

**EPA'S HPV CHALLENGE PROGRAM: TIER I SCREENING
SIDS DOSSIER FOR STYRENE, AR-METHYL-(VINYL TOLUENE)
CAS NO. 25013-15-4**

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June 28, 2002
Revised: February 24, 2003

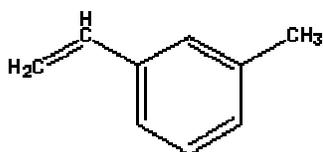
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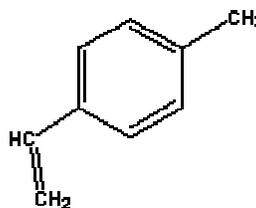
OVERVIEW

The Deltech Corporation hereby resubmits for review and public comment the test plan for vinyl toluene (VT; presume mixtures of meta- and para- isomers in ~60/40% ratio; CAS NO.: 25013-15-4) under Environmental Protection Agency's (EPA) High Production Volume (HPV) Chemical Challenge Program. It is the intent of Deltech Corporation to use both the existing data on VT in conjunction with data from para-methylstyrene and styrene to adequately fulfill all the Screening Information Data Set (SIDS) endpoints. These data are adequate to fulfill all the requirements of the HPV program without the need for the conduct of any new or additional tests. Furthermore, they follow the principles contained in the letter the EPA sent to all HPV Challenge Program participants on October 14, 1999, in which participants are directed to maximize the use of existing data for scientifically appropriate related chemicals in order to minimize animal testing. The Introduction below is taken from the National Toxicology Program, Technical Report Series No. 375.

INTRODUCTION



meta isomer
(65%-71%)



para isomer
(32%-35%)

VINYL TOLUENE (mixed isomers)

C₉H₁₀ Molecular weight 118.2

Synonyms: 3-Vinyl toluene and 4-vinyl toluene (mixed isomers)

Use, Production, and Properties

Vinyl toluene (methylstyrene) is used as a monomer in the plastics and surface-coating industries (Kuney, 1983), block backing component for radioactive waste (Bingham *et al.*, 2001), and as a component in insecticides (Clayton and Clayton, 1981). As many as 73,000 employees in 7,000 plants are potentially exposed to vinyl toluene (NIOSH, 1989).

Vinyl toluene is produced by the dehydrogenation of *m*- and *p*-ethyltoluene and by catalytic reforming. In 1979, it was estimated that approximately 50% of vinyl toluene was used as a chemical intermediate for unsaturated polyester resins, 40% for alkyd coating resins, and 10% as a chemical intermediate for drying oils (TDB, 1982). The annual production of vinyl toluene is in the range of 18,000 to 23,000 tons per year (Kirk-Othmer, 1997).

Vinyl toluene is a colorless, combustible liquid with a strong, disagreeable odor. It is an alkylated benzene that occurs as a mixture primarily of the *m*- (50%-70%) and *p*- (30%-45%) isomers, with a density of 0.8946 at 25°C, a boiling point of 167°-172°C, and a vapor pressure of 1.6 mm mercury at 20°C. At elevated temperatures, vapors mixed with air may be explosive, and polymerization may occur under explosive expansion.

Metabolism

Vinyl toluene is excreted mainly in urine in the form of metabolites. The major metabolites which have been detected in rats after a single IP dose of vinyl toluene were *p*-methylmandelic acid, *p*-methylglyoxylic acid, *p*-methylebenzoic acid, *p*-methylbenzoylglycine, *p*-methylphenylacetyl glycine, *p*-vinylbenzoylglycine, *p*-methylphenylacetic acid, *p*-methylphenylacetyl glycine, *p*-vinylbenzoyl acid, and thioethers (N-acetyl-S-(2-(*p*-tolyl-2-hydroxyethyl)) cysteine and N-acetyl-S-(1-(tolyl)-2-hydroxyethyl)cysteine). A large proportion of the metabolites were as thioethers at low doses of vinyl toluene rather than at high doses (50 mg/kg/body weight vs 350-500 mg/kg/body weight, when given IP). With the exception of *p*-vinylbenzoic acid and *p*-vinylbenzoylglycine all other metabolites are formed by cytochrome P450-dependent oxidation of vinyl toluene with vinyltoluene-7,8-oxide (*p*-methylphenylethylene-7,8-oxide) as an intermediate (Snyder, 1987), with subsequent conjugation to glutathione or hydration to diols (Heinonen, 1984).

Systemic Toxicity

In humans, vinyl toluene is irritating to the eyes, upper respiratory tract, and skin at concentrations greater than 400 ppm, with prolonged or high doses causing a depression of the central nervous system (Clayton and Clayton, 1981; Mackison *et al.*, 1981). The American Conference of Governmental Industrial Hygienists recommends a threshold limit value (time-weighted average) of 50 ppm (240 mg/m³) for occupational exposure to vinyl toluene (ACGIH, 1980). The recommended short-term exposure limit is 100 ppm (485 mg/m³). The current Occupational Safety and Health Administration standard is 100 ppm, averaged over an 8-hour work shift (Mackison *et al.*, 1981). There is inadequate evidence in humans for the carcinogenicity of vinyl toluene, and therefore is not classifiable as to its carcinogenicity to humans (ACGIH, 2002).

The oral LD₅₀ in rats is approximately 4 g/kg (Wolf *et al.*, 1956). Inhalation exposure (approximately 100 exposures of up to 8 hours/exposure) at 1,130 ppm leads to fatty degeneration of the liver in guinea pigs, rabbits, monkeys, and rats and to death in rats. In fifteen day inhalation studies, rats were exposed to 0, 200, 400, 800, or 1,300 ppm vinyl toluene, and mice were exposed to 0, 10, 25, 50, 100, or 200 ppm (NTP, 1990). All rats lived to the end of the studies. The mean body weights at necropsy of rats exposed to 400-1,300 ppm were 13%-19% lower than that of controls for males and 9-13% lower for females. Most male rats exposed to 1,300 ppm had centrilobular necrosis and focal inflammatory cell infiltration of the liver, whereas minimal centrilobular vacuolization of the liver was seen in all female rats exposed to 1,300 ppm. Dysplasia of the bronchial epithelial lining, chronic bronchitis, and lymphoid hyperplasia of the lung were observed in all rats exposed to 1,300 ppm.

Three of five male mice exposed to 200 ppm vinyl toluene for 15 days died before the end of the study. Four of five male mice exposed to 200 ppm had moderate-to-severe hepatocellular necrosis; all female mice exposed to 200 ppm had hyperplasia of the epithelium of the intrapulmonary bronchi and centrilobular necrosis, vacuolization, and inflammatory cell infiltrates in the liver (NTP, 1990).

Rats were exposed to 0, 25, 60, 160, 400, or 1,000 ppm vinyl toluene for 13 weeks. All rats lived to the end of the studies. The final mean body weights of rats exposed to 400-1,000 ppm were 8%-19% lower than that of controls for males and 6%-12% lower for females (NTP, 1990). Relative liver weights for rats at 1,000 ppm were significantly greater than those for controls. The severity of nephropathy was increased in male rats exposed to 160, 400, or 1,000 ppm. Compound-related lesions were not observed in female rats.

Mice were exposed to 0, 10, 25, 60, or 160 ppm vinyl toluene for 13 weeks. The final mean body weights of mice exposed to 25-160 ppm were 12%-20% lower than that of controls for males and 13%-16% lower for females. Inflammation of the lung was observed in 5/10 male and 3/9 female mice exposed to 160 ppm. Metaplasia of the nasal turbinates was seen in all exposed groups (NTP, 1990).

Reproductive Toxicity

No reproductive toxicity tests were available. Surrogate studies using para-methylstyrene and styrene will be used to fill data gaps.

Developmental Toxicity/Teratogenicity

Female rats, intraperitoneal administration of 3750 mg/kg at 1-15 days of pregnancy caused post-implantation mortality and stunted fetus. Administration of 250 mg/kg/day to pregnant rats did not produce an increase in birth defects in offspring in spite of induction of fetal toxicity (SJW, 1981). A dose of 6 ppm for 4 months or 6200 ppm for 1 month was teratogenic in guinea pigs. However this study was referenced incorrectly in Patty's Industrial Hygiene and Toxicology, 4th edition, 1991; a full review of this study could not be done. PMS or styrene developmental/teratogenicity studies are adequate as surrogate studies for vinyl toluene.

Genetic Toxicology

Vinyl toluene did not induce gene mutations in *S. typhimurium* strains TA98, TA100, TA1535, or TA1537 with or without exogenous metabolic activation (S9) (NTP, 1990). Vinyl toluene was positive in the mouse lymphoma assay for induction of trifluorothymidine resistance in L5178T/TK cells in the absence of S9; it was not tested with S9 (NTP, 1990). Vinyl toluene did not induce sister chromatid exchanges or chromosomal aberrations in CHO cells with or without S9 (NTP, 1990).

Long-Term Toxicity and Carcinogenicity

In 2-year studies, mean body weights of male rats exposed to 300 ppm vinyl toluene and those of female rats exposed to 100 and 300 ppm were generally 4%-11% lower than

those of controls (NTP, 1990). No significant differences in survival were seen between any groups of rats of either sex. Mean body weights of mice exposed to 10 ppm showed a weight decrement that was generally less than 10%. The survival of male mice exposed to 25 ppm was significantly greater than that of controls. No other significant differences in survival were seen between any groups of mice of either sex.

Nonneoplastic and Neoplastic Effects in the Two-Year Studies: Degenerative and nonneoplastic proliferative lesions of the nasal mucosa were observed at increased incidences in exposed rats (NTP, 1990). These lesions included diffuse hyperplasia (goblet cell) of the respiratory epithelium with intraepithelial mucous cysts and focal erosion of the olfactory epithelium with cystic dilatation (cysts) of the Bowman's glands. Focal respiratory epithelial metaplasia of the olfactory epithelium was seen in some exposed males, and cells with homogeneous eosinophilic cytoplasm in the olfactory epithelium occurred at increased incidences in exposed female rats. Neoplasms of the nasal mucosa were not seen in male or female rats. There were no chemically related increases in neoplasm incidence in exposed male or female rats.

Degenerative and inflammatory lesions of the nasal mucosa were observed at increased incidences in exposed mice (NTP, 1990). These lesions included focal chronic active inflammation and diffuse hyperplasia of the respiratory epithelium. Chronic active inflammation of the bronchioles occurred in many exposed mice but not in controls. Neoplasms of the nasal passage were not observed in mice. There were no chemically related increases in neoplasm incidence in exposed male or female mice.

Environmental Fate & Exposure

The following information on vinyl toluene was obtained from reputable textbooks and/or journal articles referenced within the Hazardous Substance Data Base (HSDB). If released to soil, vinyl toluene is predicted to be moderately mobile. This compound has the potential to undergo photolysis on surface soils. Volatilization may be a significant removal process. If released to water, vinyl toluene could potentially volatilize (estimated half-life 10 days from a model pond), photolyze, react with naturally occurring oxidants found in the water (half-life approximately 8 days), or adsorb to suspended solids and sediments in water. An adsorption coefficient (K_{oc}) of 370 was estimated using a linear regression equation based on a measured water solubility of 89 mg/L at 25°C. This K_{oc} value is indicative of moderate mobility in soil and moderate adsorption to suspended solids and sediments in water. Based upon BCF values, bioaccumulation in aquatic organisms is not expected to be an important fate process. The relatively high vapor pressure of the commercial mixture of vinyl toluene suggests that the o-, m-, and p-isomers would exist almost entirely in the vapor phase in the atmosphere. If released to the atmosphere, vinyl toluene may react with photochemically generated hydroxyl radicals and ozone molecules (estimated overall half-life 6 hours) or it may photolyze.

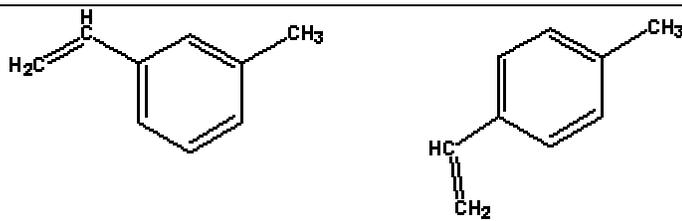
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SIDS PROFILE

HPV Test Plan: Part A

DATE: June 28, 2002 REVISED: February 24, 2003

1.01A	CAS NO.	25013-15-4
1.01C	CHEMICAL NAME	Styrene, ar-methyl- (Vinyl toluene, mixed isomers)
1.01D	CAS DESCRIPTOR	Not applicable
1.01G	STRUCTURE AND FORMULA	 <p style="text-align: center;">meta isomer para isomer</p> <p style="text-align: center;">C₉H₁₀</p>

TEST PLAN JUSTIFICATION/ ISSUES FOR DISCUSSION	<p>PHYSICAL/CHEMICAL PROPERTY TESTS DATA GAPS: SIDS testing required: None.</p> <p>ENVIRONMENTAL FATE AND PATHWAY TESTS DATA GAPS: Commercial vinyl toluene consists of a mixture of meta- and para- isomers in ~60/40% ratio. Biodegradation study using a closed system to minimize the effects of volatilization is recommended.</p> <p>ECOTOXICITY TESTS DATA GAPS: Vinyl toluene consists of a mixture of meta- and para- isomers in ~60/40% ratio. Acute toxicity to fish, acute toxicity to aquatic invertebrates, and acute toxicity to algae of the para isomer will be used as substitute studies for vinyl toluene. No testing for vinyl toluene is proposed.</p> <p>HEALTH EFFECTS TESTS DATA GAPS: Vinyl toluene consists of a mixture of meta- and para- isomers in ~60/40% ratio. All data gaps for vinyl toluene will be satisfied using completed studies for the para isomer. No testing for vinyl toluene is proposed.</p>
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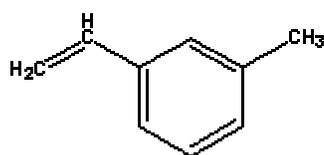
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DATE: June 28, 2002 REVISED: February 24, 2003

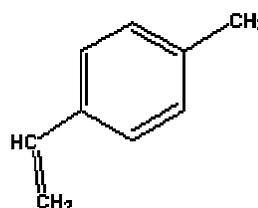
HPV Test Plan: Part B							
CAS No:	InfoAvail?	GLP	OECD Study	Other Study	Estim. Meth.	Acceptable?	SIDS Testing Required?
	Y/N	Y/N	Y/N	Y/N	Y/N	Y/N	Y/N
Physicochemical							
Melting Point	Y	N	*	Y		Y	N
Boiling Point	Y	N	*	Y		Y	N
Density ¹							
Vapor Pressure	Y	N	*	Y		Y	N
Oct: water part.coef	Y	N	*	Y		Y	N
Water solubility pKa	Y	N	*	Y		Y	N
Other		-	--	--	--	--	--
Environmental Fate and Pathway							
Photodeg	Y	N	*	Y		Y	N
Stability in water	Y	N	*	Y		Y	N
Monit. Data ¹							
Transp/Dist	Y	N	*		Y	Y	N
Biodeg	Y	N	*	Y		N	Y
Other		--	--	--	--	--	--
Ecotoxicology							
Acute Fish	Y	Y	Y	Y		Y	N
Acute Daph.	Y	Y	Y	Y		Y	N
Acute Algae	Y	Y	Y	Y		Y	N
Chron. Daph ²							
Terr. Tox. ²							
Other		--	--	--	--	--	--
Toxicology							
Acute Rep.	Y	Y	N	Y		Y	N
DoseGenetic	Y	Y	N	Y		Y	N
Repro	Y	Y	N	Y	--	Y	N
Devel/Terat	Y	Y	N	Y		Y	N
Human Experience ²							
Other		--	--	--	--	--	--
* Unknown ¹ Not required for SIDS Base Set ² Conditional SIDS studies							

1.0 GENERAL INFORMATION

- A. CAS NUMBER 25013-15-4
- B. Molecular Weight 118.18
- C. OECD Name styrene, ar-methyl-
- D. CAS Descriptor Not applicable
- E. Structural Formula C₉H₁₀



meta isomer



para isomer

2.0 PHYSICAL/CHEMICAL DATA

2.1 Melting Point

Value:	-76.67°C
Decomposition:	No Data
Sublimation:	No Data
Method:	No Data
GLP:	Yes[] No[] ?[X]
Remarks:	None
Reliability:	[4] Not assignable because limited study information was available; however, the value for this endpoint was obtained from a reputable source.
Reference:	ACGIH, 1986

2.2 Boiling Point

Value:	170-171°C
Decomposition:	No Data
Method:	No Data
GLP:	Yes[] No[] ?[X]
Remarks:	None
Reliability:	[4] Not assignable because limited study information was available; however, the value for this endpoint was obtained from a reputable source.
Reference:	ACGIH, 1986

- 2.3 Water Solubility 89 mg/L at 25°C; the value for this endpoint was obtained from a reputable textbook referenced within the Hazardous Substance Data Base (HSDB).
- 2.4 Vapor Pressure 1.6 mm Hg [220 Pa] at 20°C; the value for this endpoint was obtained from a reputable textbook referenced within the Hazardous Substance Data Base (HSDB).
- 2.5 Partition Coefficient $\text{Log } P_{ow} = 3.58$; the value for this endpoint was obtained from the NTP Chemical Repository.
- 2.6 Water Stability No testing required; vinyl toluene does not have a functional group that is susceptible to hydrolysis and so hydrolysis is not expected to occur in the environment.

3.0 ENVIRONMENTAL FATE

Photodegradation, biodegradation, and stability in water studies of the para isomer will be used as substitute studies for vinyl toluene. The following information on vinyl toluene was obtained from reputable textbooks and/or journal articles referenced within the Hazardous Substance Data Base (HSDB). If released to soil, vinyl toluene is predicted to be moderately mobile. This compound has the potential to undergo photolysis on surface soils. Volatilization may be a significant removal process. If released to water, vinyl toluene could potentially volatilize (estimated half-life 10 days from a model pond), photolyze, react with naturally occurring oxidants found in the water (half-life approximately 8 days), or adsorb to suspended solids and sediments in water. An adsorption coefficient (K_{oc}) of 370 was estimated using a linear regression equation based on a measured water solubility of 89 mg/L at 25°C. This K_{oc} value is indicative of moderate mobility in soil and moderate adsorption to suspended solids and sediments in water. Based upon BCF values, bioaccumulation in aquatic organisms is not expected to be an important fate process. The relatively high vapor pressure of the commercial mixture of vinyl toluene suggests that the o-, m-, and p-isomers would exist almost entirely in the vapor phase in the atmosphere. If released to the atmosphere, vinyl toluene may react with photochemically generated hydroxyl radicals and ozone molecules (estimated overall half-life 6 hours) or it may photolyze.

- 3.1 Transport Between Environmental Compartments (Fugacity): Level III Fugacity Model (Mackay, 1991). Results show major partitioning to environmental media when 1000 kg/h is discharged to each compartment (air, water, and soil; total 3000 kg/h): air, 5.99%; water, 88.48%; soil, 3.39%, and sediment, 2.15%.

4.0 ECOTOXICITY

Acute toxicity to fish, acute toxicity to aquatic invertebrates, and acute toxicity to algae of the para isomer will be used as substitute studies for vinyl toluene. The robust summary for para-methylstyrene is submitted with this test plan.

5.0 HEALTH EFFECTS TESTS

Commercial vinyl toluene is usually a mixture of the meta and para isomers in ~60/40% ratio, but often the toxicological literature does not distinguish between the various forms. The toxicological properties appear to be similar to para-methylstyrene (PMS), and PMS studies will be substituted for any vinyl toluene data gaps. Additional endpoints for vinyl toluene can be found in reputable textbooks and/or journal articles referenced within the Hazardous Substance Data Base (HSDB).

5.1 Acute Toxicity

5.11 Single,oral LD₅₀

Species:	Wistar Rat
Value:	4.0 g/kg
Method:	Single oral doses; surviving rats observed or two weeks.
Test Substance:	Vinyl toluene (mixed isomers: 55%-70% meta and 30%-45% para-isomer)
GLP:	Yes[]No[]?[] <input checked="" type="checkbox"/>
Remarks:	When the rats were autopsied, slight liver changes and, in some instances, some kidney involvement of questionable significance was observed.
Reliability:	[2] reliable with restrictions
Reference:	Wolf <i>et al</i> , 1956. Am. Med. Assoc. Arch. Ind. Health 14:387-398.

5.2 Repeated Dose Toxicity

5.21 15-day Inhalation, Rat

Species:	Fischer 344/N rats
Value:	No effects at 200 ppm
Method:	Inhalation exposure for 6 hours per day, 5 days per week, for 15 days at 0, 200, 400, 800, and 1300 ppm to male and female rats.
Test Substance:	Vinyl toluene (mixed isomers: 65-71% meta and 32-35% para)
GLP:	Yes[X]No[]?[]
Remarks:	All rats lived to the end of the study. The mean body weights at necropsy of rats exposed to 400 – 1,300 ppm

were 13 to 19% lower than that of controls for males and 9 to 19% lower for females. Most male rats exposed to 1,300 ppm exhibited centrilobular necrosis and focal inflammatory cell infiltration of the liver, whereas minimal centrilobular vacuolization of the liver was seen in all female rats exposed to 1,300 ppm. Dysplasia of the bronchial epithelial lining, chronic bronchitis, and lymphoid hyperplasia of the lung were observed in all rats exposed to 1,300 ppm.

Reliability: [1] reliable without restrictions
Reference: NIH Pub. No. 90-2830.

5.22 15-day Inhalation, Mouse

Species: B6C3F₁ Mice
Value: No effects at 100 ppm
Method: Inhalation exposure for 6 hours per day, 5 days per week, for 15 days at 0, 10, 25, 50, 100, and 200 ppm to male and female mice.
Test Substance: Vinyl toluene (mixed isomers: 65-71% meta and 32-35% para)
GLP: Yes[X]No[]?[]
Remarks: Three of five male mice exposed to 200 ppm died before the end of the study. Four of five male mice exposed to 200 ppm had moderate to severe hepatocellular necrosis; all female mice exposed to 200 ppm had hyperplasia of the epithelium of the intrapulmonary bronchi and centrilobular necrosis, vacuolization, and inflammatory cell infiltrates in the liver.
Reliability: [1] reliable without restrictions
Reference: NIH Pub. No. 90-2830.

5.23 13-week Inhalation, Rat

Species: Fischer 344/N rats
Value: No effects at 60 ppm
Method: Inhalation exposure for 6 hours per day, 5 days per week, for 13 weeks at 0, 25, 60, 160, 400, and 1000 ppm to male and female rats.
Test Substance: Vinyl toluene (mixed isomers: 65-71% meta and 32-35% para)
GLP: Yes[X]No[]?[]
Remarks: All rats lived to the end of the study. The final mean body weights of rats exposed to 400 – 1,000 ppm were 8 to 19% lower than that of controls for males and 6 to 12% lower for females. Relative liver weights for rats at 1,000 ppm were significantly greater than those for controls. The severity of nephropathy was increased in male rats exposed

to 160, 400, and 1000 ppm. Compound-related lesions were not observed in female rats.
 Reliability: [1] reliable without restrictions
 Reference: NIH Pub. No. 90-2830.

5.24 13-week Inhalation, Mouse

Species: B6C3F₁ Mice
 Value: No effects at 10 ppm
 Method: Inhalation exposure for 6 hours per day, 5 days per week, for 13 weeks at 0, 10, 25, 60, and 160 ppm to male and female mice.
 Test Substance: Vinyl toluene (mixed isomers: 65-71% meta and 32-35% para)
 GLP: Yes[X]No[]?[]
 Remarks: The final mean body weights of mice exposed to 25 – 160 ppm were 12 to 20% lower than controls for males and 13 to 16% lower for females. Inflammation of the lung was observed in 5/10 male and 3/9 female mice exposed to 160 ppm. Metaplasia of the nasal turbinates was seen in all exposed groups.
 Reliability: [1] reliable without restrictions
 Reference: NIH Pub. No. 90-2830.

5.25 2-year Inhalation, Rats

Species: Fischer 344/N rats
 Value: No evidence of carcinogenesis at 100 or 300 ppm
 Method: Inhalation exposure for 6 hours per day, 5 days per week, for 103 weeks at 0, 100, and 300 ppm to male and female rats.
 Test Substance: Vinyl toluene (mixed isomers: 65-71% meta and 32-35% para)
 GLP: Yes[X]No[]?[]
 Remarks: Mean body weights of male rats exposed to 300 ppm and those of female rats exposed to 100 and 300 ppm were generally 4 to 11% lower than those of controls. No significant differences in survival were seen between any groups of rats of either sex (male: control, 19/49; low dose, 17/50; high dose, 19/50; female: control, 31/50; low dose, 28/50; high dose, 26/50). Degenerative and nonneoplastic proliferative lesions of the nasal mucosa were observed at increased incidences in exposed rats. These lesions included diffuse hyperplasia (goblet cell) of the respiratory epithelium with intraepithelial mucous cysts and focal erosion of the olfactory epithelium with cystic dilation (cysts) of the Bowman's glands. Focal respiratory epithelial metaplasia of the olfactory epithelium was seen

in exposed males, and cells with homogeneous eosinophilic cytoplasm in the olfactory epithelium occurred at increased incidences in exposed female rats. Neoplasms of the nasal mucosa were not seen in male or female rats. There were no chemically related increases in neoplasm incidence in exposed male or female rats.

Reliability: [1] reliable without restrictions
 Reference: Technical Report Series No. 375, NIH Pub. No. 90-2830.
 (Peer review 11/89)

5.26 2-year Inhalation, Mice

Species: B6C3F₁ Mice
 Value: No evidence of carcinogenesis at 10 or 25 ppm
 Method: Inhalation exposure for 6 hours per day, 5 days per week, for 103 weeks at 0, 10, and 25 ppm to male and female mice.
 Test Substance: Vinyl toluene (mixed isomers: 65-71% meta and 32-35% para)
 GLP: Yes[X]No[]?[]
 Remarks: Mean body weights of mice exposed to 25 ppm were 10 to 23% lower than those of controls after week 8, whereas mice exposed to 10 ppm showed a weight decrement that was generally less than 10%. The survival of male mice exposed to 25 ppm was significantly greater than that of controls. No other significant differences in survival were seen between any groups of mice of either sex (male: control, 33/50; low dose, 30/50; high dose, 41/50; female: control, 36/50; low dose, 37/50; high dose, 34/50). Degenerative and inflammatory lesions of the nasal mucosa were observed at increased incidences in exposed mice. These lesions included focal chronic active inflammation and diffuse hyperplasia of the respiratory epithelium. Chronic active inflammation of the bronchioles occurred in many exposed mice but not in controls. Neoplasms of the nasal passage were not observed in mice. There were no chemically related increases in neoplasm incidence in exposed male or female mice. Exposure-related decreased incidences included alveolar/bronchiolar neoplasms (control, 12/50; low dose, 5/49; high dose, 2/49) and malignant lymphomas (control, 7/50; low dose, 3/50, high dose, 0/50) in males and hepatocellular neoplasms (control, 9/48; low dose, 5/16; high dose, 2/49) in females.
 Reliability: [1] reliable without restrictions
 Reference: Technical Report Series No. 375, NIH Pub. No. 90-2830.
 (Peer review 11/89)

5.27 139-day Inhalation

Species: Wistar Rat
 Value: LOAEL,1,130 ppm, based on growth depression, increase in liver weights and liver histopathology.
 Method: Inhalation exposure for 8 hours per day, 5 days per week, for 139 days at 580, 1130, and 1350 ppm to male and female mice.
 Test Substance: Vinyl toluene (mixed isomers: 55%-70% meta and 30-45% para)
 GLP: Yes[]No[]? [X]
 Remarks: No effects were seen at 580 ppm. At 1130 and 1350 ppm, liver histopathology characterized by fatty degeneration in the midzonal and central cells of the liver lobule was observed. A moderate degree of growth depression and increase in liver weight was also observed at 1130 and 1350 ppm. A moderate amount of mortality was seen in the 1350 ppm exposed animals. The NOAEL was 580 ppm for rats exposed by inhalation of vinyl toluene (7-8 hours/day, 5 days/week, for 139 days). This effect was based on growth depression, increase in liver weights and liver histopathology.
 Reliability: [2] reliable with restrictions
 Reference: Wolf et al., 1956. Am. Med. Assoc. Arch. Ind. Health 14:387-398.

5.28 139-day Inhalation

Species: Albino guinea pigs
 Value: LOAEL,1,130 ppm, based on growth depression, increase in liver weights and liver histopathology.
 Method: Inhalation exposure for 8 hours per day, 5 days per week, for 139 days at 580, 1130, and 1350 ppm to male and female guinea pigs.
 Test Substance: Vinyl toluene (mixed isomers: 55%-70% meta and 30-45% para)
 GLP: Yes[]No[]? [X]
 Remarks: No effects were seen at 580 ppm. At 1130 and 1350 ppm, liver histopathology characterized by fatty degeneration in the midzonal and central cells of the liver lobule was observed. A slight degree of growth depression and increase in kidney weight was also observed at 1130 and 1350 ppm. In addition, a slight increase in liver weights was observed at 1350 ppm. The NOAEL was 580 ppm for exposed by inhalation of vinyl toluene. This effect was based on growth depression, increase in kidney weights and liver histopathology.
 Reliability: [2] reliable with restrictions

Reference:	Wolf et al., 1956. Am. Med. Assoc. Arch. Ind. Health 14:387-398.
5.29 139-day Inhalation	
Species:	White rabbits
Value:	LOAEL,1,130 ppm, based on a slight increase in kidney weights.
Method:	Inhalation exposure for 7-8 hours per day, 5 days per week, for 139 days at 580, 1130, and 1350 ppm to male and female white rabbits.
Test Substance:	Vinyl toluene (mixed isomers: 55%-70% meta and 30-45% para)
GLP:	Yes[]No[]?[X]
Remarks:	No effects were seen at 580 ppm. At 1130 and 1350 ppm, a slight increase in kidney weights was observed. In addition, at 1350 ppm, liver histopathology which was characterized by fatty degeneration in the midzonal and central cells of the liver lobule was observed. The NOAEL was 580 ppm for white rabbits exposed by inhalation of vinyl toluene.
Reliability:	[2] reliable with restrictions
Reference:	Wolf et al., 1956. Am. Med. Assoc. Arch. Ind. Health 14:387-398.

5.30 139-day Inhalation

Species:	Rhesus monkeys
Value:	LOAEL, \geq 1,130 ppm, no effects were observed.
Method:	Inhalation exposure for 8 hours per day, 5 days per week, for 139 days at 580, 1130, and 1350 ppm to male and female Rhesus monkeys.
Test Substance:	Vinyl toluene (mixed isomers: 55%-70% meta and 30-45% para)
GLP:	Yes[]No[]?[X]
Remarks:	No effects were seen at any dose level.
Reliability:	[2] reliable with restrictions
Reference:	Wolf et al., 1956. Am. Med. Assoc. Arch. Ind. Health 14:387-398.

5.3 Toxicity to Reproduction

Although no reproductive studies were available for vinyl toluene, evaluation of reproductive organs from repeated dose studies (see rat and mouse 2 generation robust summaries) is sufficient to address endpoints. No morphological or histological abnormalities to male or female reproductive organs were observed in rats or mice. In addition, a reproduction study using p-methylstyrene (PMS) is adequate as a surrogate study for vinyl toluene. Briefly, dose levels of 25, 200, 500, and 600 mg/kg/day PMS were administered by oral gavage for 404 days in a 2-generation reproduction study in rats. There were no effects on the viability of

pups from dams dosed at 25 or 200 mg/kg/day. In addition, there was no effect on mating, fertility, gestation, delivery of pups, or lactation index at these dose levels. Mortality, reduced weight gain in adults and slight increase in pup mortality (first generation only) was observed at 500 mg/kg/day. Therefore, the NOAEL and LOAEL were 200 and 500 mg/kg/day, respectively.

5.4 Developmental Toxicity/Teratogenicity

Species: Sprague-Dawley rats
 Value: No teratogenic effects at 250 mg/kg despite increase incidence of resorptions and altered fetal sex ratio.
 Method: Daily IP injections of the methyl styrene (250 mg/kg) at days 1-15 of gestation.
 Test Substance: Methyl styrene; unknown purity and mixture of isomers
 GLP: Yes[]No[]?[X]
 Remarks: Not teratogenic effects despite fetal toxicity.
 Reliability: [2] reliable with restrictions
 Reference: Hardin et al., 1981. Scand. J. Work Environ. Health, 7(4):66.

In another study, a dose of 6 ppm for 4 months or 6200 ppm for 1 month was teratogenic in guinea pigs. However this study was referenced incorrectly in Patty's Industrial Hygiene and Toxicology, 4th edition, 1991; a full review of this study could not be done. Regardless, PMS or styrene developmental/teratogenicity studies are sufficient as surrogate studies for vinyl toluene (Table 1).

5.5 Genetic Toxicity

In vitro cytogenetics: vinyl toluene did not induce sister chromatid exchanges or chromosomal aberrations in CHO cells with or without metabolic activation. VT produced chromosome damage and an increase in sister chromatid exchanges in human lymphocytes *in vitro* (0.33 to 4 mM).

Mouse lymphoma: Positive in the mouse lymphoma assay for induction of trifluorothymidine resistance in L5178Y/TK cells in absence of metabolic activation; not tested with metabolic activation.

VT did not induce gene mutations in *S. typhimurium* strains TA98, TA100, TA1535, or TA1537 with or without metabolic activation.

JUSTIFICATION OF USE OF SURROGATE DATA

A careful review of the acute and chronic toxicity data, developmental and reproductive toxicity data, metabolism, and mechanism of action for vinyl toluene (mixture of *m*- and *p*-isomers in ~60/40% ratio), para-methylstyrene and styrene indicate that no major differences are apparent. A comparison of the toxicity data is presented in Table 1. Animal studies have shown that vinyl toluene, para-methylstyrene and styrene have low acute toxicities. In repeated 139-day inhalation studies, experiments show that between these compounds there is only a slightly greater twofold difference in LOAELs between the most toxic and the least toxic compound (Table 1).

Studies also show that the main metabolites of *m*-, *p*-, and *o*-isomers of methylstyrene are similar to the corresponding styrene metabolites. For example, after ortho-, meta- and para-vinyl toluenes were injected intraperitoneally into male albino Wistar rats, 11 urinary metabolites were distinguished /para-vinylbenzoic acid, para-vinylbenzoyl glycine, vinyltoluene-7,8-oxide, para-methylphenyl acetaldehyde, para-methylphenylacetic acid, para-methylphenylacetyl glycine, para-methylphenylethylene glycol, para-methylmandelic acid, para-methylbenzoic acid, para-methylphenylglyoxylic acid, para-methylbenzoyl glycine/. The main metabolites were similar to the corresponding styrene metabolites and included ethylene glycol, mandelic acid, glyoxylic acid derivatives and N-acetylcysteine and glucuronide conjugates. Over 90% of the recovered metabolites were excreted within 24 hours. N-Acetylcysteine derivatives substituted at carbon 8 greatly exceeded (> 80%) those substituted at carbon 9 in Sprague Dawley rats, in spite of steric hindrance by the methyl group.

[IARC. Monographs on the Evaluation of the Carcinogenic Risk of Chemicals to Man. Geneva: World Health Organization, International Agency for Research on Cancer, 1972-PRESENT. (Multivolume work).,p. V60 380 (1994)]**PEER REVIEWED**

In addition, these compounds have similar neurotoxic mechanisms of action. Adult male rabbits were exposed to high concentrations (750 ppm, 12 hr/day for 7 days) of toluene, xylenes, styrene, ethylbenzene, vinyltoluene (3-methylstyrene), and 7-methyl-styrene vapors or were dosed with 4 mM/kg/day ip of hippuric, methylhippuric, mandelic, phenylglyoxylic, 7-methyl-mandelic acids. Styrene, vinyltoluene and ethylbenzene caused a marked depletion of striatal and tuberoinfundibular dopamine. Such an effect was also caused by treatment with phenylglyoxylic and mandelic acids. Dopamine depletion was associated with an increase in homovanilic acid concentration in the same regions. These results indicate that dopamine metabolism is a target for the neurotoxic effects of some monocyclic aromatic hydrocarbons and their metabolites, a lateral vinyl or ethyl chain being crucial for the structure activity relationship of such compounds. [Romanelli A et al; J Appl Toxicol 6 (6): 431-6 (1986)]**PEER REVIEWED**

Efforts were made to clarify the molecular basis of styrene toxicity on the dopaminergic systems and to evaluate whether the same mechanism was common to other solvents. Groups of male New Zealand rabbits were exposed to 750 ppm toluene, xylene, styrene, ethylbenzene, vinyltoluene, 7-methyl-styrene, or fresh air (control group). A significant depletion in both striatal and tubero infundibular dopamine was caused by styrene, ethylbenzene, and vinyltoluene. Methylation of the aromatic ring of styrene did not change its activity, whereas methylation of the side chain drastically reduced its effect on dopamine. Treatment carried out with the main metabolites of aromatic solvents indicated

that acidic metabolites of some solvents caused striatal and tubero infundibular dopamine depletion. Present data suggested a chemical reaction between dopamine and some acidic metabolites. The active metabolites have an alpha-keto acid as the side chain or as a part of their molecule. These keto acids condense nonenzymatically with dopamine.

[Mutti A; Toxicol 49 (1): 77-82 (1988)]**PEER REVIEWED**

In view of these considerations, para-methylstyrene and styrene toxicity data can be used to fill data gaps for vinyl toluene. Specifically, the reproductive study for para-methylstyrene is recommended to fill the data gap for vinyl toluene. In a 2-generation oral rat study, no effects were observed on the success of reproduction or health of offspring exposed at 200 mg/kg/day; mortality, reduced weight gain in adults and slight increase in pup mortality (first generation only) was observed at 500 mg/kg/day. In repeated inhalation studies with vinyl toluene, no effects on reproductive organs in either male or female animals were observed. LOAELs in these studies ranged from 100 to 1130 ppm (Table 1). In 2-year inhalation studies, no significant effect on reproductive organs was observed in rats exposed to 100 or 300 ppm or in mice exposed to 10 or 25 ppm. Summaries of the nonneoplastic lesions in reproductive organs are provided in the respective robust summaries.

Table 1: Toxicity Endpoint Comparisons for Vinyl Toluene, Para-methylstyrene and Styrene

Toxicity Endpoint	Vinyl Toluene (m-, p-isomers in ~60/40% ratio)	Para-methylstyrene	Styrene
Acute Toxicity	Oral LD ₅₀ , Rat, 4.0 g/kg ¹ Oral LD ₅₀ , Rat, 5.7 g/kg ² Oral LD ₅₀ , Mouse, 3.16 g/kg ² Oral LD ₅₀ , Rat, 2.255 g/kg ³ Inhal LC ₅₀ , Mouse, 62 ppm ² IP LD ₅₀ , Rat, 2.324 g/kg ³	IP LD ₅₀ , Mouse, 0.77 g/kg ⁶ Oral LD ₅₀ , Rat, 2.52 g/kg ⁷ Oral LD ₅₀ , Mouse, 1.15 g/kg ⁸ Oral LD ₅₀ , Mouse, 1.07 g/kg ⁹ Inhal LC ₅₀ , Rat, >3500 ppm ¹⁰	Oral LD ₅₀ , Rat, 4.92 g/kg ²¹ Inhal LC ₅₀ , Rat, 2700 ppm ²¹ Oral LD ₅₀ , Mouse, 0.32 g/kg ²² Oral LD ₅₀ , Rat, 1 g/kg ²³ IP LD ₅₀ , Rat, 0.898 g/kg ²² Inhal LC ₅₀ , Mouse, 4940 ppm, 2 hr ²⁴ Inhal LC ₅₀ , Rat, 2770 ppm, 4 hr ²⁴
Repeat Dose Toxicity	Inhalation, rat, guinea pig, rabbit 139 d, LOAEL, 1130 ppm ¹ Inhal 15-day, rat LOAEL, 400 ppm ⁴ Inhal 15-day, mouse LOAEL, 200 ppm ⁴ Inhal 13-wk, rat LOAEL, 160 ppm ⁴ Inhal 13-wk, mouse LOAEL, 25 ppm ⁴ No evidence of cancer in rats exposed to 100 or 300 ppm ⁴ No evidence of cancer in mice exposed 10 or 25 ppm ⁴	Inhalation, rat, guinea pig, rabbit 139 d, LOAEL, 600 ppm ¹ Oral 28-day dog, LOAEL 300 mg/kg ¹¹ Inhal 13-wk, rat LOAEL 1313 ppm ¹² Oral 13-wk, rat LOAEL 700 mg/kg ¹³ No evidence of cancer in rats exposed to oral 50 mg/kg/day (males) and 500 mg/kg/day (females) ¹⁴ No evidence of cancer in mice exposed to oral 50 mg/kg/day (females); males exposed to 10 to 250 mg/kg/day exhibited reduced survival ¹⁵ Oral, 16-month, rat LOAEL 200 mg/kg/day ¹⁶	Inhalation, rat, guinea pig, rabbit 139 d, LOAEL, 1300 ppm ¹ Oral 102-wk, rat, LOAEL 500 mg/kg/day ²⁵ Oral 185-d, rat, LOAEL 285 mg/kg/day ²⁵ Inhal 13-wk, mice, LOAEL 62.5 ppm ²⁵ Inhal 13-wk, rat, LOAEL 500 ppm ²⁵ No evidence of cancer in rats or mice exposed orally to 1000 or 150 mg/kg/day, respectively, for 78 weeks ²⁶ Lung adenomas and carcinomas observed in mice orally treated with 300 or 1350 mg/kg/day for 100 days ²¹ No brain tumors found in rats exposed to 300 ppm for 52 weeks ²¹
Repro Toxicity	No studies found	2-generation rat, oral; no effects on the success of reproduction or health of offspring observed at 200 mg/kg/day; mortality, reduced weight gain in adults and slight increase in pup mortality (first generation only) at 500 mg/kg/day ¹⁷	Rats exposed to 0, 125, or 250 ppm styrene in drinking water for three generations; reduction in survival was observed in high-dose F1 and F2 pups but the F3 generation was unaffected ²⁵
Develop Tox/ Teratology	IP rat (1-15 day pregnancy); 250 mg/kg caused post-implantation mortality but no teratology ⁵ Inhal, Guinea pig, teratogenic effects observed at 6 ppm for 4 months or 6200 ppm for 1 month ²	Oral rat (6-19 days gestation); no teratogenic effect at 600 mg/kg/day or less ¹⁸ Oral treatment with PMS did not produce a teratogenic effect to rabbits at 150 mg/kg/day ¹⁹ ; 200 mg/kg/day would be considered excessive for a teratology study in rabbits ²⁰	Oral rat (6-19 days gestation); no teratogenic effects at 90 or 150 mg/kg/day ²¹ Inhalation rat and rabbit; no developmental toxicity at 300 or 600 ppm; mice exhibited maternal and fetal death at 500 and 700 ppm ²⁵

- ¹Wolf, M.A., Rowe, V.K., McCollister, D.D., Hollingsworth, R.C., and Oyen, F. (1956) Am. Med. Assoc. Arch. Ind. Health. 14:387.
- ²Danishefsky, I. and Willhite, M. (1954) J. Biol. Chem. 211:549 (Incorrect reference)
- ³Acute Toxicity Data. Journal of the American College of Toxicology, Part B. (Mary Ann Liebert, Inc., New York, NY, V.1, 77, 1990.
- ⁴Toxicology and Carcinogenesis Studies of Vinyl Toluene (Mixed Isomers; 65-71% meta isomer and 32-35% para-isomer) in F344/N Rats and B6C3F₁ Mice (Inhalation Studies). National Toxicology Program Technical Report Series No. 375, NIH Publication No. 90-2830.
- ⁵Scandinavian Journal of Work, Environment and Health, 1981, Volume 7 (Suppl 4), 66.
- ⁶Acute Intraperitoneal Toxicity (LD50) Study in Mice with MCTR-86-79. International Research and Development Corporation #450-004, December 3, 1979.
- ⁷Acute Oral Toxicity Study in Male and Female Rats: MCTR-112-79. Hazleton Laboratories America, Inc. #230-196, December 21, 1979.
- ⁸Oral LD50 of Para-Methylstyrene (PMS) in Swiss-Webster Mice after a Single Exposure: Effect on Corn Oil/Olive Oil Vehicle and Comparison of Three PMS Samples. Mobile Environmental and Health Science Laboratory #441-80, December 18, 1980.
- ⁹Acute Oral Toxicity (LD50) Study in Mice with MCTR-86-79. International Research and Development Corporation #450-003, December 12, 1979.
- ¹⁰An Acute Inhalation Toxicity Study of MCTR-142-79 in the Rat. Bio/dynamics, Inc., Project No. 79-7347, May 19, 1980.
- ¹¹One-Month Oral Toxicity Study in Dogs with PMS. Mobil Environmental and Health Science Laboratory Project No.:230-230, September 3, 1981.
- ¹²A 13-week Inhalation Toxicity Study of para-methylstyrene in the rat. Bio/dynamics, Inc., Project No. 79-7327, November 11, 1980.
- ¹³Subchronic Toxicity Study in Rats, MCTR-144-79. Hazleton Laboratories Project No. 230-217, July 25, 1980.
- ¹⁴Evaluation of the Chronic Toxicity and Oncogenic Potential of para-Methylstyrene (PMS) in Rats. Study No. BT106bis (MEHSL Study No. 43-80) and Study No. BT106 (MEHSL Study No. 41-80), reported July 13, 1984 by The Institute of Oncology, Bologna, Italy.
- ¹⁵Evaluation of the Chronic Toxicity and Oncogenic Potential of para-Methylstyrene (PMS) in Mice. Study No. BT107 (MEHSL Study No. 291-80) reported July 13, 1984 by The Institute of Oncology, Bologna, Italy.
- ¹⁶Chronic Toxicity of p-Methylstyrene (PMS) in Rats. Hazleton Laboratories Project No. 2151-80, March 17, 1983.

- ¹⁷Reproductive Effects of p-Methylstyrene Administered Orally via Gavage to Crl:COBSCD(SD) BR Rats for Two Generations. Argus Research Laboratories, Report No. 2161-80, September 22, 1982.
- ¹⁸Teratology Study in the Rat on PMS Dosed by Oral Route. International Research and Development Corporation, Report No. 3020-79, October 8, 1981.
- ¹⁹Teratology Study for Rabbits. International Research and Development Corporation, Report No. 3030-79, January 6, 1982.
- ²⁰Teratology Study for Rabbits. International Research and Development Corporation, Report No. 311-79, October 27, 1981.
- ²¹U.S. EPA. 1984. Environmental Protection Agency. Health and Environmental Effects Profile for Styrene. Office of Research and Development, U.S. EPA, Washington, D.C. ECAO-CIN-P103.
- ²²Lewis, R.J. Sax's Dangerous Properties of Industrial Materials. 9th ed. Volumes 1-3. New York, NY: Van Nostrand Reinhold, 1996. 3027.
- ²³Verschuere, K. Handbook of Environmental Data of Organic Chemicals. 2nd ed. New York, NY: Van Nostrand Reinhold, 1983. 1057.
- ²⁴American Conference of Governmental Industrial Hygienists, Inc. Documentation of the Threshold Limit Values and Biological Indices. 6th ed. Volumes I, II, III. Cincinnati, OH: ACGIH, 1991. 1436.
- ²⁵U.S. EPA. 1994. Environmental Protection Agency. Integrated Risk Information System (IRIS) Online. Office of Health and Environmental Assessment, U.S. EPA, Cincinnati, OH.
- ²⁶NCI. 1979. National Cancer Institute. Bioassay for styrene for possible carcinogenicity. Technical Report Series No. 185, 44 pp.