

AR201-13757A

**EPA'S HPV CHALLENGE PROGRAM: TIER I SCREENING
SIDS DOSSIER FOR P-ETHYLTOLUENE
CAS NO. 622-96-8**

DELTECH CORPORATION
BATON ROUGE, LOUISIANA

PREPARED BY:
Kevin N. Baer, Ph.D.
The University of Louisiana at Monroe

March 21, 2002

02 MAY 22 PM 12:29

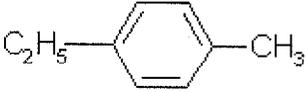
RECEIVED
EPA/MDIC

CONTENTS

	PAGE
SIDS PROFILE: HPV TEST PLAN PART A	3
TEST PLAN JUSTIFICATION	3
TIER I: HPV TEST PLAN PART B	4
1.0 GENERAL INFORMATION	5
A. CAS Number	5
B. Molecular Weight	5
C. OECD Name	5
D. CAS Descriptor	5
E. Structural Formula	5
2.0 PHYSICAL/CHEMICAL DATA	5
2.1 Melting Point	5
2.2 Boiling Point	5
2.3 Water Solubility	6
2.4 Vapor Pressure	6
2.5 Partition Coefficient	7
3.0 ENVIRONMENTAL FATE	7
4.0 ECOTOXICITY	7
5.0 HEALTH EFFECTS TESTS	7
5.1 Acute Toxicity	7
5.2 Repeated Dose Toxicity	7
5.3 Toxicity to Reproduction	7
5.4 Developmental/Teratogenicity	8
5.5 Genetic Toxicity	9
JUSTIFICATION FOR USING THE STUDY ENTITLED "REPRODUCTIVE EFFECTS OF P-METHYLSTYRENE ADMINISTERED ORALLY VIA GAVAGE TO RATS FOR TWO GENERATIONS" AS AN ANALOGUE REPRODUCTIVE STUDY FOR P-ETHYLTOLUENE	11

SIDS PROFILE
HPV Test Plan: Part A

DATE: March 21, 2002

1.01A	CAS NO.	622-96-8
1.01C	CHEMICAL NAME	P-ETHYLTOLUENE
1.01D	CAS DESCRIPTOR	Not applicable
1.01G	STRUCTURE AND FORMULA	 C_9H_{12}

<p>TEST PLAN JUSTIFICATION/ISSUES FOR DISCUSSION</p>	<p>PHYSICAL/CHEMICAL PROPERTY TESTS DATA GAPS: SIDS testing required: Water solubility, and partition coefficient.</p> <p>ENVIRONMENTAL FATE AND PATHWAY TESTS DATA GAPS: SIDS testing required: Photodegradation, biodegradation, stability in water, and transport (EQC Level III Fugacity Model).</p> <p>ECOTOXICITY TESTS DATA GAPS: SIDS testing required: Acute toxicity to fish, acute toxicity to aquatic invertebrates, and acute toxicity to algae.</p> <p>HEALTH EFFECTS TESTS DATA GAPS: Toxicity to Reproduction; recommend submission of Oral, 2-Generation, Rat study with p-methylstyrene as analogue study for PET. Justification is discussed below.</p>
--	--

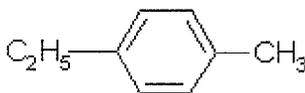
Tier I

DATE: January 15, 2002

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
Boiling Point	Y	*	*			*	N
Density ¹	Y	*	*			*	N
Vapor Pressure	Y	*	*	--	--	*	N
Oct: water part.coef	N						Y
Water solubility	N						Y
pKa							
Other		-	--	--	--	--	--
Environmental Fate and Pathway							
Photodeg	N						Y
Stability in water	N						Y
Monit. Data ¹	N	--	--	--	--	--	
Transp/Dist	N						Y
Biodeg	N						Y
Other		--	--	--	--	--	--
Ecotoxicology							
Acute Fish	N						Y
Acute Daph.	N						Y
Acute Algae	N						Y
Chron. Daph ²	N						
Terr. Tox. ²	N						
Other		--	--	--	--	--	--
Toxicology							
Acute	Y	*	N			*	N
Rep.	Y	Y	N			Y	N
DoseGenetic	Y	Y	N			Y	N
Repro	N			Y	--		N
Devel/Terat	Y	Y	N			Y	N
Human Experience ²	N						
Other		--	--	--	--	--	--
* Unknown ¹ Not required for SIDS Base Set ² Conditional SIDS studies							

1.0 GENERAL INFORMATION

- A. CAS NUMBER 622-96-8
B. Molecular Weight 120.194
C. OECD Name p-ethyltoluene
D. CAS Descriptor Not applicable
E. Structural Formula C₉H₁₂



2.0 PHYSICAL/CHEMICAL DATA

2.1 Melting Point

Value: -62°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
Reference: Acros Organics (MSDS)

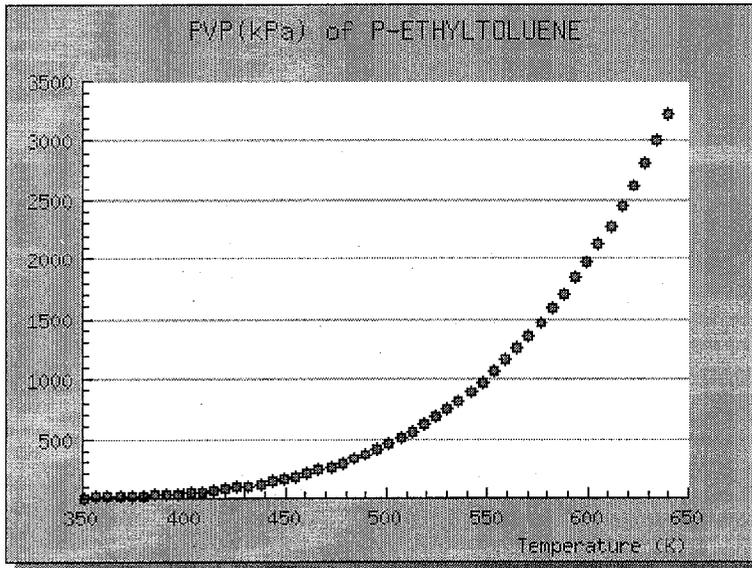
2.2 Boiling Point

Value: 162°C at 760 mm Hg
Decomposition No Data
Method No Data
GLP Yes[] No[] ?[X]
Remarks: None
Reliability: [4] Not assignable because limited study information was available
Reference: Acros Organics (MSDS)

2.3 Water Solubility No data available
 Remarks: No testing is needed if water solubility values are $\leq 1 \mu\text{g/L}$.

2.4 Vapor Pressure 28 mm Hg at 150°F
 Remarks: Coefficients available

PVP] Vapor pressure of P-ETHYLTOLUENE



Equation Name	Wagner Equation	
Equation	$\ln(P_{vp}/P_c) = (A*x + B*x^{1.5} + C*T^3 + D*T^6) / (1-x)$ where $x = 1-T/T_c$	
Coefficient A	-7.68892E+00	
Coefficient B	1.92605E+00	
Coefficient C	-5.51788E+00	
Coefficient D	2.76399E+00	
Coefficient E		
Coefficient F		
Coefficient G		
T range , from	351	K
T range , to	640	K

2.5 Partition Coefficient No data available
Remarks: Calculated or estimated values are acceptable.

3.0 **ENVIRONMENTAL FATE (Inadequate information)**

4.0 **ECOTOXICITY (Inadequate Information)**

5.0 **HEALTH EFFECTS TESTS**

5.1 Acute Toxicity (The following tests are available but have not been reviewed)

Oral LD ₅₀ , Rat	4850 mg/kg
Acute Dermal Toxicity	Moderate skin irritant
Eye Irritation	Moderate eye irritant
Skin Irritation	Moderate skin irritant
LC ₅₀ , Rat	>3900 ppm
14-Day Dermal	No deaths; severe local skin toxicity

5.2 Repeated Dose Toxicity

5.21 13-Week Oral, Rat

Species:	Fischer 344 rats
Value:	No effects at 100 mg/kg
Method:	Repeated oral gavage doses at 100, 300, and 900 mg/kg daily for 13 consecutive weeks to male and female rats.
Test Substance:	p-ethyltoluene
GLP	Yes[]No[]? [X]
Remarks:	Dose-related mortality, body-weight depression, increase in liver weights, and increases in SGPT, ALP and albumin levels were observed for the 300 and 900 mg/kg males and females. Dose-related reductions in testes/epididymides weights of 300 and 900 mg/kg males were observed.
Reliability:	[2] valid with restrictions
Reference:	MEHSL Sample No. 701-81, Borriston Labs, Inc. 1983

5.22 13-Week Inhalation No effect at 305 ppm; minimal effects at 979 ppm
(Not reviewed)

5.23 Range-Finding, Oral Rat (Not reviewed)

5.3 Toxicity to Reproduction (Inadequate Information; p-methylstyrene will be used as an analogue study, see attached justification below).

5.4 Developmental Toxicity/Teratogenicity

5.41 Teratology, Rat

Species: Pregnant Charles River COBS®CD® rats
Value: Treatment with PET did not produce a teratogenic response when administered orally to pregnant rats at a dosage level of 200 mg/kg/day or less.

Method: Oral gavage doses at 25, 100, and 200 mg/kg were administered as a single daily dose on days 6 through 19 of gestation.

Test Substance: p-ethyltoluene in corn oil (0.5 ml/kg)
GLP Yes No [X]

Remarks: Survival was 100% in all dosage groups. There were no biologically meaningful or statistically significant differences in any endpoint; mean numbers of corpora lutea, total implantations, early resorptions, postimplantation loss, viable fetuses, or number of litters with malformations.

Reliability: [2] valid with restrictions
Reference: (M-3040-79), International Research and Development Corporation, 1981.

5.42 Teratology, Rabbit

Species: Pregnant Dutch Belted rabbits
Value: PET did not produce a teratogenic response when administered orally to pregnant rabbits at a dose level of 200 mg/kg/day or less.

Method: Oral gavage doses at 25, 125, and 200 mg/kg/day were administered as a single daily dose on days 6 through 27 of gestation.

Test Substance: p-ethyltoluene in corn oil (0.5 ml/kg)
GLP Yes No [X]

Remarks: No effect related to treatment on Cesarean section parameters or the number of fetuses with malformations occurred in 25, 125, and 200 mg/kg/day. There was an increase in the occurrence of one genetic and developmental variation (13th rudimentary ribs) in the 200 mg/kg/day group. However, 13th rudimentary ribs are considered a skeletal variant and not a malformation.

Reliability: [2] valid with restrictions
Reference: (M-3050-79), International Research and Development Corporation, 1981.

- 5.43 Pilot Teratology, Rat (Not reviewed)
- 5.44 Pilot Teratology, Rabbit (Not reviewed)
- 5.45 Pilot Teratology, Rabbit (Not reviewed)
- 5.5 Genetic Toxicity – *In Vitro*
- 5.51 Sister Chromatid Exchange Analysis

Species: Male mouse bone marrow cells
 Route of Admin. Oral gavage
 Doses: 0.75, 1.0, and 1.25 g/kg
 Test Substance: p-ethyltoluene suspended in Methocel K4M Premium
 Methods: Bone marrow cells were collected 24 hours after dosing and examined microscopically for sister chromatid exchange.
 Results: PET did not significantly increase the number of sister chromatid exchanges above the baseline vehicle controls.
 GLP Yes No [X]
 Remarks: PET does not induce SCE in this test system.
 Reliability [2] valid with restrictions
 Reference: (731-82), Mobile Environmental and Health Science Laboratory, 1983.

5.52 Unscheduled DNA Synthesis

Species: Male Sprague-Dawley rat hepatocytes
 Route of Admin. Oral gavage
 Doses: 0.5, 0.75, 1.0, 1.25, and 1.7 g/kg
 Test Substance: p-ethyltoluene
 Methods: Hepatocytes were isolated two hours after dosing and exposed in culture to ³H-thymidine.
 Results: A significant overall increase in UDS was evident in all assays at doses up to 1.0 g/kg. At higher doses, UDS was diminished, possibly as a function of cytotoxicity.
 GLP Yes No [X]
 Remarks: PET is capable of causing primary DNA damage in this test system.
 Reliability [2] valid with restrictions
 Reference: (732-82), Mobile Environmental and Health Science Laboratory, 1983.

5.53 Mitotic Recombination

Specie/Strain: *Saccharomyces cerevisiae* D₅
Doses: 0.020 to 0.312 µl per 3 ml
Test Substance: p-ethyltoluene
Methods: PET was tested for the induction of mitotic recombination in yeast with and without metabolic activation from a rat liver S-9 mixture.
Results: PET did not induce mitotic recombinations in any of the assays conducted.
GLP Yes No
Remarks: PET is considered genetically inactive to the indicator strain *Saccharomyces cerevisiae* strain D₅.
Reliability [2] valid with restrictions
Reference: (733-82), Litton Bionetics, 1982.

The following tests are available but have not been reviewed:

In Vitro

Ames Assay	Not mutagenic
Mouse Lymphoma	Not mutagenic
DNA Repair	Negative
Cell Transformation	Negative

In Vivo

Drosophila Mutagenicity	Not mutagenic
Dominant Lethal Assay	A statistically significant increase in preimplantation loss was observed in litters sired by male mice given 1300 mg/kg PET in corn oil orally for five days. Genetically induced preimplantation loss cannot be distinguished from failure of fertilization. No increase in fetal death or embryonic resorption occurred at any dose of PET.

Summary of mutagenicity of PET: Although PET demonstrated interaction with DNA in rat hepatocytes and increased preimplantation loss was observed in the dominant lethal test, neither occurrence constitutes a mutagenic event. All other tests which evaluated PET for mutagenesis or cell transformation were negative. There is no clear-cut demonstration of mutagenic activity for PET (Final Status Report, p-methylstyrene, January, 1989).

JUSTIFICATION FOR USING THE STUDY ENTITLED “REPRODUCTIVE EFFECTS OF P-METHYLSTYRENE ADMINISTERED ORALLY VIA GAVAGE TO RATS FOR TWO GENERATIONS” AS AN ANALOGUE REPRODUCTIVE STUDY FOR P-ETHYLTOLUENE

A review was conducted of the available acute and chronic toxicity data and relevant developmental/teratogenicity data for p-methylstyrene and p-ethyltoluene. In my opinion, there are no biological meaningful differences between any endpoints. A brief comparison follows:

p-methylstyrene

Oral LD50 Rat	2523 mg/kg
Inhalation LC50	>3500 ppm
13-week Oral	No effects at 100 mg/kg
13-week Inhalation	No effects at 500 ppm
2-Generation, Rat	No reproductive effects at 200 mg/kg
Teratology, Rat	No effects at 600 mg/kg/day or less
Teratology, Rabbit	No effects at 150 mg/kg/day or less

p-ethyltoluene

Oral LD50 Rat	4850 mg/kg
Inhalation LC50	>3900 ppm
13-week Oral	No effects at 100 mg/kg
13-week Inhalation	No effect at 305 ppm; minimal effects at 979 ppm
Teratology, Rat	No effect at 200 mg/kg/day (highest dose)
Teratology, Rabbit	No effect at 200 mg/kg/day

The OECD SIDS program accepts an existing, adequate 90-day repeat dose study that “demonstrates no effects on reproductive organs, in particular the testes, then a developmental study can be considered as an adequate test for information on reproduction/development effect” (SIDS Manual, Section 3.3, paragraph 13). In a 90-day oral study with Fischer 344 rats, PET was administered at 100, 300, and 900 mg/kg/day for 13 consecutive weeks. Dose-related reduction in absolute and relative testes/epididymides weights of the mid and high dose males were observed. Microscopically, these rats had testicular atrophy and hypospermatogenesis of the testes and hypospermia or aspermia of the epididymides in the high dose males; a number of these animals had sperm granulomas in the epididymides. No microscopic indication of atrophy was seen in the testicles from at 300 mg/kg/day rats; however, two of the animals showed minimal hypospermatogenesis. Testicle sections from all low dose male rats appeared normal. There were no effects at 100 mg/kg/day.

In a teratology study with pregnant rats, PET was administered orally at dose levels of 25, 100, and 200 mg/kg/day. There were no biologically meaningful or statistically significant differences in the mean numbers of corpora lutea, total implantations, early resorptions, postimplantation loss, viable fetuses, the fetal sex distribution, mean fetal

body weight, or the number of litters with malformations in any treatment group. Therefore, the conclusion of this study is that treatment with PET did not produce a teratogenic response to pregnant rats at a dose level of 200 mg/kg/day.

These two studies provide adequate test information on reproduction/developmental effects for PET.

Furthermore, comparing the relevant PET endpoints to p-methylstyrene gives relevance in using the p-methylstyrene reproductive toxicity study as an analogue study for PET. For example, a 13-week oral study in rats was conducted with p-methylstyrene using dose levels of 50, 100, 300, 700, and 1500 mg/kg/day. Increases in liver weights were observed at 300 mg/kg/day and decreases in testes weights were observed at 700 mg/kg/day. No significant effects were observed at 100 mg/kg/day.

In the teratology study with pregnant rats, p-methylstyrene was administered orally at dose levels of 60, 190, and 600 mg/kg/day. There were no significant differences in pregnancy, implantation, number of live fetuses, numbers of dead fetuses, or numbers of resorptions per dam between any test level and control. The NOEL was greater than 600 mg/kg/day.

In view of these considerations, the reproduction study using p-methylstyrene should suffice as an analogue study for PET. Dose levels of 25, 200, 500, and 600 mg/kg/day p-methylstyrene were administered by oral gavage daily for 404 days. 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. Therefore the NOAEL and LOAEL were 200 and 500 mg/kg/day, respectively.

Previously, similar comparisons were conducted between p-methylstyrene, vinyl toluene, and styrene. The same conclusions were made; no meaningful differences were apparent between studies. The main metabolites of the isomers of methylstyrene are similar to the corresponding styrene metabolites. There is no indication that metabolites of PET would be different from these related compounds. Therefore, the use of a p-methylstyrene reproductive study as an analogue study for PET is appropriate. The reproductive study for p-methylstyrene was reviewed as part of the Tier II EPA Robust Summary and was determined to be acceptable.