SCREENING-LEVEL HAZARD CHARACTERIZATION

Diisopropylbenzene Category

***m*-Diisopropylbenzene**	**CASRN 99-62-7**
***p*-Diisopropylbenzene**	**CASRN 100-18-5**
Mixed diisopropylbenzene isomers	**CASRN 25321-09-9**

The High Production Volume (HPV) Challenge Program[1] 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.

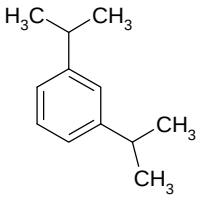
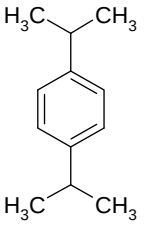
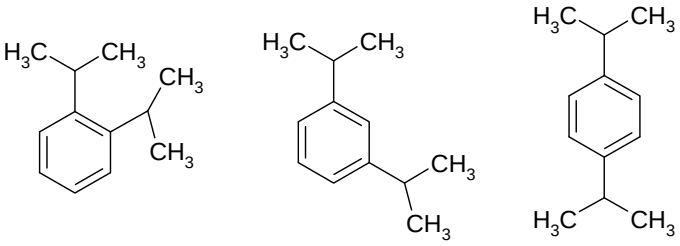
The evaluation is performed according to established EPA guidance[2,3] and is based primarily on hazard data provided by sponsors; however, in preparing the hazard characterization, EPA considered its own comments and public comments on the original submission as well as the sponsor's responses to comments 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

[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.

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.

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)	**99-62-7** **100-18-5** **25321-09-9**
Chemical Abstract Index Name	**Benzene, 1,3-bis(1-methylethyl)-** **Benzene, 1,4-bis(1-methylethyl)-** **Benzene, bis(1-methylethyl)-**
Structural Formula	 **CASRN 99-62-7**
	 **CASRN 100-18-5**
	 **CASRN 25321-09-9** Representative structures showing the ortho, meta, and para isomers of Benzene, bis(1-methylethyl)-

Summary

The diisopropylbenzenes are clear, colorless liquids with moderate water solubility and moderate vapor pressure. The diisopropylbenzenes are expected to have moderate mobility in soil. Volatilization of the diisopropylbenzenes is considered high based on their Henry's Law constants. The rate of hydrolysis is negligible. The rate of atmospheric photooxidation is considered moderate. The diisopropylbenzenes are expected to have moderate persistence (P2) and moderate bioaccumulation potential (B2).

The acute oral toxicity of CASRNs 99-62-7, 100-18-5 and 2532-09-9 in rats is low. The acute inhalation toxicity of CASRN 2532-09-9 in rats is moderate and the acute dermal toxicity of CASRN 2532-09-9 in rabbits is low. A 28-day oral repeated-dose toxicity study in rats with CASRN 99-62-7 showed a dose-dependent increase in gastric irritation (hyperkeratosis, edema and focal necrosis) in the non-glandular region, beginning at 100 mg/kg-bw/day (lowest dose tested); the NOAEL for systemic toxicity is not established. A 28-day oral repeated-dose toxicity study in rats with CASRN 25321-09-9 showed increased relative and absolute liver weight, hepatocyte hypertrophy, and blood chemistry changes at 750 mg/kg-bw/day; the NOAEL for systemic toxicity is 150 mg/kg-bw/day. A combined reproductive/developmental toxicity screening study in rats with CASRN 25321-09-9 showed no treatment related effects on any of the reproductive and developmental parameters; the NOAEL for reproductive, maternal and developmental toxicity is 750 mg/kg-bw/day (highest dose tested). CASRN 25321-09-9 was not mutagenic in bacteria and did not induce chromosomal aberrations in mammalian cells *in vitro*. CASRN 25321-09-9 is irritating to rabbit skin and eyes.

OECD SIDS acute toxicity data were available for fish, aquatic invertebrates, and aquatic plants, however, the toxicity results were above the water solubility limit of the substance (*m*-; 0.072 mg/L and *p*-; 0.0405 mg/L). The chronic 21-d Daphnia ChV is 0.220 mg/L. The chronic 21-d Daphnia ChV is 0.220 mg/L.

No data gaps were identified under the HPV Challenge Program.

The sponsor, the Hydroquinone Precursors and Derivatives Panel DIPB Task Force of the American Chemistry Council, submitted a Test Plan and Robust Summaries to EPA for the Diisopropyl Benzenes category on November 14, 2002. EPA posted the submission on the ChemRTK HPV Challenge website on December 4, 2002 (http://www.epa.gov/oppt/chemrtk/pubs/summaries/diprplbz/c14072tc.htm). EPA comments on the original submission were posted to the website on April 8, 2003. Public comments were also received and posted to the website. The sponsor submitted updated/revised documents on September 29, 2003, which were posted to the ChemRTK website on November 5, 2003.

Category Justification

In the original and revised test plans, the sponsor proposed the diisopropyl benzenes category consisting of *m*-diisopropylbenzene (mDIPB) (>95% purity), *p*-diisopropylbenzene (pDIPB) (>99% purity) and mixed diisopropylbenzene isomers (xDIPB) typically containing an average of 2.4, 55.8 and 34.5% of the *ortho*-, *meta*-, and *para*- diisopropylbenzene isomers, respectively. The sponsor justified the chemical grouping for this category based on similar structural, physicochemical, environmental fate and toxicological properties. In comments on the original test plan, EPA agreed that the sponsor adequately supported the chemicals grouped in the diisopropylbenzenes category and noted that measured and estimated properties for the individual and mixed isomers support this grouping for the majority of the SIDS-level endpoints.

CASRN 25321-09-9 was assessed in the OECD HPV program at SIAM 15 (2002). The data are available for review at the following link: http://www.chem.unep.ch/irptc/sids/OECDSIDS/DIISOPROPYLBENZ.pdf.

Justification for Supporting Chemicals

The sponsor provided data using the following supporting chemicals for reproductive and developmental toxicity endpoints:

Isopropylbenzene (cumene)	CASRN 98-82-8
Ethylbenzene	CASRN 100-41-4
o-Diethylbenzene	CASRN 135-01-3
m-Diethylbenzene	CASRN 141-93-5
p-Diethylbenzene	CASRN 105-05-5

EPA agreed that the supporting chemicals were appropriate for read-across to the category members; however, because a full SIDS data set is available for one of the category members, EPA has not used supporting chemical data in the preparation of this hazard characterization.

1. Chemical Identity

1.1 Identification and Purity

In the diisopropylbenzenes category, the pure isomers (CASRN 99-62-7 and CASRN 100-18-5) are industrial intermediates in the synthesis of other chemicals. The commercial mixture CASRN

25340-17-4 is primarily a raw material for chemical manufacture and is also used as a component in an industrial cleaning formulation.

The following is an excerpt from the Test Plan:

In general, the individual meta- and para-isomers are quite pure when sold. The purity of CASRN 99-62-7 is >95% and CASRN 100-18-5 is >99%, with the primary contaminants consisting of various other diisopropylbenzene isomers. The mixed isomer category member, CASRN 25340-17-4, typically contains an average of 2.4%, 55.8%, and 34.5% of the respective *ortho-, meta-,* and *para* isomers and may contain small amounts of cumene and other aromatic hydrocarbon impurities. They are all manufactured and transported in closed systems and have a very limited number of customers who also handle them in closed systems.

1.2 Physical-Chemical Properties

The compounds of the diisopropylbenzenes category are clear, colorless liquids with moderate water solubility and moderate vapor pressure.

The physical-chemical properties of are summarized in Table 1.

Table 1. Physical-Chemical Properties of the Monoesters of the Diisopropyl Benzenes Category[1]

Property	Benzene, 1,3-bis(1-methylethyl)- Value	Benzene, 1,4-bis(1-methylethyl)- Value	Benzene, bis(1-methylethyl)- Value
CASRN	99-62-7	100-18-5	25321-09-9
Molecular Weight	162.28	162.28	162.28
Physical State	Liquid	Liquid	Liquid
Melting Point	-61°C (measured)	-17.1°C (measured)	-40°C (measured)[2]
Boiling Point	203.2°C (measured)	210.3°C (measured)	205°C (measured)
Vapor Pressure	1 mm Hg at 34.7°C (measured) 0.393 mm Hg at 25°C (measured)[2]	1 mm Hg at 40.0°C (measured) 0.246 mm Hg at 25°C (measured)[2]	0.25–0.39 mm Hg at 25°C (measured)
Water Solubility	7.01 mg/L at 25–30°C (measured)	3.0 mg/L (measured)	4.325 mg/L at 25°C (estimated)
Dissociation Constant (pK_a)	Not applicable	Not applicable	Not applicable
Henry's Law Constant	2.8×10^{-2} atm-m^3/mole (estimated)[3]	2.8×10^{-2} atm-m^3/mole (estimated)[3]	2.8×10^{-2} atm-m^3/mole (estimated)[3]

Table 1. Physical-Chemical Properties of the Monoesters of the Diisopropyl Benzenes Category[1]			
	Benzene, 1,3-bis(1-methylethyl)-	**Benzene, 1,4-bis(1-methylethyl)-**	**Benzene, bis(1-methylethyl)-**
Property	**Value**	**Value**	**Value**
Log K_{ow}	4.9 (estimated)	4.9 (estimated)	4.1 (measured)[2]

[1] American Chemistry Council's Hydroquinone Precursors and Derivatives Panel, Diisopropylbenzene Task Force. 2003. Revised Robust Summary and Test Plan for Diisopropylbenzene Category. Available online at http://www.epa.gov/chemrtk/pubs/summaries/diprplbz/c14072tc.htm as of November 5, 2003.
[2] SRC. 2010. The Physical Properties Database (PHYSPROP). SRC: Syracuse, NY. Available online at http://www.srcinc.com/what-we-do/free-demos.aspx as of July 5, 2010.
[3] U.S. EPA. 2010. Estimation Programs Interface Suite™ for Microsoft® Windows, v4.00. U.S. Environmental Protection Agency, Washington, DC, USA. Available online at http://www.epa.gov/opptintr/exposure/pubs/episuitedl.htm as of July 5, 2010.

2. General Information on Exposure

2.1 Production Volume and Use

The diisopropylbenzenes category chemicals had an aggregated production and/or import volume in the United States between 61 million pounds and 160 million pounds in calendar year 2005.

- CASRN 99-62-7: 1 to <10 million pounds;
- CASRN 100-18-5: 50 to <100 million pounds;
- CASRN 2532-10-9: 10 to <50 million pounds;

CASRN 99-62-7 and 100-18-5:
Non-confidential information in the IUR indicated that the industrial processing and uses of the chemicals include other basic organic chemical manufacturing as intermediates. No commercial and consumer uses were reported.

CASRN 2532-10-9:
Non-confidential information in the IUR indicated that the industrial processing and uses of the chemical include petrochemical manufacturing as fuels. Non-confidential commercial and consumer uses of this chemical include lubricants, greases and fuel additives.

2.2 Environmental Exposure and Fate

The diisopropylbenzenes are expected to have moderate mobility in soil. Benzene, 1,4-bis(1-methylethyl)- (CASRN 100-18-5) achieved 0% of its theoretical biochemical oxygen demand over the course of a 21-day incubation period using an activated sludge inoculum and the modified MITI test (OECD 301C). A mixture of isomers, benzene, bis(1-methylethyl)- (CASRN 25321-09-9) was determined to be not readily biodegradable, achieving 2% of its theoretical biochemical oxygen demand over the course of a 21-day incubation period in a second MITI test (OECD 301C). Volatilization of the diisopropylbenzenes is considered high based on their Henry's Law constants. The diisopropylbenzenes are not expected to undergo hydrolysis. The

diisopropylbenzenes are expected to have moderate persistence (P2) and moderate bioaccumulation potential (B2).

Table 2. Environmental Fate Characteristics of the Diisopropyl Benzenes Category

Property	Benzene, 1,3-bis(1-methylethyl)-	Benzene, 1,4-bis(1-methylethyl)-	Benzene, bis(1-methylethyl)-
CASRN	99-62-7	100-18-5	25321-09-9
Photodegradation Half-life	8.3 hours (estimated)[1]	12.7 hours (estimated)[1]	8.3–12.7 hours (estimated)[1]
Hydrolysis Half-life	Stable	Stable	Stable
Biodegradation	0% after 21 days (based on data for Benzene, 1,4-bis(1-methylethyl)-) (Not readily biodegradable)[2]	No data	2% degradation by BOD and 0% degradation by gas chromatography after 21 days (Not readily biodegradable)[2]
Bioaccumulation Factor	BAF = 1,300 (estimated)[1]	BAF = 1,400 (estimated)[1]	1,300–1,400 (estimated)[1]
Log K_{oc}	3.5 (estimated)[1]	3.5 (estimated)[1]	3.5 (estimated)[1]
Fugacity (Level III Model)[1]			
Air (%)	5.2	7.1	5.2–7.1
Water (%)	26.8	26.3	26.3–26.8
Soil (%)	62.9	61.7	61.7–62.9
Sediment (%)	5.1	5.0	5.0–5.1
Persistence[3]	P2 (moderate)	P2 (moderate)	P2 (moderate)
Bioaccumulation[3]	B2 (moderate)	B2 (moderate)	B2 (moderate)

[1] U.S. EPA. 2010. Estimation Programs Interface Suite™ for Microsoft® Windows, v4.00. U.S. Environmental Protection Agency, Washington, DC, USA. Available online at http://www.epa.gov/opptintr/exposure/pubs/episuitedl.htm as of July 5, 2010.

[2] American Chemistry Council's Hydroquinone Precursors and Derivatives Panel, Diisopropylbenzene Task Force. 2003. Revised Robust Summary and Test Plan for Diisopropylbenzene Category. Available online at http://www.epa.gov/chemrtk/pubs/summaries/diprplbz/c14072tc.htm as of November 5, 2003.

[3] Federal Register. 1999. Category for Persistent, Bioaccumulative, and Toxic New Chemical Substances. *Federal Register* 64, Number 213 (November 4, 1999) pp. 60194–60204.

Conclusion: The diisopropylbenzenes are clear, colorless liquids with moderate water solubility and moderate vapor pressure. The diisopropylbenzenes are expected to have moderate mobility in soil. Volatilization of the diisopropylbenzenes is considered high based on their Henry's Law constants. The rate of hydrolysis is negligible. The rate of atmospheric photooxidation is considered moderate. The diisopropylbenzenes are expected to have moderate persistence (P2) and moderate bioaccumulation potential (B2).

3. Human Health Hazard

A summary of health effects data submitted for SIDS endpoints is provided in Table 4. The table also indicates where data for tested category members are read-across (RA) to untested members of the category.

Acute Oral Toxicity

***m*-Diisopropylbenzene (CASRN 99-62-7)**
Sprague-Dawley rats (5/sex/dose) were administered *m*-diisopropylbenzene (95.2% purity) via oral gavage at 0, 1250, 2500 or 5000 mg/kg-bw and observed for 14 days following dosing. No mortalities were observed.
LD_{50} > 5000 mg/kg-bw

***p*-Diisopropylbenzene (CASRN 100-18-5)**
Rats (4/sex/dose, strain not specified) were administered *p*-diisopropylbenzene (99.6% purity) via oral gavage at 0, 1600 or 3200 mg/kg-bw and observed for 14 days following dosing. No mortalities were observed.
LD_{50} > 3200 mg/kg-bw

Mixed diisopropylbenzene isomers (CASRN 25321-09-9)
Sprague-Dawley albino rats (5/dose, 2 – 3 males and females) were administered mixed diisopropylbenzene isomers via oral gavage at 0, 3160, 3980, 5010 or 6310 mg/kg-bw and observed for 14 days following dosing. Mortalities were observed at doses 3980 (3/5), 5010 (3/5) and 6310 (5/5) mg/kg-bw.
LD_{50} = 3900 mg/kg-bw

Acute Inhalation Toxicity

Mixed diisopropylbenzene isomers (CASRN 25321-09-9)
In an acute inhalation toxicity study, six male Sprague-Dawley rats were exposed (experimental details not provided) to mixed diisopropylbenzene isomers at 2.1 mg/L for 6 hours and observed for 14 days after exposure. No mortalities were observed. (TSCATS OTS0545756)
LC_{50} > 2.1 mg/L

Acute Dermal Toxicity

Mixed diisopropylbenzene isomers (CASRN 25321-09-9)
New Zealand albino rabbits were exposed via the skin (experimental details not provided) to mixed diisopropylbenzene isomers at doses of 1000, 2000, 3160, 5010, and 7940 mg/kg-bw for 24 hours and observed for 14 days. Mortality occurred at the 2 highest doses (1 female at each dose). (TSCATS OTS0545756)
LD_{50} > 3160 mg/kg-bw

Repeated-Dose Toxicity

m-Diisopropylbenzene (CASRN 99-62-7)

Sprague-Dawley rats (5/sex/dose) were administered *m*-diisopropylbenzene (95.2% purity) in water via oral gavage at 0, 100, 300 or 1000 mg/kg-bw/day for 29 days (21 doses administered over 29 days). Organ weights were evaluated only for liver and kidney, although microscopic examinations were conducted on comprehensive tissues. No treatment-related effects were noted on body weight or feed consumption or on other hematological or clinical chemistry parameters. Excessive salivation was noted at 1000 mg/kg-bw/day in a few animals on days 27 and 28 of dosing. Gastric irritation (hyperkeratosis) was noted in the non-glandular region at all doses with increasing incidence and severity, but no histopathology is mentioned. Hyaline droplet formation was observed in the renal proximal tubules of male rats at 100, 300 or 1000 mg/kg-bw/day. The robust summary did not provide any information on whether alpha 2μ-globulin was measured[4]. At 300 mg/kg-bw increased relative liver weight occurred in both sexes and was significant in females. One male had enlarged hepatocytes. Effects in the 1000 mg/kg-bw/day (highest dose) group included a small but significant decrease in serum glucose and an increase in serum creatinine levels of males, increased absolute liver weights in males and relative weights in both sexes (significance not indicated), and hepatocyte hypertrophy in all males.
LOAEL = 100 mg/kg-bw/day (based on gastric irritation and male kidney effects)
NOAEL = Not established

Mixed diisopropylbenzene isomers (CASRN 25321-09-9)

Sprague-Dawley rats (12/sex/dose control and high dose; 6/sex/dose other doses) were administered mixed diisopropylbenzene isomers (99.8% purity) in corn oil via oral gavage at 0, 6, 30, 150 or 750 mg/kg-bw/day for 28 days. In the control and high-dose groups, animals were followed for a 14-day post-treatment recovery period. No effects were observed at 6 and 30 mg/kg-bw/day; however, a complete list of the outcome measures assessed was not provided. Mydriasis (dilated pupils) was observed in both sexes at 150 (2 males and 2 females) and 750 (10 males and 12 females) mg/kg-bw/day. Blood chemistry effects at 750 mg/kg-bw/day included decreased serum chloride in both sexes, increased potassium in males and increased total protein, total cholesterol and phospholipids in females. Relative and absolute liver weight was significantly increased (~20%) in both sexes and kidney weight in males was significantly increased (~11%) at 750 mg/kg-bw/day. In males, absolute spleen weight was significantly decreased, but relative spleen weight was significantly increased. Histopathological analysis revealed significant centrilobular hypertrophy of hepatocytes in both sexes. An increase in eosinophilic bodies in the renal proximal tubules of males occurred at 750 mg/kg-bw/day. Following the 14-day recovery period, no differences were observed between the control and 750 mg/kg-bw/day animals (only dose in recovery).
LOAEL = 750 mg/kg-bw/day (based on increased relative and absolute liver weight, hepatocyte hypertrophy, and blood chemistry changes)
NOAEL = 150 mg/kg-bw/day

[4] Nephropathy seen in male rats may be occurring by an alpha 2μ-globulin-mediated mechanism (which is male rat-specific and not considered relevant to humans). EPA's Risk Assessment Forum has outlined key events and data that are necessary to demonstrate this mode of action (Alpha 2μ-Globulin: Association with Chemically Induced Renal Toxicity and Neoplasia in the Rat, EPA/625/3-91/019F).

Reproductive/Developmental Toxicity

Mixed diisopropylbenzene isomers (CASRN 25321-09-9)
In a combined reproductive/developmental toxicity screening test [OECD TG 421], Sprague-Dawley rats (12/sex/dose) were administered mixed diisopropylbenzene isomers in corn oil via oral gavage at 0, 6, 30, 150 or 750 mg/kg-bw/day for 51-53 days in males and until lactation day 4 in females. No significant differences in body weight or food consumption were observed in males or females over the dosing period. At 750 mg/kg-bw/day, two males displayed bilateral exophthalmos, one female had mydriasis, and two females had vacuolization of the eye lens. Reproductive organs were weighed and histopathology was performed for reproductive organs and organs with abnormal gross pathology. There were no significant differences in absolute or relative ovary weights. No significant effects on sperm parameters were observed. No significant differences between the treated groups and controls were observed in estrus cycle, fertility and pregnancy, number of corpora lutea, implantation, lactation, litter size, sex ratio, litter weight, litter survival, or external observations.
NOAEL (reproductive toxicity) = 750 mg/kg-bw/day (highest dose tested)
NOAEL (maternal toxicity) = 750 mg/kg-bw/day (highest dose tested)
NOAEL (developmental toxicity) = 750 mg/kg-bw/day (highest dose tested)

Genetic Toxicity – Gene Mutation

In vitro
Mixed diisopropylbenzene isomers (CASRN 25321-09-9)
Salmonella typhimurium strains TA98, TA100, TA1535 and TA1537 and *Escherichia coli* strain WP2 uvrA were exposed to mixed diisopropylbenzene isomers (99.8% purity) in DMSO at concentrations up to 5000 µg/plate, with and without metabolic activation. Positive controls were included. No responses were induced in any of the tester strains. Cytotoxicity was observed at 6.25 µg/plate (TA1535, 1537) and 12.5 µg/plate (TA100, TA98), 5000 µg/plate (WP2 uvrA) without activation and at 100 µg/plate (TA100, TA1535, TA98, TA 1537) and 500µg /plate (WP2 uvrA) with activation.
Mixed diisopropylbenzene isomers was not mutagenic in this assay.

Genetic Toxicity – Chromosomal Aberrations

In vitro

Mixed diisopropylbenzene isomers (CASRN 25321-09-9)
Chinese hamster lung cells (CHL/IU) were exposed to mixed diisopropylbenzene isomers in the presence and absence of metabolic activation for 6, 24, or 48 hours at concentration from 0.0019 to 0.12 mg/mL. Severe cytotoxicity occurred at concentrations ≥ 0.015 mg/mL. Negative and positive controls were run, but the results were not given. Structural chromosomal aberrations or polyploidy were not seen under the experimental conditions.
Mixed diisopropylbenzene isomers did not induce chromosomal aberrations in this assay.

Additional Information

Skin Irritation

Mixed diisopropylbenzene isomers (CASRN 25321-09-9)
Five New Zealand Albino rabbits (sex unspecified) were administered 0.5 mL of undiluted mixed diisopropylbenzene isomers to the skin (24-hour exposure, conditions not specified). Animals were observed for 14 days following dosing. Severe skin irritation was observed, with skin sloughing off in 10 – 14 days following dosing. (TSCATS OTS0545756)
Mixed diisopropylbenzene isomers was highly irritating to rabbit skin in this study.

Eye Irritation

Mixed diisopropylbenzene isomers (CASRN 25321-09-9)
Six New Zealand Albino rabbits (sex unspecified) were administered 0.1 mL of undiluted mixed diisopropylbenzene isomers to the eye for 24 hours (conditions not specified). Animals were observed for 7 days following dosing. Mild to moderate conjunctival erythema, slight conjunctival edema and moderate to copious ocular discharge were observed. No effects to the iris or cornea were observed. (TSCATS OTS0545756)
Mixed diisopropylbenzene isomers was slightly irritating to rabbit eyes in this study.

Conclusion: The acute oral toxicity of CASRNs 99-62-7, 100-18-5 and 2532-09-9 in rats is low. The acute inhalation toxicity of CASRN 2532-09-9 in rats is moderate and the acute dermal toxicity of CASRN 2532-09-9 in rabbits is low. A 28-day oral repeated-dose toxicity study in rats with CASRN 99-62-7 showed a dose-dependent increase in gastric irritation (hyperkeratosis, edema and focal necrosis) in the non-glandular region, beginning at 100 mg/kg-bw/day (lowest dose tested); the NOAEL for systemic toxicity is not established. A 28-day oral repeated-dose toxicity study in rats with CASRN 25321-09-9 showed increased relative and absolute liver weight, hepatocyte hypertrophy, and blood chemistry changes at 750 mg/kg-bw/day; the NOAEL for systemic toxicity is 150 mg/kg-bw/day. A combined reproductive/developmental toxicity screening study in rats with CASRN 25321-09-9 showed no treatment related effects on any of the reproductive and developmental parameters; the NOAEL for reproductive, maternal and developmental toxicity is 750 mg/kg-bw/day (highest dose tested). CASRN 25321-09-9 was not mutagenic in bacteria and did not induce chromosomal aberrations in mammalian cells *in vitro*. CASRN 25321-09-9 is irritating to rabbit skin and eyes.

Table 4. Summary of the Screening Information Data Set as Submitted under the U.S. HPV Challenge Program – Human Health Data			
Endpoints	**SPONSORED CHEMICAL *m*-Diisopropylbenzene (99-62-7)**	**SPONSORED CHEMICAL *p*-Diisopropylbenzene (100-18-5)**	**SPONSORED CHEMICAL Mixed Diisopropyl-benzene (25321-09-9)**
Acute Oral Toxicity LD_{50} (mg/kg-bw)	**> 5000**	**> 3200**	**3900**
Acute Inhalation Toxicity LC_{50} (mg/L)	No Data > 2.1 (RA)	No Data > 2.1 (RA)	**> 2.1**
Acute Dermal Toxicity LD_{50} (mg/kg-bw)	No Data > 3160 (RA)	No Data > 3160 (RA)	**> 3160**
Repeated-Dose Toxicity NOAEL/LOAEL Oral (mg/kg-day)	**NOAEL = Not established** **LOAEL = 100**	No adequate data NOAEL= 150 LOAEL = 750 (RA)	**NOAEL = 150** **LOAEL = 750**
Reproductive Toxicity NOAEL/LOAEL Oral (mg/kg-day)	No Data NOAEL = 750 (RA)	No Data NOAEL = 750 (RA)	**NOAEL = 750** **(highest dose tested)**
Developmental Toxicity NOAEL/LOAEL Oral (mg/kg-day)			
Maternal Toxicity	No Data NOAEL = 750 (RA)	No Data NOAEL = 750 (RA)	**NOAEL = 750** **(highest dose tested)**
Developmental Toxicity	No Data NOAEL = 750 (RA)	No Data NOAEL = 750 (RA)	**NOAEL = 750** **(highest dose tested)**
Genetic Toxicity – Gene Mutation *In vitro*	No Data Negative (RA)	No Data Negative (RA)	**Negative**
Genetic Toxicity – Chromosomal Aberrations *In vitro*	No Data Negative (RA)	No Data Negative (RA)	**Negative**
Additional Information			
Skin irritation	–	–	**Highly irritating**
Eye irritation	–	–	**Slightly irritating**

Measured data in bold text; (RA) = Read Across; – indicates that endpoint was not assessed for this substance

4. Hazard to the Environment

A summary of aquatic toxicity data submitted for SIDS endpoints is provided in Table 4. Test data for CASRN 25321-09-9 were found in the OECD SIDS document (http://www.chem.unep.ch/irptc/sids/OECDSIDS/DIISOPROPYLBENZ.pdf).

Acute Toxicity to Fish and Aquatic Invertebrates and Toxicity to Aquatic Plants

OECD SIDS aquatic toxicity data were provided for these three endpoints, however, the toxicity results were above the water solubility limit of the substance (*m*-; 0.072 mg/L and *p*-; 0.0405 mg/L).

Chronic Toxicity to Aquatic Invertebrates

A 21-day *Daphnia magna* chronic toxicity test was conducted for CASRN 25321-09-9. The measured concentrations were control, solvent control, 0.009, 0.024, 0.063, 0.168, 0.431 mg/L. The NOEC was determined based on the cumulative number of juveniles produced per adult alive for 21 days.
21-d *Daphnia* ChV = 0.220 mg/L
21-d *Daphnia* NOEC = 0.063 mg/L

A 21-d ChV for *Daphnia* estimated by ECOSAR v 1.00a was used to support the chronic toxicity of CASRN 25321-09-9.
21-d *Daphnia* ChV = 0.055 mg/L

Conclusion: OECD SIDS acute toxicity data were available for fish, aquatic invertebrates, and aquatic plants, however, the toxicity results were above the water solubility limit of the substance (*m*-; 0.072 mg/L and *p*-; 0.0405 mg/L). The chronic 21-d Daphnia ChV is 0.220 mg/L.

Table 5. Summary Table of the Screening Information Data Set as Submitted under the U.S. HPV Challenge Program – Aquatic Toxicity Data

Endpoints	SPONSORED CHEMICAL *m*-Diisopropyl-benzene (99-62-7)	SPONSORED CHEMICAL *p*-Diisopropyl-benzene (100-18-5)	SPONSORED CHEMICAL Mixed diisopropyl-benzene (25321-09-9)
Fish 96-h LC_{50} (mg/L)	No adequate data*		
Aquatic Invertebrates 48-h EC_{50} (mg/L)	No adequate data*		
Aquatic Plants 72-h EC_{50} (mg/L)	No adequate data*		
Chronic Toxicity to Aquatic Invertebrates **21-d ChV (mg/L)** **21-day NOEC (mg/L)**	No Data 0.220 0.063 (RA)	No Data 0.220 0.063 (RA)	 **0.220** **0.063**

(m) = measured data (i.e., derived from testing); (RA) = Read Across; * the toxicity results were above the water solubility limit of the substance (*m*-; 0.072 mg/L and *p*-; 0.0405 mg/L).