

SCREENING-LEVEL HAZARD CHARACTERIZATION *p*-Ethyltoluene (CASRN 622-96-8)

The High Production Volume (HPV) Challenge Program¹ was conceived as a voluntary initiative aimed at developing and making publicly available screening-level health and environmental effects information on chemicals manufactured in or imported into the United States in quantities greater than one million pounds per year. In the Challenge Program, producers and importers of HPV chemicals voluntarily sponsored chemicals; sponsorship entailed the identification and initial assessment of the adequacy of existing toxicity data/information, conducting new testing if adequate data did not exist, and making both new and existing data and information available to the public. Each complete data submission contains data on 18 internationally agreed to “SIDS” (Screening Information Data Set^{1,2}) endpoints that are screening-level indicators of potential hazards (toxicity) for humans or the environment.

The Environmental Protection Agency’s Office of Pollution Prevention and Toxics (OPPT) is evaluating the data submitted in the HPV Challenge Program on approximately 1400 sponsored chemicals by developing hazard characterizations (HCs). These HCs consist of an evaluation of the quality and completeness of the data set provided in the Challenge Program submissions. They are not intended to be definitive statements regarding the possibility of unreasonable risk of injury to health or the environment.

The evaluation is performed according to established EPA guidance^{2,3} and is based primarily on hazard data provided by sponsors; however, in preparing the hazard characterization, EPA considered its own comments and public comments on the original submission as well as the sponsor’s responses to comments and revisions made to the submission. In order to determine whether any new hazard information was developed since the time of the HPV submission, a search of the following databases was made from one year prior to the date of the HPV Challenge submission to the present: (ChemID to locate available data sources including Medline/PubMed, Toxline, HSDB, IRIS, NTP, ATSDR, IARC, EXTOXNET, EPA SRS, etc.), STN/CAS online databases (Registry file for locators, ChemAbs for toxicology data, RTECS, Merck, etc.) and Science Direct. OPPT’s focus on these specific sources is based on their being of high quality, highly relevant to hazard characterization, and publicly available.

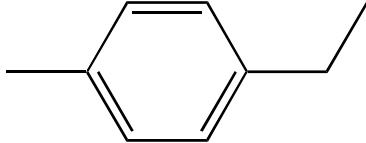
OPPT does not develop HCs for those HPV chemicals which have already been assessed internationally through the HPV program of the Organization for Economic Cooperation and Development (OECD) and for which Screening Initial Data Set (SIDS) Initial Assessment Reports (SIAR) and SIDS Initial Assessment Profiles (SIAP) are available. These documents are presented in an international forum that involves review and endorsement by governmental authorities around the world. OPPT is an active participant in these meetings and accepts these documents as reliable screening-level hazard assessments.

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

² U.S. EPA. HPV Challenge Program – Information Sources; <http://www.epa.gov/chemrtk/pubs/general/guidocs.htm>.

³ U.S. EPA. Risk Assessment Guidelines; <http://cfpub.epa.gov/ncea/raf/rafguid.cfm>.

These hazard characterizations are technical documents intended to inform subsequent decisions and actions by OPPT. Accordingly, the documents are not written with the goal of informing the general public. However, they do provide a vehicle for public access to a concise assessment of the raw technical data on HPV chemicals and provide information previously not readily available to the public.

Chemical Abstract Service Registry Number (CASRN)	<p style="text-align: center;">622-96-8</p>
Chemical Abstract Index Name	<p style="text-align: center;">Benzene, 1-ethyl-4-methyl-</p>
Structural Formula	
<p style="text-align: center;">Summary</p> <p><i>p</i>-Ethyltoluene is a liquid with moderate water solubility and high vapor pressure. It is expected to have moderate mobility in soil. Volatilization of this chemical from water and moist soil is considered high based on its Henry's Law constant. The rate of hydrolysis is considered negligible. The rate of atmospheric photooxidation is considered slow. This chemical is expected to have low persistence (P1) and low bioaccumulation potential (B1).</p> <p>The acute oral and inhalation toxicity of this chemical to rats, and the acute dermal toxicity to rabbits are low. Repeated-dose subchronic toxicity studies of this chemical in rats via the oral route showed effects on mortality, body weight, organ weights, clinical chemistry and hematological parameters at 300 mg/kg/day; the NOAEL for systemic toxicity was 100 mg/kg/day. Repeated-dose subchronic toxicity studies of this chemical in rats via inhalation showed significant changes in liver and gonad weights at 4.8 mg/L/day; the NOAEL was 1.5 mg/L/day. No reproductive toxicity studies of this chemical are available. Evaluation of effects on reproductive organs in the repeated-dose subchronic toxicity studies showed testicular atrophy and decreased spermatogenesis at 300 mg/kg/day. An oral prenatal developmental toxicity study of this chemical in rabbits showed mortality in the dams at 250 mg/kg/day; the NOAEL for maternal toxicity was 200 mg/kg/day. In this study, there was developmental toxicity at 125 mg/kg/day as demonstrated by increased number of fetuses with 13th rib; the NOAEL for developmental toxicity was 25 mg/kg/day. This chemical was not mutagenic in bacterial or mammalian cells <i>in vitro</i>. It did not induce mitotic recombination in yeast <i>in vitro</i>, sister chromatid exchanges in bone marrow of mice or dominant lethal effects in rats <i>in vivo</i>, but induced unscheduled DNA synthesis in rat hepatocytes. This chemical was irritating to rabbit eyes and skin.</p> <p>The measured aquatic toxicity values for <i>p</i>-ethyltoluene are based on the analog mixed diethylbenzenes (CASRN 25340-17-4). The 96-hour LC₅₀ of CASRN 25340-17-4 to fish is 0.673 mg/L, the 48-hour EC₅₀ to aquatic invertebrates is 2.01 mg/L, and the 72-hour EC₅₀ to aquatic plants is 1.21 mg/L (growth) and 1.00 mg/L (biomass).</p> <p>Acute toxicity to fish, aquatic invertebrates and aquatic plants were identified as data gaps under the HPV Challenge Program.</p>	

The sponsor, Deltech Corporation, submitted a Test Plan and Robust Summaries to EPA for *p*-ethyltoluene (CASRN 622-96-8) on March 21, 2002. EPA posted the submission on the ChemRTK HPV Challenge website on June 14, 2002 (<http://www.epa.gov/oppt/chemrtk/pubs/summaries/pethtoln/c13757tc.htm>). EPA comments on the original submission were posted to the website on October 10, 2002. Public comments were also received and posted to the website. The sponsor has not submitted a response to EPA comments or revised/updated documents.

1 Chemical Identity

1.1 Identification and Purity

1.2 Physical-Chemical Properties

The physical-chemical properties of CASRN 622-96-8 are summarized in Table 1. CASRN 622-96-8 is a liquid with moderate water solubility and high vapor pressure.

Table 1. Physical-Chemical Properties of <i>p</i>-Ethyltoluene¹	
Property	Sponsored Chemical
	<i>p</i>-Ethyltoluene
CASRN	622-96-8
Molecular Weight	120.194
Physical State	Liquid
Melting Point	-62°C
Boiling Point	162°C
Vapor Pressure	28 mm at 65.6 °C (measured) ₃ 3 mm Hg at 25°C (measured) ²
Water Solubility	94.9 mg/L at 25°C (measured) ²
Dissociation Constant (pK _a)	Not applicable
Henry's Law Constant	5.0×10 ⁻³ atm-m ³ /mole (estimated) ³
Log K _{ow}	3.63 (measured) ²

¹Deltech Corporation. May 22, 2002. Test Plan and Robust Summary for *p*-Ethyltoluene.

<http://www.epa.gov/hpv/pubs/summaries/pethtoln/c13757tc.htm>.

²SRC. The Physical Properties Database (PHYSPROP). Syracuse, NY: Syracuse Research Corporation. Available from <http://www.srcinc.com/what-we-do/databaseforms.aspx?id=386>

2 General Information on Exposure

2.1 Production Volume and Use Pattern

This chemical had an aggregated production volume in the United States of 10 million to 50 million pounds during calendar year 2005.

There was no use information reported in the IUR submissions. There was no use information reported in the HPV submission.

2.2 Environmental Exposure and Fate

Based on the relatively high domestic production volume, there is potential for domestic environmental releases to water, land and/or air during manufacturing.

The environmental fate properties are provided in Table 2. This chemical is expected to have moderate mobility in soil. Volatilization of this chemical from water and moist soil is considered high based on its Henry's Law constant. The rate of hydrolysis is considered negligible. The rate of atmospheric photooxidation is considered slow. This chemical is expected to have low persistence (P1) and low bioaccumulation potential (B1).

Table 2. Environmental Fate Characteristics of <i>p</i>-Ethyltoluene¹	
Property	Sponsored Chemical
	<i>p</i>-Ethyltoluene
CASRN	622-96-8
Photodegradation Half-life	1.44 days (estimated) ²
Hydrolysis Half-life	Stable
Biodegradation	100% after 25 days (measured; aerobic, non-ready test using activated sludge and gasoline mixture test substance) ³ ; Inherently biodegradable (ethylbenzene) ⁴ ; Readily biodegradable (toluene) ⁴
Bioconcentration	BCF = 125 (estimated) ²
Log K _{oc}	2.92 (estimated) ²
Fugacity (Level III Model) ²	Air = 4.48% Water = 20.3% Soil = 74% Sediment = 1.18%
Persistence ⁵	P1 (low)
Bioaccumulation ⁵	B1 (low)

¹Deltech Corporation. March 21, 2002. Test Plan and Robust Summary for *p*-Ethyltoluene.

<http://www.epa.gov/hpv/pubs/summaries/pethtoln/c13757tc.htm>.

²U.S. EPA. 2008. Estimation Programs Interface Suite™ for Microsoft® Windows, v 3.20. United States Environmental Protection Agency, Washington, DC, USA.

<http://www.epa.gov/opptintr/exposure/pubs/episuite.htm>.

³Solano-Serena F, Marchal R, Ropars M, et al. 1999. Biodegradation of gasoline: Kinetics, mass balance and fate of individual hydrocarbons. *J. Appl. Microbiol.* 86(6):1008–1016.

⁴National Institute of Technology and Evaluation. 2002. Biodegradation and Bioaccumulation of the Existing Chemical Substances under the Chemical Substances Control Law.

http://www.safe.nite.go.jp/english/kizon/KIZON_start_hazkizon.html.

⁵Federal 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 is provided in Table 3.

Acute Toxicity

Sprague-Dawley rats (5/sex/dose) were administered *p*-ethyltoluene at doses of 3000, 4000, 5000 or 6000 mg/kg-bw via gavage and observed for 14 days. Mortality occurred at all doses.

LD₅₀ = 4850 mg/kg-bw

Acute Inhalation Toxicity

Sprague-Dawley rats (5/sex/group) were exposed to *p*-ethyltoluene by inhalation to average measured concentrations of 1960 or 3900 ppm (approximately 9.6 or 19 mg/L) for 6 hours and observed for 14 days. No mortality was reported at either concentration level.

LC₅₀ > 19 mg/L

Acute Dermal Toxicity

New Zealand White rabbits (5/sex) were administered *p*-ethyltoluene dermally to clipped, intact (3/sex) or abraded (2/sex) skin at 5000 mg/kg-bw. The material remained in contact with the skin under occluded conditions for 24 hours and animals were observed for 14 days. No mortalities were observed.

LD₅₀ > 5000 mg/kg-bw

Repeated-Dose Toxicity

(1) In a 13-week oral repeated-dose study, Fischer 344 rats (20/sex/dose) were administered *p*-ethyltoluene via gavage in olive oil at doses of 0, 100, 300 or 900 mg/kg-bw/day for 94 days. Hematological, clinical chemistry and urinalysis parameters were examined at weeks 5 and 13. A comprehensive set of tissues and organs from control and high-dose rats were examined microscopically. Histopathological examinations of the low- and mid-dose rats were restricted to the liver, kidney and testes. Mortalities were reported only in males and females at the mid- and high-doses. Statistically significant ($p < 0.05$) decreases in body weights were observed in males at 300 and 900 mg/kg-bw/day. Increases in absolute liver weight were statistically significant ($p < 0.05$) at doses ≥ 100 mg/kg-bw/day in females and 900 mg/kg-bw/day in males. Relative liver weight was significantly ($p < 0.05$) increased at doses ≥ 100 mg/kg-bw/day in both sexes. Increases in alanine aminotransferase and alkaline phosphatase activities (indicative of liver toxicity) and albumin were observed in mid- and high-dose males at week 5 and high-dose males at week 13. Markedly lower mean platelet counts were observed in high-dose males during week 5 and for mid- and high-dose males and low- and mid-dose females during week 13. Reductions in total cholesterol and glucose levels were observed in mid- and high-dose males at weeks 5 and 13. Reductions in absolute and relative testes/epididymides weight were observed in males at 300 and 900 mg/kg-bw/day. At the high-dose, 14 of 20 males exhibited testicular atrophy and decreased spermatogenesis, compared with 1/20 control male rats. Sperm were also decreased or absent from the epididymides in these animals. Eight of these high-dose animals

also had sperm granulomas and four had atrophy of the seminal vesicles. Testes from 100 and 300 mg/kg-bw/day male rats were similar to controls, with the exception that 2 of 20 rats treated with 300 mg/kg-bw/day showed minimal hypospermatogenesis. No exposure-related increases in histopathologic lesions were found in other tissues in exposed male rats, compared with controls. There were no exposure-related changes in the reproductive organs or other tissues of exposed female rats, compared with controls.

LOAEL = 300 mg/kg-bw/day (based on mortality and changes in body weight, organ weights, biochemical and hematological parameters)

NOAEL = 100 mg/kg-bw/day

(2) In a 13-week repeated-dose study, Fischer 344 rats (15/sex/concentration) were exposed to *p*-ethyltoluene via inhalation at nominal concentrations of 0, 100, 300 or 1000 ppm for 6 hours/day, 5 days/week. Measured concentrations were 0, 104, 305 and 979 ppm (or approximately 0.5, 1.5 or 4.8 mg/L/day). Hematological, clinical chemistry and urinalysis parameters were examined at weeks 5 and 13. A comprehensive set of tissues and organs from the control and high-concentration rats were examined microscopically. No treatment-related mortalities were observed. Significant ($p < 0.05$) reduction of absolute gonad weight and significant ($p < 0.01$) increases in absolute liver weight in males and relative liver weight in males and females were observed in the high exposure group. No other exposure-related effects were found on hematological, blood chemistry, organ weight, urinalysis, ophthalmoscopic or histopathological endpoints.

LOAEL = 4.8 mg/L/day (based on changes in organ weights)

NOAEL = 1.5 mg/L/day

Reproductive Toxicity

The sponsor did not submit a reproductive toxicity test. Evaluation of effects on reproductive organs in the repeated-dose toxicity studies and the availability of a developmental toxicity study address the reproductive toxicity endpoint for the purposes of the HPV Challenge Program. In addition, the sponsor submitted a dominant lethal assay demonstrating effects on fertility.

(1) In the 13-week oral repeated-dose study in Fischer 344 rats described previously, exposure to *p*-ethyltoluene resulted in reductions in absolute and relative testes/epididymides weight in males at the mid- and high-dose (300 and 900 mg/kg-bw/day). At the mid-dose, two male animals had hypospermatogenesis. At the high-dose, 14 of 20 males exhibited testicular atrophy and decreased spermatogenesis; sperm were decreased or absent from the epididymides, and eight of these animals also had sperm granulomas and four had atrophy of the seminal vesicles. There were no changes in the reproductive organs of female animals.

(2) In the 13-week inhalation repeated-dose study in Fischer 344 rats described previously, exposure to *p*-ethyltoluene resulted in decreased absolute gonad weight in high-dose males. No treatment-related histopathological changes in male or female reproductive tissues were noted.

(3) In dominant lethal assay, male Sprague-Dawley rats (10/dose) were administered *p*-ethyltoluene via gavage at concentrations of 0.15, 0.5 or 1.5 mL/kg-bw/day once daily for 5 days. Three days after the last treatment, each male was mated with two virgin females per week for 7 weeks. Females were sacrificed 14 days after the midpoint of each mating period;

endpoints evaluated included fertility index, average number of implantations per pregnant female, pre-implantation losses per pregnant female, dead implants per pregnant female, proportion of pregnant females with one or more dead implants, dead implants per total implants and live implants per pregnant female. Positive and negative controls were tested concurrently and responded appropriately. At the high-dose, there was a significant ($p < 0.05$) increase in pre-implantation loss, but no treatment-related effects were observed on the number of dead or live implants per female. The lack of effects on fetal death endpoints indicated that no dominant lethal mutations were induced by *p*-ethyltoluene.

***p*-Ethyltoluene did not affect fertility in this assay.**

Developmental Toxicity

(1) In a prenatal developmental toxicity study, pregnant Charles River COBS CD rats (25/dose) were administered *p*-ethyltoluene via gavage in corn oil at 0, 25, 100 or 200 mg/kg-bw/day on days 6 through 19 of gestation. There were no effects on maternal body weight, appearance or behavior. The mean number of corpora lutea, total implantations, early resorptions, post-implantation loss, number of viable fetuses, fetal sex distribution and mean fetal body weights were comparable to controls in all groups. There were no differences in the number of litters with malformations or variations in any of the treated groups compared to controls.

NOAEL (maternal toxicity) = 200 mg/kg-bw/day

NOAEL (developmental toxicity) = 200 mg/kg-bw/day

(2) In a prenatal developmental toxicity study, pregnant Dutch Belted rabbits (16/dose) were administered *p*-ethyltoluene via gavage in corn oil at 0, 25, 125, 200 or 250 mg/kg-bw/day during days 6 through 27 of gestation. On gestation day 28, surviving rabbits were sacrificed and uterine contents were examined for a number of endpoints including visceral and skeletal malformations or variations in fetuses. Maternal mortality was increased in the high-dose group; the deaths in the control I (untreated), control II (vehicle), 25, 125, 200 and 250 mg/kg-bw/day groups were 2, 0, 1, 3, 0, and 12, respectively. No statistically significant ($p < 0.05$) differences in the mean number of corpora lutea, total implantations, early or late resorptions, post-implantation loss, number of viable fetuses, fetal sex ratio or mean fetal body weight were observed at 25, 125 or 200 mg/kg-bw/day when compared to the control groups or historical averages. No statistically significant ($p < 0.05$) differences were observed in the numbers of litters with malformations in the 25, 125 or 200 mg/kg-bw/day dose levels when compared to controls or historical averages. The number of fetuses (or litters) with variations was not statistically significantly altered in the 25 mg/kg-bw/day group compared with controls. However, in the 125 mg/kg-bw/day group, the number of fetuses with 13th full ribs exceeded the range of historical control values. The number of fetuses with 13th rudimentary rib at 200 mg/kg-bw/day also exceeded the range of historical control values. Due to the mortality-related decreased group size at 250 mg/kg-bw/day, meaningful comparisons could not be made for any developmental parameters evaluated.

LOAEL (maternal toxicity) = 250 mg/kg-bw/day (based on increased mortality)

NOAEL (maternal toxicity) = 200 mg/kg-bw/day

LOAEL (developmental toxicity) = 125 mg/kg-bw/day (based on increased number of fetuses with full 13th rib)

NOAEL (developmental toxicity) = 25 mg/kg-bw/day

Genetic Toxicity – Gene Mutation

In vitro

(1) *Salmonella typhimurium* strains TA98, TA100, TA1535, TA1537 and TA1538 were exposed to *p*-ethyltoluene at concentrations of 0.0035, 0.018, 0.09, 0.18 or 0.35 $\mu\text{L}/\text{plate}$ in the presence and absence of metabolic activation. Positive controls were tested concurrently and responded appropriately. The cytotoxic concentration was 0.29 $\mu\text{L}/\text{plate}$ for strain TA100 without metabolic activation.

***p*-Ethyltoluene was not mutagenic in this assay.**

(2) L5178Y mouse lymphoma cells were exposed to *p*-ethyltoluene at concentrations of 0.0042 – 0.056 $\mu\text{L}/\text{mL}$ in the absence of metabolic activation or 0.0075 – 0.1 $\mu\text{L}/\text{mL}$ in the presence of metabolic activation and examined for mutation induction at the thymidine kinase (TK) locus. Positive controls were tested concurrently and responded appropriately, but marked cell toxicity was observed at all concentrations of the test material.

***p*-Ethyltoluene was not mutagenic in this assay.**

In vivo

Drosophila melanogaster were exposed to *p*-ethyltoluene via inhalation for 30 minutes (adult flies) or 40 minutes (larvae) at a concentration of 0.05 mL per half-pint bottle. All flies were anesthetized during the exposure period and about one-third died. Positive controls were tested concurrently and responded appropriately.

***p*-Ethyltoluene was not mutagenic in this assay.**

Genetic Toxicity – Chromosomal Aberrations

EPA evaluated all of the submitter's genotoxicity study summaries (including those that the submitter described as not reviewed) and based on a weight-of-evidence approach concluded that the data are adequate for both gene mutations and chromosomal aberrations.

Genetic Toxicity – Other

In vitro

In a mitotic recombination assay, *Saccharomyces cerevisiae* strain D5 were exposed to *p*-ethyltoluene at concentrations of 0.020, 0.039, 0.078, 0.156 or 0.312 μL per 3 mL in the presence and absence of metabolic activation. Positive and negative controls were tested concurrently and responded appropriately. The cytotoxic concentration was 0.312 μL per 3 mL.

***p*-Ethyltoluene did not induce mitotic recombination in this assay.**

In vivo

(1) In an unscheduled DNA synthesis assay, male Sprague-Dawley rats (4/dose, 2/control) were administered *p*-ethyltoluene via gavage at concentrations of 500, 750, 1000, 1250 or 1700 mg/kg-bw. Two hours after dosing, hepatocytes were isolated by liver perfusion, cultured and evaluated for unscheduled DNA synthesis. Positive and negative controls were tested concurrently and responded appropriately. A significant overall increase ($p < 0.05$) in

unscheduled DNA synthesis was evident at doses up to 1000 mg/kg-bw. At higher doses, unscheduled DNA synthesis was diminished, possibly as a result of cytotoxicity.

***p*-Ethyltoluene induced unscheduled DNA synthesis in this assay.**

(2) Male Swiss Webster mice (5/dose) were administered *p*-ethyltoluene (in Methocel K4M vehicle) via gavage at concentrations of 750, 1000 or 1250 mg/kg-bw. Positive and negative controls were tested concurrently and responded appropriately. No detectable cell cycle delay or increase in sister chromatid exchanges was observed.

***p*-Ethyltoluene did not induce sister chromatid exchange in this assay.**

(3) Male Sprague-Dawley rats (10/dose) were administered *p*-ethyltoluene via gavage at concentrations of 0.15, 0.5 or 1.5 mL/kg-bw/day once daily for 5 days. Three days after the last treatment, each male was mated with two virgin females per week for 7 weeks. Females were sacrificed 14 days after the midpoint of each mating period; endpoints evaluated included fertility index, average number of implantations per pregnant female, pre-implantation losses per pregnant female, dead implants per pregnant female, proportion of pregnant females with one or more dead implants, dead implants per total implants and live implants per pregnant female. Positive and negative controls were tested concurrently and responded appropriately. At the high-dose, there was a significant ($p < 0.05$) increase in pre-implantation loss, but no treatment-related effects were observed on the number of dead or live implants per female. The lack of effects on fetal death endpoints indicated that no dominant lethal mutations were induced by *p*-ethyltoluene.

***p*-Ethyltoluene did not induce dominant lethal effects in this assay.**

Additional Information

Skin Irritation

p-Ethyltoluene (0.5 mL) was applied to the intact and abraded skin of six New Zealand White rabbits (sex not specified) for 24 hours under occluded conditions and assessed for up to 72 hours after exposure. No deaths or clinical signs were observed. The combined erythema and edema average score at 24 hours for both intact skin and abraded skin was 2.17 (highest possible score = 4). At 72 hours, the combined average erythema and edema scores for intact skin and abraded skin were 1.67 and 2.50, respectively. The primary dermal irritation index was 2.13.

***p*-Ethyltoluene was moderately irritating to rabbit skin in this assay.**

Eye Irritation

p-Ethyltoluene (0.1 mL) was instilled into the conjunctival sac of one eye of six New Zealand White rabbits and the animals were observed for 168 hours. *p*-Ethyltoluene caused moderate chemical conjunctivitis. Redness of the conjunctivae decreased in severity, but was still evident at day 7. The cornea and iris were normal throughout the observation period.

***p*-Ethyltoluene was moderately irritating to rabbit eyes in this assay.**

Conclusion: The acute oral and inhalation toxicity of this chemical to rats, and the acute dermal toxicity to rabbits are low. Repeated-dose subchronic toxicity studies of this chemical in rats via

the oral route showed effects on mortality, body weight, organ weights, clinical chemistry and hematological parameters at 300 mg/kg/day; the NOAEL for systemic toxicity was 100 mg/kg/day. Repeated-dose subchronic toxicity studies of this chemical in rats via inhalation showed significant changes in liver and gonad weights at 4.8 mg/L/day; the NOAEL was 1.5 mg/L/day. No reproductive toxicity studies of this chemical are available. Evaluation of effects on reproductive organs in the repeated-dose subchronic toxicity studies showed testicular atrophy and decreased spermatogenesis at 300 mg/kg/day. An oral prenatal developmental toxicity study of this chemical in rabbits showed mortality in the dams at 250 mg/kg/day; the NOAEL for maternal toxicity was 200 mg/kg/day. In this study, there was developmental toxicity at 125 mg/kg/day as demonstrated by increased number of fetuses with 13th rib; the NOAEL for developmental toxicity was 25 mg/kg/day. This chemical was not mutagenic in bacterial or mammalian cells *in vitro*. It did not induce mitotic recombination in yeast *in vitro*, sister chromatid exchanges in bone marrow of mice or dominant lethal effects in rats *in vivo*, but induced unscheduled DNA synthesis in rat hepatocytes. This chemical was irritating to rabbit eyes and skin.

4 Hazards to the Environment

There were no data submitted to address the acute aquatic toxicity of *p*-ethyltoluene. The sponsor has proposed testing. Based on its structural and toxicological similarity to the sponsored chemical, EPA concluded that the analog, mixed diethylbenzenes (CASRN 25340-17-4) adequately addresses the acute ecotoxicity endpoints for the purposes of the HPV Challenge Program. Aquatic toxicity values were also estimated using ECOSAR v.1.00a to support the evaluation of the acute toxicity of *p*-ethyltoluene. A summary of aquatic toxicity data on mixed diethylbenzenes (CASRN 25340-17-4) and estimated using ECOSAR v.1.00a is provided in Table 3.

Acute Toxicity to Fish

Diethylbenzene Blend (CASRN 25340-17-4, supporting chemical)

Rainbow trout (*Oncorhynchus mykiss*) were exposed to diethylbenzene blend at nominal concentrations of 0 (control), 0 (vehicle control; 0.1 mL/L acetone), 0.50, 1.0, 2.0, 4.0 and 8.0 mg/L under static conditions using closed system for 96 hours. The measured concentrations were <0.0790 (control), <0.0790 (vehicle control), 0.308, 0.675, 1.17, 1.64 and 2.47 mg/L. The 96-h LC₅₀ was based on mean measured concentrations.

96-h LC₅₀ = 0.673 mg/L (measured)

96-h LC₅₀ = 3.78 mg/L (estimated)

Acute Toxicity to Aquatic Invertebrates

Diethylbenzene Blend (CASRN 25340-17-4, supporting chemical)

Daphnia magna were exposed to diethylbenzene blend at nominal test concentrations of 0 (control), 0 (vehicle control; 0.1 mL/L acetone), 0.50, 1.0, 2.0, 4.0, and 8.0 mg/L under static renewal conditions using closed system for 48 hours. The measured concentrations were <0.0790 (control), <0.0790 (vehicle control), 0.374, 0.665, 1.07, 1.97 and 2.70 mg/L. The 48-h EC₅₀ was based on mean measured concentrations.

48-h EC₅₀ = 2.01 mg/L (measured)

48-h EC₅₀ = 2.69 mg/L (estimated)

Toxicity to Aquatic Plants

Diethylbenzene Blend (CASRN 25340-17-4, supporting chemical)

Green algae (*Pseudokirchneriella subcapitata*) was exposed to diethylbenzene blend at nominal concentrations of 0 (control), 0 (vehicle control; 0.1 mL/L acetone), 0.50, 1.0, 2.0, 4.0, and 8.0 mg/L under static conditions for 72 hours. The measured concentrations were <0.0702 (control), <0.0702 (vehicle control), 0.292, 0.547, 1.14, 2.27 and 3.35 mg/L.

72-hr EC₅₀ (growth) = 1.21 mg/L (measured)

72-hr EC₅₀ (biomass) = 1.00 mg/L (measured)

96-h EC₅₀ = 2.54 mg/L (estimated)

Conclusion: The measured aquatic toxicity values for p-ethyltoluene are based on the analog mixed diethylbenzenes (CASRN 25340-17-4). The 96-hour LC₅₀ of CASRN 25340-17-4 to fish is 0.673 mg/L, the 48-hour EC₅₀ to aquatic invertebrates is 2.01 mg/L, and the 72-hour EC₅₀ to aquatic plants is 1.21 mg/L (growth) and 1.00 mg/L (biomass).

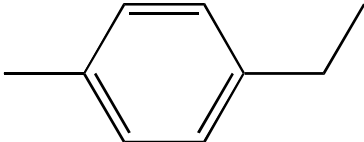
Table 3. Summary Table of the Screening Information Data Set as Submitted under the U.S. HPV Challenge Program	
Endpoints	SPONSORED CHEMICAL <i>p</i>-Ethyltoluene (CASRN 622-96-8)
Structure	
Summary of Human Health Data	
Acute Oral Toxicity LD₅₀ (mg/kg-bw)	4850
Acute Inhalation Toxicity LC₅₀ (mg/L)	> 19
Acute Dermal Toxicity LD₅₀ (mg/kg-bw)	> 5000
Repeated-Dose Toxicity NOAEL/LOAEL Oral (mg/kg-bw/day)	(rat) LOAEL = 300 NOAEL = 100
Repeated-Dose Toxicity NOAEL/LOAEL Inhalation (mg/L/day)	(rat) LOAEL = 4.8 NOAEL = 1.5
Reproductive Toxicity NOAEL/LOAEL Oral (mg/kg-bw/day)	The evaluation of reproductive organs in the 13-week oral study showed testicular atrophy and decreased spermatogenesis with decreased or absent sperm: no effects were observed in females.
Reproductive Toxicity NOAEL/LOAEL Inhalation (mg/L/day)	The evaluation of reproductive organs in the 13-week inhalation study showed decreased absolute gonad weight: no treatment-related histopathological effects were observed.

Table 3. Summary Table of the Screening Information Data Set as Submitted under the U.S. HPV Challenge Program	
Endpoints	SPONSORED CHEMICAL <i>p</i>-Ethyltoluene (CASRN 622-96-8)
Developmental Toxicity NOAEL/LOAL Oral (mg/kg-bw/day) <div style="text-align: right;">Maternal Toxicity</div> <div style="text-align: right;">Developmental Toxicity</div> <div style="text-align: right;">Maternal & Developmental Toxicity</div>	 (rabbit) LOAEL = 250 NOAEL = 200 LOAEL = 125 NOAEL = 25 (rat) NOAEL = 200
Genetic Toxicity – Gene Mutation <i>In vitro</i>	Negative
Genetic Toxicity – Gene Mutation <i>In vivo</i>	Negative
Genetic Toxicity – Other <i>In vitro</i> Mitotic Recombination Assay	Negative
Genetic Toxicity – Other <i>In vivo</i> Sister Chromatid Exchange	Negative
Genetic Toxicity – Other <i>In vivo</i> Unscheduled DNA Synthesis	Positive
Genetic Toxicity – Other <i>In vivo</i> Dominant Lethal Assay	Negative
Additional Information Skin Irritation Eye Irritation	Moderately irritating Moderately irritating
Summary of Environmental Effects – Aquatic Toxicity Data*	
Fish 96-h LC₅₀ (mg/L)	0.673 (m) ¹ 3.78 (e) ²
Aquatic Invertebrates 48-h EC₅₀ (mg/L)	2.01 (m) ¹ 2.69 (e) ²

Table 3. Summary Table of the Screening Information Data Set as Submitted under the U.S. HPV Challenge Program	
Endpoints	SPONSORED CHEMICAL <i>p</i>-Ethyltoluene (CASRN 622-96-8)
Aquatic Plants	
72-hr EC₅₀ (growth)	1.21(m) ¹
72-hr EC₅₀ (biomass)	1.00 (m) ¹
96-h EC₅₀ (mg/L) (growth)	2.54 (e) ²

* - measured data are for analog substance, mixed diethylbenzenes (CASRN 25340-17-4)

¹m or bold: measured;

²e: estimated