylmethyl-. Available online at <http://www.epa.gov/chemrtk/pubs/summaries/vinyltol/c13843tc.htm>. as of June 10, 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 at <http://www.epa.gov/opptintr/exposure/pubs/episuitedi.htm> as of June 10, 2010.

³ Ogata, M; Fujisawa, K; Ogino, Y; Mano E. 1984. Partition coefficients as a measure of bioconcentration potential of crude oil compounds in fish and shellfish. Bull Environ Contam Toxicol 33:561–567.

⁴ Deltech Corporation. 2001. Robust Summary and Test Plan for p-Methylstyrene <http://www.epa.gov/chemrtk/pubs/summaries/pmstyrn/c13044tc.htm>.

⁵ Federal 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

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

Acute Oral Toxicity

Vinyl toluene (CASRN 25013-15-4)

Male Wistar rats (42 animals) were administered CASRN 25013-15-4 (approximately 55-70% meta-isomer; 30-45% para-isomer) via gavage at unspecified doses in olive oil or corn oil.

LD₅₀ = 4000 mg/kg

Repeated-Dose Toxicity

Vinyl toluene (CASRN 25013-15-4)

(1) In a National Toxicology Program (NTP) study, F344/N rats (5/sex/dose) were exposed to CASRN 25013-15-4 via inhalation as a vapor at 0, 25, 60, 160, 400 or 1000 ppm (approximately 0, 0.12, 0.29, 0.78, 1.95 and 4.87 mg/L/day) for 6 hours/day for 64 exposures over 13 weeks. Necropsy examinations were performed on all animals and histopathological examinations were performed on all animals of the high-concentration group and control groups. Effects observed included decreased body weights at ≥ 400 ppm (males: 8-19%; females: 6-12%). Mild nephropathy was observed in males at ≥ 160 ppm. Liver-to-body weight ratios were increased at the highest test concentration (<http://ntp.niehs.nih.gov/?objectid=0708F6F4-F4AF-5855-7EC1FF9B50EC24BE>).

LOAEL ~ 0.78 mg/L (based on nephropathy)

NOAEL ~ 0.29 mg/L

(2) In an NTP study, B6C3F1 mice (5/sex/dose) were exposed to CASRN 25013-15-4 via inhalation as a vapor at 0, 10, 25, 60 or 160 ppm (approximately 0, 0.05, 0.12, 0.29 and 0.77 mg/L/day) as a vapor 6 hours/day for 64 exposures over 13 weeks. Necropsy examinations were performed on all animals and histopathological examinations were performed on all animals (9 males and 10 females) of the control group and all animals of the 25, 60 and 160 ppm groups. Effects observed included decreased body weights at ≥ 25 ppm (males: 12 to 20%; females: 13-16%). Lesions in the nasal passages were seen at all doses, and inflammation of the lungs was observed at the highest dose tested (<http://ntp.niehs.nih.gov/?objectid=0708F6F4-F4AF-5855-7EC1FF9B50EC24BE>).

LOAEL (systemic) ~ 0.12 mg/L (based on decreased body weights)

NOAEL (systemic) ~ 0.05 mg/L

LOAEL (local) ~ 0.05 mg/L (based on nasal lesions)

NOAEL (local) ~ Not established

(3) Male and female Wistar rats (10 – 25/dose) were exposed to CASRN 25013-15-4 via inhalation at 0, 580, 1130 or 1350 ppm (approximately 0, 2.83, 5.51 and 6.58 mg/L/day) for 7 – 8 hours/day, 5 days/week for 139 days. Necropsy examinations were performed and selected organs and tissues were weighed and examined histopathologically. Hematological parameters, urea nitrogen concentrations and bone marrow counts were also evaluated. At the two higher test concentrations, growth depression, increased liver weights and liver histopathology (characterized by fatty degeneration in the mid-zonal and central cells of the liver lobule) were seen. The study summary reported that “a moderate amount of mortality” was seen at the highest concentration (no further details provided).

LOAEL ~ 5.51 mg/L (based on growth depression, liver effects)

NOAEL ~ 2.83 mg/L

(4) Male and female albino guinea pigs (5 – 10/group) were exposed to CASRN 25013-15-4 via inhalation at 0, 580, 1130 or 1350 ppm (approximately 0, 2.83, 5.51 and 6.58 mg/L/day) for 7 – 8 hours/day, 5 days/week for 139 days. Necropsy examinations were performed and selected organs and tissues were weighed and examined histopathologically. Hematological parameters, urea nitrogen concentrations and bone marrow counts were also evaluated. At the two higher test concentrations, growth depression, increased kidney weights and liver histopathology (characterized by fatty degeneration in the mid-zonal and central cells of the liver lobule) were seen. Increased liver weights were seen at the highest test concentration.

LOAEL ~ 5.51 mg/L (based on growth depression and histopathological changes in the liver)
NOAEL ~ 2.83 mg/L

(5) Male and female white rabbits (1 – 2/group) were exposed to CASRN 25013-15-4 via inhalation at 0, 580, 1130 or 1350 ppm (approximately 0, 2.83, 5.51 and 6.58 mg/L/day) for 7 – 8 hours/day, 5 days/week for 139 days. Necropsy examinations were performed and selected organs and tissues were weighed and examined histopathologically. Hematological parameters, urea nitrogen concentrations and bone marrow counts were also evaluated. At the two higher test concentrations, a slight increase in kidney weights was observed. At the high test concentration, fatty degeneration in the midzonal and central cells of the liver was observed.

LOAEL ~ 6.58 mg/L (based on histopathology of the liver)

NOAEL ~ 5.51 mg/L

(6) Male and female rhesus monkeys (1 – 2/group) were exposed to CASRN 25013-15-4 via inhalation at 0, 580, 1130 or 1350 ppm (approximately 0, 2.83, 5.51 and 6.58 mg/L/day) for 7 – 8 hours/day, 5 days/week for 139 days. Necropsy examinations were performed and selected organs and tissues were weighed and examined histopathologically. Hematological parameters, urea nitrogen concentrations and bone marrow counts were also evaluated. No effects were seen at any test concentration.

NOAEL ~ 6.58 mg/L (highest concentration tested)

(7) In an NTP study, F344/N rats (5/sex/group) were exposed to CASRN 25013-15-4 (65-71% meta-isomer; 32-35% para-isomer) via inhalation as a vapor at 0, 200, 400, 800 or 1300 ppm (approximately 0, 0.97, 1.95, 3.90 and 6.33 mg/L/day) for 6 hours/day for 10 exposures over 15 days. Necropsy examinations were performed on all animals and histopathological examinations were performed on all animals of the high-concentration group. Effects observed included markedly decreased mean body weights in males at ≥ 400 ppm (13-19% lower than controls) and in females at all test concentrations (9-13% lower than controls). At the highest concentration, males exhibited centrilobular necrosis and infiltration of inflammatory cells into the liver, and females exhibited mild centrilobular vacuolization. Dysplasia of the bronchial epithelial lining, chronic bronchitis and lymphoid hyperplasia of the lung were seen in all rats at 1,300 ppm (<http://ntp.niehs.nih.gov/?objectid=0708F6F4-F4AF-5855-7EC1FF9B50EC24BE>).

LOAEL (male) ~1.95 mg/L (based on decreased body weights)

NOAEL (male) ~ 0.97 mg/L

LOAEL (female) ~ 0.97 mg/L (based on decreased body weights)

NOAEL (female) = Not established

(8) In an NTP study, B6C3F1 mice (5/sex/group) were exposed to CASRN 25013-15-4 (65-71% meta-isomer; 32-35% para-isomer) via inhalation as a vapor at 0, 10, 25, 50, 100 or 200 ppm (approximately 0, 0.05, 0.12, 0.24, 0.48 and 0.97 mg/L/day) for 6 hours/day for 10 exposures over 15 days. Necropsy examinations were performed on all animals and histopathological examinations were performed on all animals at the highest concentration and one animal/sex of the control group. At 200 ppm, three males died and four of five males exhibited moderate-to-severe hepatocellular necrosis. All female mice at 200 ppm exhibited epithelial hyperplasia in the intrapulmonary bronchi and centrilobular necrosis, vacuolization and increased inflammatory

cells in the liver (<http://ntp.niehs.nih.gov/?objectid=0708F6F4-F4AF-5855-7EC1FF9B50EC24BE>).

LOAEL ~ 0.97 mg/L (based on decreased survival in males and liver and pulmonary effects)

NOAEL ~ 0.48 mg/L

Reproductive Toxicity

No adequate reproductive toxicity studies were provided for the sponsored or supporting chemicals. Although EPA agreed that data for *p*-methylstyrene could be used to address this endpoint in previous comments, information provided by the sponsor subsequent to those comments showed excessive mortality in dams. Therefore, the study is not adequate for this analysis.

No effects on reproductive organs were observed in 13-week and 2-year inhalation studies discussed in the repeated-dose and carcinogenicity sections.

Developmental Toxicity

***p*-Methylstyrene (CASRN 622-97-9, supporting chemical)**

(1) Pregnant Sprague-Dawley rats (20/dose) were administered CASRN 622-97-9 via gavage at 0, 60, 190 or 600 mg/kg/day on gestation days 6 through 15. Parameters evaluated included clinical signs and body weights in dams, numbers of corpora lutea, resorptions sites, implantation sites, resorptions sites, live and dead fetuses, sex of fetuses and fetal body weights. Additionally, all fetuses were examined for external abnormalities while one third were examined for visceral examination and the remaining were examined for skeletal abnormalities. Dams did not exhibit any effects. Increases in litters with rudimentary ribs at 60 mg/kg/day and extra ribs at 190 mg/kg/day were observed. In addition, fetuses exhibited an increase in incomplete ossification of vertebrae at 60 and 190 mg/kg/day. However, fetuses from dams treated at 600 mg/kg/day showed no effects compared with controls.

NOAEL (maternal and developmental toxicity) = 600 mg/kg/day (highest dose tested)

(2) Pregnant CD-1 rats (25/dose) were administered CASRN 622-97-9 via gavage at 0, 50, 300 or 600 mg/kg/day on gestation days 6 through 19. Dams were evaluated for clinical signs, body weight changes and gross necropsy of the thoracic cavity and organs. Developmental parameters evaluated included uterine weight, number and location of viable and nonviable fetuses, number of early and late resorptions, number of total implantations and corpora lutea. All fetuses were weighed and examined for external malformations and variations while one half were examined for visceral malformations and the other half were examined for skeletal variations. A dose-related reduction in mean body weight gain was seen in dams from all treatment levels (statistical significance not stated). In addition, a statistically significant ($p < 0.05$) reduction in mean fetal body weight was seen in all treated groups. The study summary reported that the test controls and treatment groups all had body weights that were higher than historical controls; however, given the comparison with the current control groups, EPA considered change in body weight in the current study to be associated with treatment. One malformation (meningocele) was observed in a fetus at the highest dose. There was a statistically significant ($p < 0.05$) reduction in the mean number of corpora lutea at 600 mg/kg/day, but this was not considered

treatment-related because ovulation and implantation occurred prior to test substance administration.

LOAEL (maternal and developmental toxicity) = 50 mg/kg/day (based on decreased body weight gain in dams and decreased fetal weights)

NOAEL (maternal and developmental toxicity) = Not established

(3) Pregnant Dutch rabbits (16/dose) were administered CASRN 622-97-9 via gavage at 0, 50, 100 or 150 mg/kg/day on gestation days 6 through 27. Dams were evaluated for clinical signs, body weight, uterine weight and gross necropsy. Developmental parameters evaluated included number and location of viable and nonviable fetuses, early and late resorptions, number of implantations and corpora lutea. All fetuses were weighed, sexed and examined for visceral and skeletal malformations and variations. The summary reported that no biological effects were seen and no teratogenic response was observed.

NOAEL (maternal and developmental toxicity) = 150 mg/kg/day (highest dose tested)

Genetic Toxicity – Gene Mutations

In vitro

Vinyl toluene (CASRN 25013-15-4)

(1) In an NTP assay, *Salmonella typhimurium* strains TA98, TA100, TA1535 and TA1537 were exposed to CASRN 25013-15-4 at concentrations of 0, 1, 3.3, 10, 33, 100, 333 or 1000 µg/plate in the presence or absence of metabolic activation. Positive and negative controls were tested concurrently and responded appropriately. The lowest cytotoxic concentration was 333 or 1000 µg/plate depending on the strain (http://ntp-apps.niehs.nih.gov/ntp_tox/index.cfm?searchterm=25013-15-4&fuseaction=ntpsearch.searchresults).

CASRN 25013-15-4 was not mutagenic in this assay.

(2) In an NTP assay, mouse lymphoma cells (L5178Y/TK) were exposed to CASRN 25013-15-4 at concentrations of 12.5, 25, 50 or 100 µg/mL in trial 1; 10, 20, 40, 60 or 80 µg/mL in trial 2; and 40, 45, 50, 55, 60 or 65 µg/mL in trial 3, all in the absence of metabolic activation. Positive and negative controls were tested concurrently and exhibited appropriate responses. Cytotoxicity was observed at ≥ 60 µg/mL (http://ntp-apps.niehs.nih.gov/ntp_tox/index.cfm?searchterm=25013-15-4&fuseaction=ntpsearch.searchresults).

CASRN 25013-15-4 was mutagenic in this assay.

Genetic Toxicity – Chromosomal Aberrations

In vitro

Vinyl toluene (CASRN 25013-15-4)

(1) In an NTP assay, Chinese hamster ovary (CHO) cells were exposed to CASRN 25013-15-4 in the absence of metabolic activation at concentrations of 1.6, 5, 16 or 50 µg/mL and in the presence of metabolic activation at 10, 25, 50 or 75 µg/mL. Positive and negative controls were tested concurrently and exhibited appropriate responses. Data on cytotoxicity were not indicated (http://ntp-apps.niehs.nih.gov/ntp_tox/index.cfm?searchterm=25013-15-4&fuseaction=ntpsearch.searchresults).

CASRN 25013-15-4 did not induce chromosomal aberrations in this assay.

In vivo

Vinyl toluene (CASRN 25013-15-4)

Male C57BL/6 mice (4-5/dose) were administered a single dose of CASRN 25013-15-4 intraperitoneally at 100, 200, 300 or 500 mg/kg/day and bone marrow was collected 30 hours later. Thirteen controls received olive oil. At 500 mg/kg/day, 3 of 5 animals died. At 100-300 mg/kg/day, the ratio of polychromatic to normochromatic erythrocytes was significantly lower than controls. Significant increases in micronucleated polychromatic erythrocytes were observed at ≥ 200 mg/kg/day. Micronuclei were not increased in normochromatic erythrocytes (Norppa, 1981).

CASRN 25013-15-4 induced micronuclei in this assay.

Genetic Toxicity – Other

Vinyl toluene (CASRN 25013-15-4)

In an NTP assay, CHO cells were exposed to CASRN 25013-15-4 in the absence of metabolic activation at concentrations of 1.6, 5, 16 or 50 $\mu\text{g/mL}$ in trial 1; 5, 10, 25, 50, 75 100 or 150 $\mu\text{g/mL}$ in trial 2 and 25, 50, 75 or 100 $\mu\text{g/mL}$ in trial 3. In the presence of metabolic activation, cells were exposed to 5, 16 or 50 $\mu\text{g/mL}$ in trial 1 and 10, 25, 50 or 75 $\mu\text{g/mL}$ in trial 2. Positive and negative controls were tested concurrently and exhibited appropriate responses. Data on cytotoxicity were not indicated (http://ntp-apps.niehs.nih.gov/ntp_tox/index.cfm?searchterm=25013-15-4&fuseaction=ntpsearch.searchresults).

CASRN 25013-15-4 did not induce sister chromatid exchanges in this assay.

Additional Information

Skin Irritation

Vinyl toluene (CASRN 25013-15-4)

White rabbits (strain, sex and number not specified) were administered CASRN 25013-15-4 (approximately 55-70% meta-isomer; 30-45% para-isomer) via the dermal route to the ear or bandaged areas of the shaved torso for 10 – 20 applications over 2 – 4 weeks. Perceptible to definite erythema, edema, superficial necrosis and blistering were observed.

CASRN 25013-15-4 was moderately irritating to rabbit skin in this assay.

One rabbit (strain and sex not specified) was administered CASRN 25013-15-4 undiluted or as a 10% solution in butyl carbitol acetate in a 24-hr application to the ear and shaven abdomen. In another experiment, one rabbit (strain and sex not specified) was administered CASRN 25013-15-4 undiluted to the ear and shaven abdomen in 10 applications over 13 days; moderate irritation resulted and healing was not complete 10 days after the last application. With similar applications of 1 or 10% CASRN 25013-15-4 in butyl carbinol acetate, very slight irritation resulted and healing was quick and complete (TSCATS submission – OTS 0557250; <http://www.srcinc.com/what-we-do/databaseforms.aspx?id=384>).

CASRN 25013-15-4 was slightly to moderately irritating to rabbit skin in this assay.

Eye Irritation

Vinyl toluene (CASRN 25013-15-4)

White rabbits (strain, sex and number not specified) were administered two drops (approximately 90 mg) of CASRN 25013-15-4 (approximately 55-70% meta-isomer; 30-45% para-isomer) to the eye and observed for 7 days. Slight conjunctival irritation was observed.

CASRN 25013-15-4 was mildly irritating to the rabbit eye in this assay.

Neurotoxicity

Vinyl toluene (CASRN 25013-15-4)

(1) Male Wistar rats (20/concentration) were exposed to CASRN 25013-15-4 via inhalation to 0, 50, 100 or 300 ppm (approximately 0, 0.24, 0.48 and 1.45 mg/L) as a vapor for 6 hours/day, 5 days/week for up to 15 weeks. Exposures occurred in the dark. Motor conduction velocity (MCV) of the tail nerve of immobilized rats was measured at the start of the study, and after 4, 8, 12 and 15 weeks. Myelin-deprived axons from the spinal cord were analyzed for protein composition. Exposed animals were inactive and body weights at 300 ppm were lower than controls (424 vs. 449 g). At both the 100 and 300 ppm concentrations, MCVs were slightly lower than controls at 12 and 15 weeks ($p < 0.05$ or 0.01 at week 12; < 0.001 at week 15). The amplitude of evoked muscle action potential was lower at both of these concentrations than the controls at 12 weeks, and protein composition of the axons at these concentrations differed from controls at 15 weeks (Seppäläinen and Savolainen, 1982).

CASRN 25013-15-4 resulted in decreased amplitudes of evoked muscle action potentials and changes in protein composition of axons.

(2) Male Sprague-Dawley rats (10/concentration) were exposed to CASRN 25013-15-4 via whole-body inhalation exposure to 100 and 300 ppm (approximately 0.48 and 1.45 mg/L) as a vapor for 6 hours/day, 5 days/week for up to 21 weeks. Body weights of the 300 ppm rats were lower than controls (although not statistically significant at a p-level of 0.05). Motor and sensory nerve conduction velocities of the tail nerve were significantly lower than controls at 300 ppm during weeks 15, 21 and 20. This was accompanied by a significant linear relationship with length of exposure ($p < 0.02$). Histopathology of the sciatic nerve was no different from controls at 21 weeks (Gagnaire et al., 1986).

CASRN 25013-15-4 resulted in decreased motor and sensory nerve conduction velocities.

Carcinogenicity

Vinyl toluene (CASRN 25013-15-4)

(1) F344/N rats (50/sex/group) were exposed to CASRN 25013-15-4 via inhalation to 0, 100 or 300 ppm (approximately 0, 0.48 and 1.45 mg/L) as a vapor 6 hours/day, 5 days/week for 103 weeks. Decreased body weight and lesions in the nasal passages were observed at both doses. There was no evidence of carcinogenicity.

(2) B6C3F1 mice (50/sex/group) were exposed via inhalation to 0, 10 or 25 ppm (approximately 0, 0.048 and 0.12 mg/L) as a vapor 6 hours/day, 5 days/week for 103 weeks. Decreased body weight was observed at the high concentration. Nasal passages showed inflammation and

hyperplasia, and lungs/bronchioles exhibited active inflammation at both doses. There was no evidence of carcinogenicity.

Conclusion: Acute oral toxicity of CASRN 25013-15-4 to male rats is low. Following repeated inhalation exposures of CASRN 25013-15-4 for 13 weeks, rats exhibited mild nephropathy at ~0.78 mg/L/day and higher; the NOAEC for systemic toxicity is ~0.28 mg/L/day. In another 13-week repeated-dose study, mice exhibited decreased body weights at ~0.12 mg/L/day and higher; the NOAEC for systemic toxicity is ~0.05 mg/L/day. The LOAEC for local effects from this study is ~0.05 mg/L/day based on nasal lesions. Following repeated inhalation exposures of CASRN 25013-15-4 for 139 days in several species, growth depression and liver effects were reported in rats and guinea pigs at ~5.51 mg/L/day and higher, with NOAECs of ~2.83 mg/L/day for both species; liver effects were observed in rabbits at ~6.58 mg/L/day (NOAEC of ~5.51 mg/L/day); and no adverse effects were reported in monkeys up to ~6.58 mg/L/day (highest concentration tested). No specific reproductive toxicity studies are available; however, no histopathological changes were observed in 90-day and 13-week repeated-dose studies described above. Three prenatal developmental toxicity studies in rats and rabbits were conducted via gavage with the supporting chemical, CASRN 622-97-9. In one of the rat prenatal studies, dams and fetuses exhibited decreased body weights at all doses resulting in a maternal/developmental LOAEL of 50 mg/kg/day (lowest dose tested); the NOAEL was not established. No effects were seen in the other two studies, resulting in a maternal/developmental toxicity NOAEL in rats of 600 mg/kg/day and a maternal/developmental NOAEL in rabbits of 150 mg/kg/day (highest doses tested). CASRN 25013-15-4 was mutagenic in mammalian cells but not bacteria *in vitro*. CASRN 25013-15-4 did not induce chromosomal aberrations or sister chromatid exchange in mammalian cells *in vitro* but induced mouse micronuclei *in vivo*. CASRN 25013-15-4 is irritating to rabbit skin and rabbit eyes. CASRN 25013-15-4 showed neurotoxicity in male rats. No evidence of carcinogenicity was observed in rats or mice following inhalation exposure to CASRN 25013-15-4 for 103 weeks.

| Table 3. Summary of the Screening Information Data Set under the U.S. HPV Challenge Program – Human Health Data | | |
|---|--|---|
| Endpoints | SPONSORED CHEMICAL Vinyl toluene (25013-15-4) | SUPPORTING CHEMICAL p-Methylstyrene (622-97-9) |
| Acute Oral Toxicity LD ₅₀ (mg/kg) | 4000 | — |
| Repeated-Dose Toxicity NOAEL/LOAEL Inhalation (mg/L/day) | (rat) NOAEL ~ 0.29 LOAEL ~ 0.78 (mouse) NOAEL ~ 0.05 LOAEL ~ 0.12 | — |
| Reproductive Toxicity | No histopathological changes in reproductive organs evaluated in 90-day and 2- year repeated-dose studies | — |
| Developmental Toxicity NOAEL/LOAEL Oral (mg/kg/day) Maternal/Developmental Toxicity | No Data NOAEL = NE LOAEL = 50 (RA) | NOAEL = NE LOAEL = 50 |
| Genetic Toxicity – Gene Mutations <i>in vitro</i> | Positive | — |
| Genetic Toxicity – Chromosomal Aberrations <i>in vitro</i> | Negative | — |
| Genetic Toxicity – Chromosomal Aberrations <i>in vivo</i> | Positive | — |
| Additional Information Skin irritation Eye irritation Carcinogenicity Neurotoxicity | Slightly to moderately irritating Mildly irritating No evidence Some evidence | — |

Measured data in bold text; — Endpoint was not addressed for this chemical; NE - Not established

4. Hazard to the Environment

A summary of aquatic toxicity data submitted for SIDS endpoints is provided in Table 4. The table also indicates where data for the supporting chemical are read-across (RA) to the sponsored chemical.

Acute Toxicity to Fish

p-Methylstyrene (CASRN 622-97-9, supporting chemical)

(1) Bluegill sunfish (*Lepomis macrochirus*) were exposed to CASRN 622-97-9 at nominal concentrations of 0, 0.76, 1.5, 3.0, 6.1 or 12 mg/L under flow-through conditions for 168 hours. Nanograde acetone was used as a solvent. Mean measured test concentrations were 0, 0.41, 0.66, 1.2, 2.3 and 5.4 mg/L, respectively.

96-h LC₅₀ = 2.8 mg/L

168-h LC₅₀ = 2.6 mg/L

(2) Fathead minnow (*Pimephales promelas*) were exposed to CASRN 622-97-9 at nominal concentrations of 0, 1.6, 2.5, 4.0, 6.4 or 10 mg/L under semi-static conditions for 96 hours. Mean measured test concentrations were 0, 0.82, 1.3, 2.6, 4.2 and 6.8 mg/L, respectively.

96-h LC₅₀ = 5.2 mg/L

Acute Toxicity to Aquatic Invertebrates

p-Methylstyrene (CASRN 622-97-9, supporting chemical)

Water fleas (*Daphnia magna*) were exposed to CASRN 622-97-9 at nominal concentrations of 0, 0.95, 1.5, 2.4, 3.8 or 6.0 mg/L under static conditions for 48 hours. Mean measured test concentrations were 0, 0.51, 0.81, 1.5, 2.3 and 3.8 mg/L, respectively. Forty and 5% immobilization were observed at the 1.5 and 0.51 mg/L concentrations, respectively.

48-h EC₅₀ = 1.3 mg/L

Toxicity to Aquatic Plants

p-Methylstyrene (CASRN 622-97-9, supporting chemical)

Green algae (*Pseudokirchneriella subcapitata*) were exposed to CASRN 622-97-9 at nominal concentrations of 0, 1.0, 2.0, 4.0, 8.0 and 16 mg/L under static conditions for 72 hours in a closed system. Mean measured test concentrations were 0, 0.41, 0.53, 1.6, 3.7 and 8.4 mg/L, respectively.

72-h EC₅₀ (biomass) = 2.3 mg/L

72-h EC₅₀ (growth) = 4.3 mg/L

Conclusion: No data are available for CASRN 25013-15-4. The acute 96-hr LC₅₀ value for fish for the supporting chemical, CASRN 622-97-9, is 2.8 mg/L. The acute 48-hr EC₅₀ value for aquatic invertebrates for the supporting chemical, CASRN 622-97-9, is 1.3 mg/L. The 72-hr EC₅₀ values for aquatic plants for the supporting chemical, CASRN 622-97-9, on growth rate and biomass are 2.3 and 4.3 mg/L, respectively.

| Table 4. Summary of the Screening Information Data Set under the U.S. HPV Challenge Program – Aquatic Toxicity Data | | |
|--|---|--|
| Endpoints | Sponsored Vinyl toluene (25013-15-4) | Supporting p-Methylstyrene (622-97-9) |
| Fish 96-h LC₅₀ (mg/L) | No Data 2.8 (RA) | 2.8 |
| Aquatic Invertebrates 48-h EC₅₀ (mg/L) | No Data 1.3 (RA) | 1.3 |
| Aquatic Plants 72-h EC₅₀ (mg/L) Biomass Growth rate | No Data (RA) 2.3 4.3 | 2.3 4.3 |

bold = measured data (i.e., derived from testing); RA = read across

5. References

Gagnaire, F., T. Nicot, D. Zissu, P. Bonnet and J. de Ceaurriz. 1986. Assessment of tail nerve function in rats chronically exposed to vinyltoluene. *Toxicology Letters*. 30: 27-34.

Norpa, H. 1981. Styrene and vinyltoluene induce micronuclei in mouse bone marrow. *Toxicology Letters*. 8: 247-251.

Seppäläinen, Anna Maria and H. Savolainen. 1982. Impaired nerve function in rats after prolonged exposure to vinyltoluene. *Arch. Toxicol.* Suppl. 5: 100-102.