Supporting Documents for Initial Risk-Based Prioritization of High Production Volume Chemicals

m-Diisopropenylbenezene (CASRN 3748-13-8) (9th CI and CA Index Name: Benzene, 1,3-bis(1-methylethenyl)-)

Contents:

BACKGROUND

Screening-level hazard, exposure and risk characterizations for high production volume chemicals (HPV) are important contributions to the chemicals cooperation work being done in North America[1] through the EPA Chemical Assessment and Management Program (ChAMP)[2]. These screening-level characterizations are developed by EPA for individual chemicals or chemical categories to support initial Risk-Based Prioritizations (RBPs) for HPV chemicals. These screening-level characterizations are technical documents intended primarily to inform the Agency's internal decision-making process. Accordingly, they are written for assessment professionals and assume a degree of technical understanding. Each of the support documents is described below.

The Risk-Based Prioritizations are found in an accompanying document and are written for a general audience. They present EPA's initial thinking regarding the potential risks presented by these chemicals and future possible actions that may be needed.

Hazard Characterizations for HPV Chemicals

EPA's screening-level hazard characterizations are based primarily on the review of the summaries of studies and other information submitted by the chemical sponsor(s) under the HPV Challenge Program[3]. These studies included in the scope of the HPV Challenge comprise the Screening Information Data Set (SIDS) of the Organization for Economic Cooperation and Development (OECD)[4], an internationally recognized battery of tests that provides the basic data necessary to make an initial evaluation of a chemical's hazards and fate. In preparing the initial hazard characterizations, EPA also consulted a variety of reliable sources[5] for additional relevant information and 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 an HPV submission, EPA also searched publicly available databases[6] for information entered from one year prior to the HPV submission through May 2008. The screening-level hazard characterization is performed according to established EPA guidance[7]. A more detailed description of the hazard characterization process is available on the EPA website[8].

With respect to chemicals for which internationally-accepted OECD SIDS Initial Assessment Profiles (SIAP) and Initial Assessment Reports (SIAR) were available, EPA did not generate its own screening-level hazard characterization, but did check for and incorporate updated information in the risk characterization.

Exposure Characterizations for HPV Chemicals

EPA recently received exposure-related data on chemicals submitted in accordance with the requirements of Inventory Update Reporting (IUR)[9]. The 2006 IUR submissions pertain to chemicals manufactured in

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[1] U.S. EPA – U.S. Commitments to North American Chemicals Cooperation: http://www.epa.gov/hpv/pubs/general/sppframework.htm.
[2] U.S. EPA – ChAMP information: http://www.epa.gov/champ/.
[3] U.S. EPA – HPV Challenge Program information: http://www.epa.gov/hpv.
[4] U.S. EPA – Technical Guidance Document, OECD SIDS Manual Sections 3.4 and 3.5: http://www.epa.gov/chemrtk/pubs/general/sidsappb.htm.
[5] U.S. EPA – Public Database Hazard Information: http://www.epa.gov/hpvis/hazardinfo.htm.
[6] U.S. EPA – Public Database Update Information: http://www.epa.gov/chemrtk/hpvis/updateinfo.htm.
[7] U.S. EPA – Risk Assessment Guidelines: http://cfpub.epa.gov/ncea/raf/rafguid.cfm.
[8] U.S. EPA – About HPV Chemical Hazard Characterizations: http://www.epa.gov/hpvis/abouthc.htm.
[9] U.S. EPA – Basic IUR Information: http://www.epa.gov/opptintr/iur/pubs/guidance/basic-information.htm.

(including imported into) the U.S. during calendar year 2005 in quantities of 25,000 pounds or more at a single site. The reports include the identity, the quantity, and the physical form of the chemical manufactured or imported, and the number of workers reasonably likely to be exposed during manufacture of the chemical. For chemicals manufactured or imported in quantities of 300,000 pounds or more at a single site, additional reported information includes: the industrial processing and uses of the chemical; the number of industrial processing sites and workers reasonably likely to be exposed to the chemical at those sites; the consumer and commercial uses of the chemical; and an indication whether the chemical was used in products intended for use by children under 14 years of age.

EPA's screening-level exposure characterizations are based largely on the information submitted under the IUR reporting, although other exposure information submitted to the Agency (for example, in HPV submissions) or readily available through a limited set of publicly accessible databases[10] was also considered. The screening-level exposure characterizations identify a potential (high, medium, or low) that each of five populations – the environment, the general population, workers, consumers, and children – might be exposed to the chemical. In most cases, this potential doesn't address the quantity, frequency, or duration of exposure, but refers only to the likelihood that an exposure could occur.

In many instances EPA is not able to fully disclose to the public all the IUR exposure-related data reviewed or relied upon in the development of the screening-level documents because some of the material was claimed as confidential business information (CBI) when it was submitted to the Agency. These CBI claims do limit the Agency's ability to be completely transparent in presenting some underlying exposure and use data for chemicals in public documents. EPA does consider all data, including data considered to be CBI, in the screening-level exposure and risk characterization process, and endeavors whenever possible to broadly characterize supporting materials claimed as confidential in ways that do not disclose actual CBI.

Risk Characterizations for HPV Chemicals

EPA combines the information from the screening-level exposure characterization with the screening-level hazard characterization to develop a qualitative screening-level risk characterization, as described in the Agency's guidance on drafting risk characterizations[11]. These screening-level risk characterizations are technical documents intended to support subsequent priority-setting decisions and actions by OPPT. The purpose of the qualitative screening-level risk characterization is two-fold: to support initial risk-based decisions to prioritize chemicals, identify potential concerns, and inform risk management options; and to identify data needs for individual chemicals or chemical categories.

These initial characterization and prioritization documents do not constitute a final Agency determination as to risk, nor do they determine whether sufficient data are available to characterize risk. Recommended actions reflect EPA's relative judgment regarding this chemical or chemical category in comparison with others evaluated under this program, as well as the uncertainties presented by gaps that may exist in the available data.

[10] U.S. EPA – Summary of Public Databases Routinely Searched: http://www.epa.gov/chemrtk/hpvis/pubdtsum.htm.
[11] U.S. EPA – Risk Characterization Program: http://www.epa.gov/osa/spc/2riskchr.htm.

QUALITATIVE SCREENING-LEVEL RISK CHARACTERIZATION OF HIGH PRODUCTION VOLUME CHEMICALS

SPONSORED CHEMICAL

***m*-Diisopropenylbenzene (CAS No. 3748-13-8)**
[9th CI Name: Benzene, 1,3-bis(1-methylethenyl)-]

September 2008

Prepared by

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QUALITATIVE SCREENING-LEVEL RISK CHARACTERIZATION FOR *m*-Diisopropenylbenzene (CAS No. 3748-13-8)

1. Physical-Chemical Properties and Environmental Fate

m-Diisopropenylbenzene is a liquid with low water solubility and moderate vapor pressure. It is expected to have moderate mobility in soil. Volatilization of *m*-diisopropenylbenzene is considered moderate based on its Henry's Law constant. The rate of hydrolysis is considered negligible, since *m*-diisopropenylbenzene does not contain functional groups that are subject to hydrolysis under environmental conditions. The rate of atmospheric photooxidation is considered rapid. *m*-Diisopropenylbenzene is expected to be moderately persistent (P2) and have a moderate bioaccumulation potential (B2).

2. Hazard Characterization

Aquatic Organism Toxicity. The acute toxicity of *m*-diisopropenylbenzene to fish, aquatic invertebrates and aquatic plants is moderate.

Human Health Toxicity. The acute inhalation toxicity of *m*-diisopropenylbenzene in rats is moderate. The acute oral and dermal toxicity of *m*-diisopropenylbenzene to rats and rabbits is low. *m*-Diisopropenylbenzene is slightly irritating to rabbit eyes and skin and is a dermal sensitizer in guinea pigs. An oral combined repeated-dose/reproductive/developmental toxicity study in rats showed no systemic, reproductive or developmental toxicity. An inhalation repeated-dose toxicity study in rats showed moderate toxicity. *m*-Diisopropenylbenzene was not mutagenic and did not induce chromosomal aberrations.

3. Exposure Characterization

m-Diisopropenylbenzene has an aggregated production/import volume in the United States of 1 million to 10 million pounds. Non-confidential information in the Inventory Update Reporting (IUR) indicates that the industrial processing and uses of the chemical are as intermediates in the manufacturing of other basic organic chemicals. The High Production Volume (HPV) submission for m-diisopropenylbenzene, also referred to as benzene, 1,3-bis(1-methylethenyl)-, states that the chemical is primarily used as an industrial intermediate in the production of diisocyanate monomer.

Potential Exposure to the General Population and the Environment: Based on use information, there is potential for environmental releases during manufacturing, processing, and use. *m*-Diisopropenylbenzene is expected to be moderately persistent in the environment (P2) and the bioaccumulation potential is moderate (B2). Based on the information considered, including environmental fate, known uses, and the Agency's expert judgment, EPA identifies, for the purposes of risk-based prioritization, a medium potential that the general population and the environment might be exposed to *m*-diisopropenylbenzene.

Potential Exposure to Workers: Based on the information considered, including IUR and HPV submissions, in combination with the Agency's professional judgment, EPA identifies, for the purposes of prioritization, a low relative ranking for potential worker exposure. This low ranking is based primarily on the moderate volatility, the uses of the chemical, the production volume, and the number of potentially exposed workers.

Potential Exposure to Consumers: No consumer uses are reported in the IUR submissions, nor were any found in other data sources. EPA identifies, for the purposes of risk-based prioritization, a low potential that consumers might be exposed to *m*-diisopropenylbenzene.

Potential Exposure to Children: No uses in products intended to be used by children are reported in the IUR, nor are any found in other data sources. EPA identifies, for the purposes of risk-based prioritization, that the potential for exposures to children is low.

4. Risk Characterization

The statements and rationale provided below are intended solely for the purpose of this screening-level and qualitative risk characterization and will be used for prioritizing substances for future work in the U.S. Chemical Assessment and Management Program (ChAMP).

Risk Statement and Rationale

Potential Risk to Aquatic Organism from Environmental Releases: (MEDIUM CONCERN). EPA identifies a medium potential that aquatic organisms might be exposed from environmental releases. *m*-Diisopropenylbenzene has a moderate potential for both bioaccumulation and persistence. These characteristics in combination with the moderate toxicity to fish, aquatic invertebrates and plants indicate a medium concern for potential risk to fish, aquatic invertebrates and plants.

Potential Risk to the General Population from Environmental Releases: (LOW CONCERN). EPA identifies a medium potential that the general population might be exposed from environmental releases. The potential human health hazard is expected to be low from oral exposure and medium from inhalation exposure. Based on rapid photodegradation in air, EPA assumes that air exposures to the general population will be low. Therefore, the available information suggests a low concern for potential risk to the general population from environmental releases.

Potential Risk to Workers: (LOW CONCERN). EPA identifies a low relative ranking for potential worker exposure. The potential health hazard is expected to be moderate by the inhalation route. *m*-Diisopropenylbenzene is slightly irritating to the eyes and skin and is a dermal sensitizer. Adherence to standard good industrial hygiene practices (gloves, respirators, goggles, and other protective clothing) will limit the exposure to workers. Therefore, taken together, the available information suggests a low concern for potential risks to workers.

Potential Risk to Consumers: (LOW CONCERN). No consumer uses are reported in the IUR submissions, nor were any found in other data sources. *m*-Diisopropenylbenzene is primarily used as an industrial intermediate. EPA identifies a low potential that consumers might be exposed. The potential health hazard is expected to be low by the oral route and moderate by the inhalation route. Therefore, taken together, the available information suggests a low concern for potential risks to consumers.

Potential Risk to Children: (LOW CONCERN). No uses in products intended to be used by children are reported in the IUR submissions, nor were any found in other data sources. EPA identifies a low potential that children might be exposed. There was no toxicity in an animal study with exposures during early life stages. Therefore, taken together, the available information suggests a low concern for potential risks to children.

SCREENING-LEVEL HAZARD CHARACTERIZATION OF HIGH PRODUCTION VOLUME CHEMICALS

SPONSORED CHEMICAL

_m_-Diisopropenylbenzene (CAS No. 3748-13-8)
[9th CI Name: Benzene, 1,3-bis(1-methylethenyl)-]

September 2008

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SCREENING-LEVEL HAZARD CHARACTERIZATION
m-Diisopropenylbenzene (CAS No. 3748-13-8)

Introduction

The sponsor, Cytec Industries Inc., submitted a Test Plan and Robust Summaries to EPA for *m*-diisopropenylbenzene (CAS No. 3748-13-8; 9th CI name: benzene, 1,3-bis(1-methylethenyl)-) on December 18, 2002. EPA posted the submission on the ChemRTK HPV Challenge website on January 16, 2003 (http://www.epa.gov/oppt/chemrtk/pubs/summaries/mdiisopr/c14136tc.htm). EPA comments on the original submission were posted to the website on May 13, 2003. Public comments were also received and posted to the website. The sponsor submitted updated/revised documents on July 8, 2003 and December 10, 2004, which were posted to the ChemRTK website on July 25, 2003 and February 3, 2005 respectively.

This screening level hazard characterization is based primarily on the review of the test plan and robust summaries of studies submitted by the sponsor(s) under the HPV Challenge Program. 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 2004 to May 2008: the NLM databases (ChemID to locate available data sources including Medline/PubMed, Toxline, HSDB, IRIS, NTP, ATSDR, EXTOXNET, EPA SRS, etc.), STN/CAS online databases (Registry file for locators, ChemAbs for toxicology data, RTECS, Merck, etc.) and Science Direct. A summary table of SIDS endpoint data with the structure(s) of the sponsored chemical(s) is included in the appendix. The screening-level hazard characterization for environmental and human health effects is based largely on SIDS endpoints and is described according to established EPA or OECD effect level definitions and hazard assessment practices.

Hazard Characterization

m-Diisopropenylbenzene is a liquid with low water solubility and moderate vapor pressure. It is expected to have moderate mobility in soil. Volatilization of *m*-diisopropenylbenzene is considered moderate based on its Henry's Law constant. The rate of hydrolysis is considered negligible, since *m*-diisopropenylbenzene does not contain functional groups that are subject to hydrolysis under environmental conditions. The rate of atmospheric photooxidation is considered rapid. *m*-Diisopropenylbenzene is expected to be moderately persistent (P2) and have a moderate bioaccumulation potential (B2).

The acute toxicity of *m*-diisopropenylbenzene to fish, aquatic invertebrates and aquatic plants is moderate.

The acute inhalation toxicity of *m*-diisopropenylbenzene in rats is moderate. The acute oral and dermal toxicity of *m*-diisopropenylbenzene to rats and rabbits is low. *m*-Diisopropenylbenzene is slightly irritating to rabbit eyes and skin and is a dermal sensitizer in guinea pigs. An oral combined repeated-dose/reproductive/developmental toxicity study in rats showed no systemic, reproductive or developmental toxicity. An inhalation repeated-dose toxicity study in rats showed moderate toxicity. *m*-Diisopropenylbenzene was not mutagenic and did not induce chromosomal aberrations.

No data gaps were identified under the HPV Challenge Program.

1. Physical-Chemical Properties and Environmental Fate

The physical-chemical properties of m-diisopropenylbenzene are summarized in Table 1a, while its environmental fate properties are provided in Table 1b. The structure of the compound is provided in the Appendix.

Physical-Chemical Properties Characterization

m-Diisopropenylbenzene is a liquid with low water solubility and moderate vapor pressure. The water solubility value of ca. 5.6 mg/L does not agree with the value of a close analog, diisopropylbenzene (CA 25321-09-9), which has a water solubility of 0.072 mg/L.

Table 1a. Physical-Chemical Properties of *m*-Diisopropenylbenzene[1]	
Property	**Value**
CAS No.	3748-13-8
Molecular Weight	158
Physical State	Liquid
Melting Point	-38 to -40°C (measured)
Boiling Point	231°C (measured)
Vapor Pressure	2.3 mm Hg at 69°C (measured) 0.16 mm Hg at 25°C (extrapolated)
Water Solubility	ca. 5.6 mg/L at 25°C (measured) 0.072 mg/L for diisopropylbenzene (analog)
Dissociation constants (pK_a)	Not applicable
Henry's Law constant	3.48×10^{-3} atm-m^3/mole (estimated) [2]
Log K_{ow}	4.89 (estimated)[2]

[1] Cytec Industries, Inc. December 10, 2004. Revised Robust Summary and Test Plan for m-Diisopropenylbenzene, http://www.epa.gov/hpv/pubs/summaries/mdiisopr/c14136tc.htm.
[2] US EPA. 2008. Estimation Programs Interface Suite™ for Microsoft® Windows, v3.20. United States Environmental Protection Agency, Washington, DC, USA. http://www.epa.gov/opptintr/exposure/pubs/episuite.htm.

Environmental Fate Characterization

m-Diisopropenylbenzene is expected to have moderate mobility in soil. No biodegradation of *m*-diisopropenylbenzene was observed over the course of a 28 day incubation period using an activated sludge inoculum and a closed bottle (OECD 301D) test. These results are consistent with the results of a ready biodegradation test for alpha-methylstyrene (CAS No. 98-83-9). Alpha-methylstyrene achived 0% of its theoretical BOD using an activated sludge inoculum and the modified MITI test (OECD 301C) over a 2 week incubation period. The rate of volatilization of *m*-diisopropenylbenzene from water and moist soil is considered moderate given its estimated Henry's Law constant. The rate of atmospheric photooxidation is considered rapid. The rate of hydrolysis is considered negligible, since *m*-diisopropenylbenzene does not contain functional groups that are subject to hydrolysis under environmental conditions. *m*-Diisopropenylbenzene is moderately persistent (P2) and has a moderate bioaccumulation potential (B2).

Table 1b. Environmental Fate Characteristics of m-Diisopropenylbenzene [1]	
Property	**Value**
Photodegradation Half-life	1.2 hours (estimated; assumes 12-hour day and 1.5×10^6 hydroxyl radicals/cm^3)
Hydrolysis Half-life	Negligible
Biodegradation	0% in 28 days; 0% in 14 days (alpha-methylstyrene)[3]
Bioconcentration	BCF = 1166 (estimated)[2]
Direct Photolysis	Not Applicable
Log K_{oc}	3.606 (estimated)
Fugacity (Level III Model)	Air = 0.24% Water = 24.9% Soil = 63.9% Sediment = 11.0%
Persistence	P2 (moderate)[4]
Bioaccumulation	B2 (moderate)[4]

[1] Cytec Industries, Inc. 2004. Revised Robust Summary and Test Plan for m-Diisopropenylbenzene, http://www.epa.gov/hpv/pubs/summaries/mdiisopr/c14136tc.htm.
[2] US 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.
[3] National Institute of Technology and Evaluation Biodegradation and Bioconcentration of the Existing Chemical Substances. Accessed July 9, 2008. http://www.safe.nite.go.jp/english/kizon/KIZON_start_hazkizon.html.
[4] Federal Register. 1999. Category for Persistent, Bioaccumulative, and Toxic New Chemical Substances. Federal Register 64, Number 213 (November 4, 1999) pp. 60194–60204.

Conclusion: *m*-Diisopropenylbenzene is a liquid with low water solubility and moderate vapor pressure. It is expected to have moderate mobility in soil. Volatilization of *m*-diisopropenylbenzene is considered moderate based on its Henry's Law constant. The rate of hydrolysis is considered negligible, since *m*-diisopropenylbenzene does not contain functional groups that are subject to hydrolysis under environmental conditions. The rate of atmospheric photooxidation is considered rapid. *m*-Diisopropenylbenzene is moderately persistent (P2) and has a moderate bioaccumulation potential (B2).

2. Environmental Effects – Aquatic Toxicity

Acute Toxicity to Fish

Fathead minnows (*Pimephales promelas*) were exposed to *m*-diisopropenylbenzene at nominal concentrations of 0.60, 1.2, 2.5, 5.0, 10 or 20 mg/L under static conditions for 96 hours. At 5 mg/L, mortality was 10% and 20% at 72 and 96 hours, respectively. At 10 mg/L, 0, 50, 90 and 100% of fish had died at 24, 48, 72 and 96 hours, respectively. At 20 mg/L, mortality was 0, 40, 70 and 100% at 24, 48, 72 and 96 hours, respectively.
96-h LC_{50} = 6.2 mg/L

Acute Toxicity to Aquatic Invertebrates

Water fleas (*Daphnia magna*) were exposed to *m*-diisopropenylbenzene at nominal concentrations of 1.0, 1.8, 3.2, 5.6 or 10 mg/L under static conditions for 48 hours. None of the daphnids exposed to 0, 1.0 or 1.8 mg/L died during the study. At 3.2 mg/L mortality was 10%. At 5.6 mg/L, 9 out of 10 daphnids died within 24 hours and all died by 48 hours. All daphnids exposed to 10 mg/L died within 24 hours.
48-h LC_{50} = 4.0 mg/L

Toxicity to Aquatic Plants

Green algae (*Pseudokirchneriella subcapitata*) were exposed to *m*-diisopropenylbenzene at nominal concentrations of 0, 1.8, 3.2, 5.6, 10 or 18 mg/L under static conditions for 96 hours. Inhibition of cell growth (compared with control growth) was noted at concentrations ≥ 3.2 mg/L and was observed as early as 48 hours for cells exposed to 10 and 18 mg/L. Cell counts (and percent inhibition) of cells exposed to 10 mg/L at 72 and 96 hours were 10 (87%) and 12 (95%). No growth occurred in cells exposed to 18 mg/L for 72 or 96 hours.
72-h EC_{50} (growth) = 4.93 mg/L
96-h EC_{50} (growth) = 4.92 mg/L

Conclusion: The acute toxicity of *m*-diisopropenylbenzene to fish, aquatic invertebrates and aquatic plants is moderate.

3. Human Health Effects

Acute Oral Toxicity

(1) Sprague-Dawley rats (5/sex/dose) were administered *m*-diisopropenylbenzene via gavage at 0, 8.0, 10.0, 12.6, 15.8 or 20.0 mL/kg-bw (0, 7400, 9250, 11,655, 14,615 or 18,500 mg/kg-bw based on density) and observed for up to 15 days. None of the animals treated with 0 (control) or 8 mL/kg-bw died. Mortality occurred at 10.0, 12.6, 15.8 and 20.0 mL/kg-bw.
LD_{50} = 12,200 mg/kg-bw

(2) Sprague-Dawley rats (5/sex/dose) were administered *m*-diisopropenylbenzene at 5000 mg/kg-bw and observed for 14 days. Mortality occurred at this dose level. Labored breathing was observed in these rats just prior to death. Pathological findings included red hepatization and expended lungs, indicative of acute pneumonia or pneumonitis unrelated to treatment. Gross necropsies of survivors were unremarkable.
LD_{50} > 5000 mg/kg-bw

Acute Inhalation Toxicity

Sprague-Dawley rats (5/sex/dose) were exposed to of *m*-diisopropenylbenzene at nominal concentrations of 3 or 15 mg/L for 6 hours and observed for 5 days post-exposure. The mean actual exposure concentrations (± standard deviation) were 0.545 ± 0.062 and 5.576 ± 0.417 mg/L. At 5.576 mg/L, signs of toxicity such as wet fur, red perinasal wetness, lacrimation, whole body tremors, dermal irritation, hyperactivity, ataxia and mouth breathing were observed during the first 90 minutes of exposure. A complete loss of motor activity was observed in these animals for the remainder of the exposure period and all animals eventually died. After exposure, all animals exhibited absent toe, tail pinch and surface righting reflexes, hypothermia, respiratory difficulties, wet fur and dermal irritation. One high-concentration female had eye opacity. Necropsies of the dead animals revealed discoloration of the lungs and kidneys and wet fur.
0.54 mg/L < LC_{50} < 5.6 mg/L

Acute Dermal Toxicity

New Zealand White rabbits (5/sex/dose) were administered *m*-diisopropenylbenzene at 2 g/kg-bw to abraded skin under occluded conditions for 24 hours. After exposure, the excess material was wiped off and animals were observed for signs of toxicity for 14 days post-dosing. No animals died during the observation period.
LD_{50} > 2000 mg/kg-bw

Repeated-Dose Toxicity

(1) In a combined repeated-dose/reproductive/developmental toxicity study, Sprague-Dawley rats (10/sex/dose) were administered *m*-diisopropenylbenzene via gavage at nominal doses of 0 (vehicle), 100, 300 or 1000 mg/kg-bw/day for up to 53 days. Administration to F0 males and females began 14 days prior to mating and continued through mating. Females continued receiving *m*-diisopropenylbenzene until postnatal day 5. All F0 females were

allowed to deliver naturally and rear the pups to postnatal day 5, the scheduled day of necropsy. Histopathological examinations of the F0 rats were restricted to the following in the control and high-dose groups: coagulating glands, epididymides, prostate, seminal vesicles, testes, ovaries, uterus/cervix, vagina and stomach. The study did not include hematology, clinical chemistry. One high-dose female exhibited hunched posture, tiptoe gait and excessive grooming 1 hour after dosing on one occasion. An additional high-dose female had similar signs on several occasions and exhibited signs of lethargy, piloerection, decreased respiration and ptosis on one occasion. Several findings noted in various organs and tissues of one or two treated animals of each dose were comparable with those with the controls. None of the gross lesions observed were attributed to administration of test material. No treatment-related histopathological changes were observed.
NOAEL = 1000 mg/kg-bw/day (highest dose tested)

(2) Sprague-Dawley rats (5/sex/dose) were exposed to *m*-diisopropenylbenzene vapor via inhalation at nominal concentrations of 0 (air only), 100, 500 or 1000 mg/m^3 for 6 hours/day, 5 consecutive days/week for 4 weeks. During the fourth week, all animals were exposed for 4 days and euthanized on the 5th day. The mean actual exposure concentrations (± standard deviation) were 107 ± 13, 510 ± 29 and 970 ± 54 mg/m^3 or 0.107, 0.510 and 0.970 mg/L/day for the nominal concentrations of 100, 500 and 1000 mg/m^3. None of the animals died. Average body weights and weight gains of males exposed to 510 and 970 mg/m^3 were lower than controls, but the robust summary did not report the magnitude of this effect. Increases in absolute (females only) and relative (to body weight) liver weights were observed in high-dose animals (males and females). Total urine volume of males exposed to 510 and 970 mg/m^3 was different from controls. High-dose males also had increased relative (but not absolute) brain, adrenal and testes weights. Males exposed to 510 mg/m^3 also had increased relative liver weight. The biological significance of the organ weight changes is unknown as there were no histopathological lesions.
LOAEL = 0.970 mg/L/day (based on body weight)
NOAEL = 0.510 mg/L/day

Reproductive/Developmental Toxicity

In the combined repeated-dose/reproductive/developmental toxicity study in Sprague-Dawley rats described above, the clinical signs were hunched posture, tiptoe gait and excessive grooming in females at 1000 mg/kg-bw/day 1 hour after dosing on one occasion, lethargy, piloerection, decreased respiration and ptosis. All animals recovered shortly after treatment. There was no effect on body weights and organ weights. There were no effects of treatment on fertility or mating performance. There was no effect of treatment on gestation length and no significant ($p < 0.05$) effect of treatment on the number of implantation sites. There were no significant ($p < 0.05$) effects of treatment on live birth or viability index, litter size, litter weight, pinna unfolding, surface righting reflex or sex ratio. Gross examinations were normal, with the exception of pale kidneys in more than one pup in all groups (one control, one low-dose, two mid-dose and four high-dose litters).
NOAEL (systemic toxicity) = 1000 mg/kg-bw/day (highest dose tested)
NOAEL (reproductive toxicity) = 1000 mg/kg-bw/day (highest dose tested)
NOAEL (developmental toxicity) = 1000 mg/kg-bw/day (highest dose tested)

Genetic Toxicity – Gene Mutation

In vitro
(1) *Salmonella typhimurium* strains TA1535, TA1537, TA98 and TA100 were exposed to *m*-diisopropenylbenzene at concentrations of 0, 1.5, 5, 15, 50, 150, 500, 1500 or 5000 μg/plate in the presence and absence of metabolic activation. Positive controls were tested concurrently and produced an appropriate response. Signs of cytotoxicity were apparent at concentrations of 500 μg/plate and higher.
***m*-Diisopropenylbenzene was not mutagenic in this assay.**

(2) *Escherichia coli* strain WP2uvrA- was exposed to *m*-diisopropenylbenzene at concentrations of 0, 50, 150, 500, 1500 or 5000 μg/plate in the presence and absence of activation. Positive controls were tested concurrently and produced an appropriate response. A preliminary toxicity study found no evidence for cytotoxicity at the highest concentration tested.
***m*-Diisopropenylbenzene was not mutagenic in this assay.**

Genetic Toxicity – Chromosomal Aberrations

In vitro
Chinese hamster ovary (CHO) cells were exposed to *m*-diisopropenylbenzene at concentrations of 0 – 49.38 μg/mL in the absence of metabolic activation and 0 – 197.5 μg/mL in the presence of metabolic activation. Tested concentrations were selected based on results from a preliminary cytotoxicity test. Positive controls were tested concurrently and produced an appropriate response.
***m*-Diisopropenylbenzene did not induce chromosomal aberrations in this assay.**

Additional Information

Skin Irritation

New Zealand White rabbits were administered *m*-diisopropenylbenzene to abraded skin at a dose of 2 g/kg-bw under occlusive conditions for 24 hours and observed for 14 days. The only effect of treatment was slight dermal irritation.
***m*-Diisopropenylbenzene was slightly irritating to rabbit skin in this assay.**

Eye Irritation

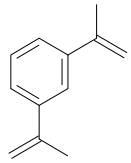
New Zealand White rabbits (9 males) were administered *m*-Diisopropenylbenzene (0.1 mL) via instillation into the cupped lower lid of the right eye. Thirty seconds after treatment, the eyes of three animals were rinsed with water for 60 seconds; no further treatment was conducted on the other six animals. The animals were observed for 13 days. No irritation to the cornea or iris was observed at any time point. Discharge, chemosis and/or redness of the conjunctivae were observed in most animals. Nasal discharge was observed in one animal with unwashed eyes on day 2 and two animals with unwashed eyes on day 3.
***m*-Diisopropenylbenzene was slightly irritating to the rabbit eye in this assay.**

Sensitization

Guinea pigs (7 – 8 per sex) were administered *m*-diisopropenylbenzene dermally to a shaved patch of the dorsal surface at a concentration of 100% during the induction phase. The test material was applied to the test site 3 times/week on alternating days until a total of 10 applications were made. Fourteen days after the last induction dose, animals were challenged with the test substance at a concentration of 100%. All animals induced and challenged with test material were rechallenged with test material 11 days after the original challenge with concentrations of 12.5, 25, 50 or 100% test material. Positive control tests were conducted concurrently.
***m*-Diisopropenylbenzene was sensitizing in this assay.**

Conclusion: The acute inhalation toxicity of *m*-diisopropenylbenzene in rats is moderate. The acute oral and dermal toxicity of *m*-diisopropenylbenzene to rats and rabbits is low. *m*-Diisopropenylbenzene is slightly irritating to rabbit eyes and skin and is a dermal sensitizer in guinea pigs. An oral combined repeated-dose/reproductive/developmental toxicity study in rats showed no systemic reproductive or developmental toxicity. An inhalation repeated-dose toxicity study in rats showed moderate toxicity. *m*-Diisopropenylbenzene was not mutagenic and did not induce chromosomal aberrations.

APPENDIX

Summary Table of the Screening Information Data Set as Submitted under the U.S. HPV Challenge Program	
Endpoints	**SPONSORED CHEMICAL** ***m*-Diisopropenylbenzene** **(3748-13-8)**
Structure	
Summary of Environmental Effects – Aquatic Toxicity Data	
Fish **96-h LC_{50} (mg/L)**	6.2
Aquatic Invertebrates **48-h EC_{50} (mg/L)**	4.0
Aquatic Plants **72-h EC_{50} (mg/L)** **(growth)**	4.93
Summary of Human Health Data	
Acute Oral Toxicity **LD_{50} (mg/kg-bw)**	> 5000
Acute Inhalation Toxicity **LC_{50} (mg/L)**	0.54 – 5.6
Acute Dermal Toxicity **LD_{50} (mg/kg-bw)**	> 2000
Repeated-Dose Toxicity **NOAEL/LOAEL** **Oral (mg/kg-bw/day)**	NOAEL = 1000 (53-d)
Repeated-Dose Toxicity **NOAEL/LOAEL** **Inhalation (mg/L/day)**	NOAEL = 0.970 (4-wk) LOAEL = 0.510 (4-wk)
Reproductive/Developmental Toxicity **NOAEL/LOAEL** **Oral (mg/kg-bw/day)** **Systemic/Reproductive/Developmental Toxicity**	NOAEL = 1000 (53-d)
Genetic Toxicity – Gene Mutation ***In vitro***	Negative
Genetic Toxicity – Chromosomal Aberrations ***In vitro***	Negative
Additional Information **Skin Irritation** **Eye Irritation** **Skin Sensitization**	 Slightly irritating Slightly irritating Sensitizing

Screening Level Exposure Characterization for HPV Challenge Chemical

m-Diisopropenylbenzene (CAS No. 3748-13-8) [9th CI Name: Benzene, 1,3-bis(1-methylethenyl)-]

September 2008

Prepared by

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Screening Level Exposure Characterization *m*-Diisopropenylbenzene (CAS No. 3748-13-8) [9th CI Name: Benzene, 1,3-bis(1-methylethenyl)-]

Non-CBI Executive Summary

m-Diisopropenylbenzene has an aggregated production/import volume in the United States of 1 million to 10 million pounds. Non-confidential information in the Inventory Update Reporting (IUR) indicates that the industrial processing and uses of the chemical are as intermediates in the manufacturing of other basic organic chemicals. The High Production Volume (HPV) submission for m-diisopropenylbenzene, also referred to as benzene, 1,3-bis(1-methylethenyl)-, states that the chemical is primarily used as an industrial intermediate in the production of diisocyanate monomer.[12]

Potential Exposure to the General Population and the Environment: Based on use information, there is potential for environmental releases during manufacturing, processing, and use. *m*-Diisopropenylbenzene is expected to be moderately persistent in the environment (P2) and the bioaccumulation potential (B2) is moderate. Based on the information considered, including environmental fate, known uses, and the Agency's expert judgment, EPA identifies, for the purposes of risk-based prioritization, a medium potential that the general population and the environment might be exposed to *m*-diisopropenylbenzene.

Potential Exposure to Workers: Based on the information considered, including IUR and HPV submissions, in combination with the Agency's professional judgment, EPA identifies, for the purposes of prioritization, a low relative ranking for potential worker exposure. This low ranking is based primarily on the moderate volatility, the uses of the chemical, the production volume, and the number of potentially exposed workers.

Potential Exposure to Consumers: No consumer uses are reported in the IUR submissions, nor were any found in other data sources. EPA identifies, for the purposes of risk-based prioritization, a low potential that consumers might be exposed to *m*-diisopropenylbenzene.

Potential Exposure to Children: No uses in products intended to be used by children are reported in the IUR, nor are any found in other data sources. EPA identifies, for the purposes of risk-based prioritization, a low potential that children might be exposed.

This exposure characterization was completed using both public, non-confidential sources, and one or more IUR submissions that were available as of this writing.

[12] Cytec, 2004. Test Plan for m-diisopropenylbenzene (CAS No. 3748-13-8). Cytec Industries Inc. DIPEB Test Plan, Final Revision. November 17, 2004. Accessed, 7/16/08.
http://www.epa.gov/chemrtk/pubs/summaries/mdiisopr/c14136rt1.pdf

Volume and Use Information

m-Diisopropenylbenzene (CAS #3748-13-8) has an aggregated production and/or import volume in the United States of 1 million to 10 million pounds.[13] Non-confidential information in the IUR indicates that this chemical was manufactured and/or imported at the following companies and sites: Deltech Corporation/Baton Rouge, LA. There may be other companies and sites that are claimed confidential. Persons submitting IUR information for 2005 asserted that some or all of the information was confidential. Only non-confidential versions of reported IUR data are included in this summary. A pre-manufacture notification for this chemical was submitted to EPA and contains data and information that are claimed confidential.

The non-confidential industrial processing use (IPU) reported in IUR submissions for this chemical is processing as a reactant/intermediate in basic organic chemical manufacturing. There may be other IPUs that are claimed confidential. No commercial/consumer uses are reported in IUR submissions.

The HPV submission for this chemical states that the chemical is used as an industrial intermediate in the production of diisocyanate monomer, with about one percent of this chemical being shipped to another facility in the United States for use as an intermediate in optical products, and about five percent of this chemical is exported.[14]

Environmental Releases

Environmental releases may impact general population and environmental exposures. Factors affecting releases include volumes produced, processed and used; numbers of sites; and processes of manufacture, processing, and use.

Based on IUR data, the maximum total number of industrial sites for manufacturing, processing, or using this chemical is confidential.

Many chemicals used as reactants/intermediates have industrial releases that are a relatively low percentage of the volume. Lower percentage releases occur when a high percentage of the chemical reacts without excess loss during its use as an intermediate. The actual percentage and quantity of release of the reported chemical associated with this use are not known.

The chemical is not on the Toxics Release Inventory.[15]

Experience has shown that air releases due to volatilization have not been an issue for chemicals with vapor pressures below 0.01 mm Hg. This chemical has a vapor pressure of 0.16 mm Hg at

[13] USEPA, 2006. Partial Updating of TSCA Chemical Inventory. http://www.epa.gov/oppt/iur/tools/data/2002-vol.htm.
[14] Cytec Industries, Inc., 2004. Test Plan for m-Diisopropenylbenzene (CAS No. 3748-13-8). http://www.epa.gov/chemrtk/pubs/summaries/mdiisopr/c14136tp.pdf.
[15] USEPA, 2006. Toxic Release Inventory. Accessed, 7/16/08. http://www.epa.gov/tri/.

25°C (extrapolated from a measured value).[16] This chemical's vapor pressure could result in air releases.

Exposures to the General Population and the Environment

Based on the available information, it is assumed that there could be releases to various media, including air, during manufacturing, processing, and use. A search of additional relevant databases did not provide any further information on releases of this chemical.

The IUR ranking for general population and the environment is medium since there may exposure from releases of this chemical based on the reported uses in the IUR data (see Table 1).

Persistence and bioaccumulation ratings for this chemical are P2 and B2.[17] These ratings suggest that this chemical is very persistent in the environment; and is bioaccumulative. *m*-Diisopropenylbenzene is a liquid with moderate water solubility and moderate vapor pressure. It is expected to have moderate mobility in soil. Volatilization of *m*-diisopropenylbenzene is considered moderate based on its Henry's Law constant. The rate of hydrolysis is considered negligible, since *m*-diisopropenylbenzene does not contain functional groups that are subject to hydrolysis under environmental conditions. The rate of atmospheric photooxidation is considered rapid.

Based on the information considered, including environmental fate, known uses, and the Agency's expert judgment, EPA identifies, for the purposes of risk-based prioritization, a medium potential that the general population and the environment might be exposed to *m*-diisopropenylbenzene.

Exposures to Workers

Based on the information considered (including IUR data and information from other selected data sources including HPV submission), in combination with the Agency's professional judgment, EPA identifies, for the purposes of risk-based prioritization, a low relative ranking for potential worker exposure. This low ranking is based primarily on the moderate volatility, the uses of the chemical, the production volume, and the number of potentially exposed workers. The following is a summary of relevant information affecting occupational exposure.

[16] USEPA, 2008. Screening-Level Hazard Characterization for High Production Chemical, m-diisopropenylbenzene (CAS No. 3748-13-8) (9th CI Name: Benzene, 1,3-bis(1-methylethenyl)-.
[17] USEPA, 2008. Screening-Level Hazard Characterization for High Production Chemical, m-diisopropenylbenzene (CAS No. 3748-13-8) (9th CI Name: Benzene, 1,3-bis(1-methylethenyl)-.

Summary of Parameters affecting Worker Exposure

Parameter	
Volume *	1 million to 10 million pounds
Physical Form(s) *	Liquid
Vapor Pressure	0.16 mm Hg at 25°C (extrapolated from a measured value)
Concentration*	Greater than 90% by weight
Number of Industrial Workers *	between 100 and 999
Uses* (including both IUR and HPV)	Intermediates
Key MSDS Info	combustible liquid; wear respirator, goggles, and gloves

* Only non-confidential IUR data are included for these parameters.

Based on IUR data, the maximum total number of workers reasonably likely to be exposed to this chemical during manufacturing and industrial processing and use may be between 100 and 999. There may be additional potentially exposed industrial workers who are not included in this estimate since not all submitters were required to report on industrial processing and use and/or there is at least one submission that contains a "Not Readily Obtainable" (NRO) response for the number of workers, for at least one use. This estimate does not include potentially exposed commercial workers. However, based on the IUR, there may not be any workers in commercial businesses who are exposed to this chemical. The National Occupational Exposure Survey (NOES) has no data for the total number of workers potentially exposed to this chemical.[18]

Based on IUR data, the chemical is manufactured in liquid forms, and worker exposures are possible for this chemical in these forms. There may be other physical forms that are claimed confidential. Also, the non-confidential maximum concentration is up to 100%. There may be other concentrations that are claimed confidential. This chemical has a vapor pressure of 0.16 mm Hg at 25°C (extrapolated from a measured value).[19] Experience has shown that worker exposures to vapors have not been an issue for chemicals with vapor pressures below 0.001 mm Hg. This chemical's vapor pressure could result in worker exposures to vapors if workers are proximal to the liquid.

This chemical does not have OSHA Permissible Exposure Limits (PELs).[20]

Exposures to Consumers

No uses in consumer products were reported in the IUR.

[18] NIOSH, 1983. National Occupational Exposure Survey (NOES, 1981-1983). Accessed, 7/16/08. http://www.cdc.gov/noes/

[19] USEPA, 2008. Screening-Level Hazard Characterization for High Production Chemical, m-diisopropenylbenzene (CAS No. 3748-13-8) (9th CI Name: Benzene, 1,3-bis(1-methylethenyl)-.

[20] NIOSH, 1988. OSHA PEL Project Documentation. http://www.cdc.gov/niosh/pel88/npelcas.html, Accessed, 7/16/08.

EPA identifies, for the purposes of risk-based prioritization, a low potential for exposures to consumers from products containing this chemical based on the IUR data.

Exposures to Children

No uses in products intended to be used by children were reported in the IUR, nor were any found in other data sources. EPA identifies, for the purposes of risk-based prioritization, that the potential for exposures to children is low.

Non Confidential IUR Data Summary: *m*-Diisopropenylbenzene

Manufacturing/Import Information

Production and import volume: 1 million to 10 million pounds
List of non-CBI companies/ sites*: Deltech Corporation / Baton Rouge, LA
Highest non-CBI maximum concentration*: up to 100% by weight
Non-CBI physical forms*: liquid
*Note: There may be other companies/ sites, concentrations, and physical forms that are claimed as confidential business information (CBI).

Table 1
Industrial Processing and Use Information
Reported in 2006 IUR

Processing Activity	**Industrial Sector**	**Function in Ind. Sector**
Processing as a reactant	Other Basic Organic Chemical Manufacturing	Intermediates
Additional line item(s) may be claimed as CBI		

Table 2
Commercial/ Consumer Uses
Reported in 2006 IUR

Commercial/ Consumer Product Category Description	**Highest maximum concentration range**	**Use in Children's Products**
None reported		